Science and Technology of Silkworm Sericin

Extractions, Modifications, and Applications



Edited by Sabu Thomas, Sneha Sabu Mathew, Hanna J. Maria, and Rangam Rajkhowa

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ELSEVIER The Textile Institute

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Contributors

Ruchi Agrawal Deakin University, Geelong, VIC, Australia; Center for Excellence in Agriculture Nanotechnology, TERI-Deakin Nanobiotechnology Center, Gurugram, Haryana, India; Department of Biotechnology, TERI School of Advanced Studies (TERI SAS) University, New Delhi, India; Renewable Resources and Enabling Sciences Center, National Renewable Energy Laboratory, Golden, CO, United States

Aamir Ali Department of Zoology, Government College University Lahore, Lahore, Pakistan

S. Wazed Ali School of Interdisciplinary Research (SIRe), Indian Institute of Technology Delhi, New Delhi, India; Department of Textile and Fibre Engineering, Indian Institute of Technology Delhi, New Delhi, India

Anjali Department of Nutrition Biology, School of Interdisciplinary & Applied Sciences, Central University of Haryana, Mahendergarh, Haryana, India

Nihan Arabaci Department of Biology, Faculty of Arts and Sciences, Cukurova University, Adana, Turkey

Pornanong Aramwit Chulalongkorn University, Department of Pharmacy Practice, Faculty of Pharmaceutical Sciences and Center of Excellence in Bioactive Resources for Innovative Clinical Applications, Bangkok, Thailand; The Academy of Science, The Royal Society of Thailand, Bangkok, Thailand; Silpakorn University, Faculty of Pharmacy, Nakhon Pathom, Thailand

Manjunath B.S. Fibroheal Woundcare Private Limited, Bangalore, Karnataka, India

Sourav Banerjee School of Interdisciplinary Research (SIRe), Indian Institute of Technology Delhi, New Delhi, India

Rashmi Rekha Baruah Nanobiotechnology and Translational Knowledge Laboratory, Department of Applied Biology, School of Biological Sciences, University of Science and Technology Meghalaya (USTM), Baridua, Meghalaya, India

Vijay Kumar Boga Department of Pharmaceutics, National Institute of Pharmaceutical Education and Research, Lucknow, Uttar Pradesh, India

Sarocha Cherdchom Chulalongkorn University, Department of Anatomy, Center of Excellence in Nanomedicine, Bangkok, Thailand

Seyma Dadi Department of Nanotechnology Engineering, Abdullah Gul University, Kayseri, Turkey

Tapan Kumar Dash Fibroheal Woundcare Private Limited, Bangalore, Karnataka, India

Ayse Demirbas Department of Seafood Processing and Technology, Faculty of Fisheries, Recep Tayyip Erdogan University, Rize, Turkey

Brinda Goda Lakshmi Didugu Department of Life Sciences, School of Science, GITAM (Deemed to be University), Visakhapatnam, Andhra Pradesh, India

Fatma Dogan Department of Analytical Chemistry, Faculty of Pharmacy, Erciyes University, Kayseri, Turkey

Balaji Doolam Department of Biotechnology, Chaitanya Bharathi Institute of Technology, Hyderabad, Telangana, India

Ana Beatriz Vitorino de Farias State University of Campinas, School of Chemical Engineering, Campinas, Brazil

Sireesha V. Garimella Department of Life Sciences, School of Science, GITAM (Deemed to be University), Visakhapatnam, Andhra Pradesh, India

Can Huang State Key Laboratory of Resource Insects, College of Sericulture, Textile and Biomass Sciences, Southwest University, Chongqing, China

Namdeo Jadhav Department of Pharmaceutics, Krishna Vishwa Vidyapeeth, Krishna Institute of Pharmacy, Karad, Maharashtra, India

Vilas Jagtap Department of Pharmacognosy, R.C. Patel Institute of Pharmacy, Shirpur, Maharashtra, India

Mangala Joshi Department of Textile and Fibre Engineering, Indian Institute of Technology Delhi, New Delhi, India

Niraj Kale Department of Pharmaceutics, Bharati Vidyapeeth College of Pharmacy, Kolhapur, Maharashtra, India

Jovita Kanoujia Department of Pharmaceutics, Amity Institute of Pharmacy, Amity University Madhya Pradesh, Gwalior, Madhya Pradesh, India

Shashi Kashyap Department of Pharmaceutics, National Institute of Pharmaceutical Education and Research, Lucknow, Uttar Pradesh, India

Divya Susan Koshy Deakin University, Geelong, VIC, Australia; Center for Excellence in Agriculture Nanotechnology, TERI-Deakin Nanobiotechnology Center, Gurugram, Haryana, India

Asha Kumari Department of Chemistry, Career Point University, Hamirpur, Himachal Pradesh, India; Centre for Nano-Science & Technology, Career Point University, Hamirpur, Himachal Pradesh, India

Seema Kumari Department of Chemistry, Career Point University, Hamirpur, Himachal Pradesh, India; Centre for Nano-Science & Technology, Career Point University, Hamirpur, Himachal Pradesh, India

Shakthi Prakash M.R. Fibroheal Woundcare Private Limited, Bangalore, Karnataka, India

Eisha Malik Department of Zoology, Government College University Lahore, Lahore, Pakistan

Anitha Mamillapalli Department of Life Sciences, School of Science, GITAM (Deemed to be University), Visakhapatnam, Andhra Pradesh, India

Mulaka Maruthi Department of Biochemistry, School of Interdisciplinary & Applied Sciences, Central University of Haryana, Mahendergarh, Haryana, India

Sakshi Y. Mastoli Department of Pharmaceutics, National Institute of Pharmaceutical Education and Research, Lucknow, Uttar Pradesh, India

Vivek Mishra Fibroheal Woundcare Private Limited, Bangalore, Karnataka, India

Yugal Kishore Mohanta Nanobiotechnology and Translational Knowledge Laboratory, Department of Applied Biology, School of Biological Sciences, University of Science and Technology Meghalaya (USTM), Baridua, Meghalaya, India

Mandira Mondal Department of Textile and Fibre Engineering, Indian Institute of Technology Delhi, New Delhi, India

Ayesha Muzamil Department of Zoology, Government College University Lahore, Lahore, Pakistan

S.N. Naik School of Interdisciplinary Research (SIRe), Indian Institute of Technology Delhi, New Delhi, India; Centre for Rural Development and Technology, Indian Institute of Technology Delhi, New Delhi, India

Sopan Nangare Department of Pharmaceutics, Krishna Vishwa Vidyapeeth, Krishna Institute of Pharmacy, Karad, Maharashtra, India

Debasis Nayak Department of Wildlife and Biodiversity Conservation, Maharaja Sriram Chandra Bhanja Deo University, Baripada, Odisha, India

Tejas Nikam Department of Pharmaceutics, National Institute of Pharmaceutical Education and Research, Lucknow, Uttar Pradesh, India

Petra Nnamani Department of Pharmaceutics, University of Nigeria, Nsukka, Enugu State, Nigeria

Ismail Ocsoy Department of Analytical Chemistry, Faculty of Pharmacy, Erciyes University, Kayseri, Turkey

Kerim Emre Öksüz Sivas Cumhuriyet University, Faculty of Engineering, Department of Metallurgical and Materials Engineering, Sivas, Turkey; Institute of Science

and Technology, Department of Bioengineering, Sivas Cumhuriyet University, Sivas, Turkey

Jibanjyoti Panda Nanobiotechnology and Translational Knowledge Laboratory, Department of Applied Biology, School of Biological Sciences, University of Science and Technology Meghalaya (USTM), Baridua, Meghalaya, India; Department of Wildlife and Biodiversity Conservation, Maharaja Sriram Chandra Bhanja Deo University, Baripada, Odisha, India

Vikas Pandey Department of Pharmaceutics, Amity Institute of Pharmacy, Amity University Madhya Pradesh, Gwalior, Madhya Pradesh, India

Jidnyasa Pantwalawalkar Department of Pharmaceutics, Bharati Vidyapeeth College of Pharmacy, Kolhapur, Maharashtra, India

Vidyullatha Peddireddy Department of Nutrition Biology, School of Interdisciplinary & Applied Sciences, Central University of Haryana, Mahendergarh, Haryana, India

Bharti Rana Department of Textile and Fibre Engineering, Indian Institute of Technology Delhi, New Delhi, India

Haroon Rashid Department of Life Sciences, School of Science, GITAM (Deemed to be University), Visakhapatnam, Andhra Pradesh, India

Caroline Santinon State University of Campinas, School of Chemical Engineering, Campinas, Brazil

Shubhini A. Saraf Department of Pharmaceutics, National Institute of Pharmaceutical Education and Research, Lucknow, Uttar Pradesh, India

Rohit Saxena Center for Excellence in Agriculture Nanotechnology, TERI-Deakin Nanobiotechnology Center, Gurugram, Haryana, India

Kashama Sharma Department of Chemistry, Career Point University, Hamirpur, Himachal Pradesh, India; Centre for Nano-Science & Technology, Career Point University, Hamirpur, Himachal Pradesh, India

Rahul Sharma Department of Chemistry, Career Point University, Hamirpur, Himachal Pradesh, India; Centre for Nano-Science & Technology, Career Point University, Hamirpur, Himachal Pradesh, India

Meuris Gurgel Carlos da Silva State University of Campinas, School of Chemical Engineering, Campinas, Brazil

Thiago Lopes da Silva State University of Campinas, School of Chemical Engineering, Campinas, Brazil

Prince Kumar Sonu Department of Nutrition Biology, School of Interdisciplinary & Applied Sciences, Central University of Haryana, Mahendergarh, Haryana, India

Bhargavi Sreepathi Department of Pharmaceutics, National Institute of Pharmaceutical Education and Research, Lucknow, Uttar Pradesh, India

Hafiz Muhammad Tahir Department of Zoology, Government College University Lahore, Lahore, Pakistan

Bharat Tandon Fibroheal Woundcare Private Limited, Bangalore, Karnataka, India

Nimet Temur Department of Analytical Chemistry, Faculty of Pharmacy, Erciyes University, Kayseri, Turkey

Melissa Gurgel Adeodato Vieira State University of Campinas, School of Chemical Engineering, Campinas, Brazil

Wedja Timóteo Vieira State University of Campinas, School of Chemical Engineering, Campinas, Brazil

Thitima Wattanavijitkul Chulalongkorn University, Department of Pharmacy Practice, Faculty of Pharmaceutical Sciences and Center of Excellence in Bioactive Resources for Innovative Clinical Applications, Bangkok, Thailand

Cemile Yilmaz Department of Analytical Chemistry, Faculty of Pharmacy, Erciyes University, Kayseri, Turkey

Lei Zhang Department of Chemical Engineering, Waterloo Institute for Nanotechnology, University of Waterloo, Waterloo, ON, Canada

Xiaoning Zhang State Key Laboratory of Resource Insects, College of Sericulture, Textile and Biomass Sciences, Southwest University, Chongqing, China

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Biographies

Professor Sabu Thomas

Professor Sabu Thomas is the Director of Centre for Nanoscience and Nanotechnology, Mahatma Gandhi University, Kottayam, Kerala, India. He is also currently the Chairman of the Trivandrum Engineering Science and Technology Research Park (TrEST Research Park), Trivandrum, Kerala, India. He was the former Vice Chancellor (President) of Mahatma Gandhi University, Kottayam, Kerala, India. Prof. Thomas is a highly committed teacher and a remarkably active researcher well-known nationally and internationally for his outstanding contributions in polymer science and nanotechnology. He has published over 1600 research articles in international refereed journals and has also edited and written 250 books. His H-index is 149 and total citations are more than 100,000. He has supervised 130 PhD theses. He has received many international and national awards and recognitions. He received 3 *honoris causa* from European Universitas and Honoured Professorship from Siberian Federal University, Krasnoyarsk. He is a recipient of Russian Mega Grant with SFU. He is in the Stanford's list of best 2% top scientists in the world for four consecutive years. Under the leadership of Prof. Thomas, Mahatma Gandhi University has been transformed into a top University.

Ms. Sneha Sabu Mathew

Ms. Sneha Sabu Mathew is a PhD researcher in Technological University Dublin. Her research is primarily focused on the design and development of biosensors for smart food packaging using biomaterials with natural pigments. Sneha's scientific background includes expertise in various areas such as electrospinning, preparation of nanocomposite and polymer composite materials, valorization of agrowaste and sericulture wastes, extraction and characterization of silk sericin, production and characterization of nanocellulose, and film characterization using various polymers. Sneha earned her BS and MS in Chemistry from Mahatma Gandhi University in Kerala, India, and received a TU Dublin scholarship to pursue her PhD. She has published

research articles in scholarly publications, edited books, contributed to book chapters, and won several awards at various international conferences.

Dr. Hanna J. Maria

Dr. Hanna J. Maria is a Senior Researcher at the School of Energy Materials, Mahatma Gandhi University, working with Prof. Sabu Thomas. She completed her Ph.D. in 2015 and has held postdoctoral positions at Qatar University; Yamaguchi University, Japan; and the CNRS, France. Dr. Maria's research focuses on natural rubber composites, thermoplastic composites, bionanocomposites, and hybrid nanocomposites. She holds an M.Sc. in Analytical Chemistry and an M.Phil. in Environmental Chemistry. She has published 30 papers, co-edited 10 books, and has an H-index of 25. She was also a Visiting Professor at the University of Lorraine, France, in 2022.

Rangam Rajkhowa

Rangam Rajkhowa received his bachelor's degree in Textile Technology from Anna University, India; a master's degree in Fibre Science and Technology from Indian Institute of Technology Delhi; and a PhD in Engineering from Deakin University, Australia. He leads the silk and natural fiber particle stream of research at the Institute for Frontier Materials at Deakin University. His research interests are silk-based biomaterials, value addition and new applications from natural fibers and fiber wastes, sustainable fiber and textile processing, recycled and sustainable color, and circular economy. He set up the fiber powder research facility at Deakin University, and his group works on the fundamental understanding of fiber and particle structures, properties, and applications.

Preface

Silkworm sericin, a versatile protein derived from the silk cocoon, has captivated researchers and industry experts alike for its remarkable properties and potential applications. From its historical association with luxurious textiles to its modern-day relevance in biomedical, cosmetic, and environmental applications, sericin stands as a testament to the transformative power of science and technology. This book, *Science and Technology of Silkworm Sericin: Extractions, Modifications and Applications*, is a comprehensive exploration of the advances and innovations surrounding this fascinating biomaterial.

The significance of sericin extends beyond its role as a byproduct of silk production. It has emerged as a key material in diverse fields, owing to its biocompatibility, antioxidant activity, and potential for chemical modification. The journey of sericin from a discarded waste product to a highly sought-after functional material epitomizes the intersection of sustainability and scientific progress. This book aims to bridge the gap between fundamental science and practical applications by providing readers with a detailed understanding of sericin's properties, extraction methods, and modifications.

Divided into three parts, this book begins with the fundamentals of sericin, offering insights into its chemical structure, biological significance, and extraction techniques. Special emphasis is placed on green and sustainable extraction methods, which align with contemporary efforts to minimize environmental impact. The second section focuses on the modifications of sericin, showcasing how chemical and physical transformations enhance its properties for specific applications. Finally, the book delves into the wide-ranging applications of sericin, including its use in drug delivery systems, tissue engineering, wound healing, and cosmetic formulations.

The collaborative efforts of researchers, scientists, and industry professionals from around the world have made this book possible. It aims to serve as a valuable resource for academicians, students, industrial practitioners, and anyone intrigued by the potential of natural biomaterials. We hope that the insights shared within these pages inspire further research and innovation, fostering the development of sustainable and impactful technologies.

As we continue to uncover the untapped potential of sericin, this book seeks to ignite curiosity and provide a foundation for future explorations in this exciting field.

The Editors

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Sericin—An introductory outlook

1

Aamir Ali, Ayesha Muzamil and Hafiz Muhammad Tahir
Department of Zoology, Government College University Lahore, Lahore, Pakistan

1. Novelty

The current chapter gives a novel approach to sericin by highlighting its possible potential and transformative usage in different fields. It emphasizes recent developments in sustainable extraction techniques and also has various industrial and therapeutic applications. The biochemical properties of sericin including immunological response, photoprotective, and metabolic activities make it more suitable and environmentally friendly to use for pharmaceutical purposes. The diverse attributes and bioactive components of sericin are highlighted in this chapter positioning sericin as a vital biomaterial for future scientific and technological advancements.

2. Sericin: A natural polymer protein

Sericulture is a developing sector of agriculture that is largely concerned with producing textile products like silk threads from the filaments derived from cocoons of the domesticated *Bombyx mori* silkworm. Sericin and fibroin make up roughly 25% and 75% of the total cocoon weight, respectively, and are the two main protein components of these cocoons (Andadari et al., 2022). Silk sericin is synthesized in the labial glands or silk glands of *B. mori*. This sericin protein is critical for the cocoon's survival since it serves as a structural component and a cohesive agent for the cocoon's filaments. Furthermore, sericin works as a cover, therefore protecting the cocoons from UV light and other environmental factors. Sericin is extracted as a by-product during the silk degumming process, as it is removed from fibroin in the silk industry to make the fibers smoother, lighter, and stain-resistant (Vaishnav & Singh, 2023, pp. 199–208).

The process that is used to extract sericin can cause differences in the molecule's molecular weight, amino acid content, conformational shape, zeta potential, particle diameters, and the range of physicochemical features and biological activities. Processing temperature, method of extraction, pH, and the chemical agents used for extraction are all important elements that determine the concentration of sericin. There is a significant amount of disparity in the molecular weights that have been reported (ranging from 10 to 400 kDa) (Veiga et al., 2024). The sericin having a molecular weight of about 20 kDa is water soluble at higher temperatures. When sericin is degraded, a variety of peptides with different molecular weights are produced. These peptides can be put for a wide variety of purposes. Higher-molecular-weight sericin

Science and Technology of Silkworm Sericin. https://doi.org/10.1016/B978-0-443-21736-4.00001-5
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peptides have been investigated primarily for biomaterial fabrication, polymer composites, functional biomembrane construction, hydrogel development, and the design of functional fibers (Arango et al., 2021; Silva et al., 2022).

Ser1, *Ser2*, and *Ser3* are the genes that synthesize sericin. *Ser1* gene was discovered first, and it is confined to chromosome 11, locus *Src*, which contains a single copy of 23 kb and encodes four major mRNAs (10.5, 9.0, 4.0, and 2.8 kb) and nine axons by alternative splicing. Similarly, by alternative splicing, the *Ser2* gene also encodes two mRNAs (3.1 and 5.0−6.4 kb) and contains 13 exons that lie in the range of 28−2574 bp. The *ser2* gene is the most variable and complex gene that is used for the encoding of silk protein. Its genetic orientation and size are similar to that of the *Ser1* gene. *Ser3* gene is present on locus *Src-2* in chromosome 11. The size of this gene is almost 3.5 bp, which consists of three exons that encode a transcript of 4.5 (Vidyashree et al., 2024).

3. Forms/types/layers/sources of sericin

Sericin can be classified into sericin A, sericin B, and sericin C based on its solubility. It can also be designated as sericin I, II, and III. The sericin forms its layers from outer to inner sides to cover the fibroin in the order of I, II, and III. Based on the solubility and ease of dissolution in warm water, their ratios are 40:40:20. The level of solubility can be assessed by UV absorption. The outermost layer is sericin A, which is sparingly soluble in warm water. It consists of 17.2% nitrogen and various amino acids, that is, glycine, aspartic acid, serine, and threonine. Acid hydrolysis of the middle layer of sericin containing 16.8% nitrogen yields similar amino acid components as sericin A along with tryptophan. The deepest and innermost layer of sericin is sericin C, which is closely bound to fibroin and insoluble in warm water. It can be isolated from fibroin when treated with alkali or hot dilute acid. It gives the amino acids of sericin B in addition to proline. It has a lower proportion of nitrogen as compared to sericin A and sericin B, that is, 16.6% nitrogen, and also contains sulfur. Sericin B can be precipitated when 15g of ammonium sulfate is added to the filtrate, and sericin A is isolated by fractional distillation (Ghosh et al., 2017; Shitole et al., 2020).

Furthermore, sericin has two subunits known as alpha and beta sericin based on sericin position within the cocoon layer. Alpha sericin is present in the outermost layer and has a high solubility in warm water, while the inner beta layer shows less solubility as compared to the α-sericin (Barajas-Gamboa et al., 2016). The presence of a lesser quantity of hydrogen and carbon atoms while the greater quantity of oxygen and nitrogen atoms in beta sericin is the major difference between these subunits. The gamma rays can be used to study these three layers of sericin. The inner layer of sericin contains longitudinal filaments, the middle layer has filaments arranged in a crossfiber layer, and the outermost layer displays filaments in the same direction (Arango et al., 2021; Manjubala et al., 2020).

The color of cocoons from which sericin is obtained also classifies sericin into different categories. The white sericin has a very low viscosity. The yellow sericin

is of medium viscosity and is mostly used as a salad topping material, whereas, yellowish green sericin is a comparatively more viscous sericin product. Due to its antioxidative properties, it is mostly used in baking bread. This very high viscous sericin also comprises flavonol pigments (Ghosh et al., 2017).

4. Sericin extraction

Sericin is extracted from silk cocoons employing degumming of the fibroin filaments. Since the silk companies merely require the sericin component, it must be removed through a degumming process. Natural organic solvents, that is, citric acid and tartaric acid as well as neutral soap, urea, alkali, and proteolytic enzymes can all be used to extract sericin from fibroin. Sericin had various molecular weights, zeta potentials, particle sizes, amino acid contents, and antityrosinase activity depending on how it was extracted using different methods. The method of extraction can also alter the composition of amino acids and sericin's biological functions (Methods for Extracting Sericin and Its Use in Cosmetic Compositions, 2022). As a result, the selection of an appropriate sericin isolation method is vital to meet the specific application requirements and to align with the type of silkworm cocoons being used.

4.1 High-temperature- and high-pressure-based extraction

To avoid complex purification processes, autoclave-based extraction is used. In this method, the silkworm cocoons are dissolved in boiling water under extreme pressure. Heating is done without adding any chemicals, so temperature and time play a key role in sericin extraction. But this method is messy, produces fumes, consumes too much time, and may damage fibroin. Only the external layer of sericin is dissolved and the sericin protein retains its properties to an extent. This extraction method produces a low yield. After the extraction of sericin, it is refined to the powder form by lyophilization method. Different techniques like ethanol precipitation, spray drying, tray or freeze drying, and membrane filtration are used to separate sericin (Bascou et al., 2022).

Sericin is also extracted by urea or heat, which is a harsh extraction method. Due to the destruction of β-sheet structures, the heating treatment denatures its high-molecular-weight fraction (Bandyopadhyay et al., 2019; Liu et al., 2022; Seo et al., 2023). Furthermore, during the degumming process, sericin bioactivities become compromised because of the destruction of peptide sequences. The use of 2-mercaptoethanol with urea solution becomes advantageous for the extraction of sericin since it has a lower degrading impact on sericin, and the damage can be minimized. This method allows for the separation of approximately 95% sericin without causing any damage. However, this method is time-consuming and expensive as it requires purification using a dialysis membrane (Miguel & Álvarez-López, 2020).

4.2 Natural soap–based extraction

Boiling silkworm cocoons in such a solution which comprises Marseille soap and sodium carbonate to extract sericin from fibroin. Although this industrial process of degumming is the most significant and conventional method for isolating silk proteins (sericin and fibroin), it is limited because of challenges in sericin recycling and the higher cost of Marseille soap. For the entire extraction of sericin, an effective degumming technique including soap and alkali is preferred. This method is not commonly utilized because separating soap from the sericin is a complex procedure, and if small amounts of soap are present, administration of sericin becomes problematic (Hossain et al., 2023).

4.3 Infrared heating

An infrared dyeing (IR) machine is utilized to heat the cocoons of *B. mori* to increase sericin's dissolution. During the process of removing sericin from silkworm cocoons, electromagnetic waves transfer energy through water molecules, which act as abrasives. This enhances the shedding of sericin. This extraction method produces a high yield as well as excellent quality silk sericin. The high molecular weight fraction of sericin, which is being extracted by the sonication method at 37°C, has a higher content of beta sheet structures than the low molecular weight) fraction. Notably, sericin, which has a higher content of beta sheets, can boost the expression of bone morphogenic proteins in phagocytic cells by the activation of toll-like receptors. As a result, such high-molecular-weight sericin protein exhibits higher osteogenic activity (Bascou et al., 2022).

4.4 Chemical reagent–based extraction

Chemical reagents are used in conjunction with heat to improve the degumming efficiency of silkworm cocoons. These reagents include citric acid, tartaric acid, sodium hydroxide, and sodium carbonate, as well as various proteases like bromelain, papain, fungal protease, and pancreatin (Biswal et al., 2022). The most commonly used method for degumming silkworm cocoons in the laboratory is to boil them in a 0.02 M sodium carbonate solution (Wöltje et al., 2021). This method effectively removes sericin from both nonmulberry (*A. mylitta*) and mulberry (*B. mori*) silkworm cocoons. Extraction conditions such as cocoon-to-water ratio, chemical reagents, temperature, as well as time, determine the molecular weight or properties of the extracted sericin. An alkaline reagent and a higher temperature boost the sericin's yield. On the other hand, these factors can cause degradation and denaturation of sericin protein. Furthermore, sericin protein can be extracted from silkworm cocoons by using a 6 M lithium bromide (LiBr) solution at 35°C. The extracted silk sericin (SS) protein has a molecular weight of 250 kDa. This extraction approach provides higher sericin yield (>90%) and preserves the protein structures as well (Liu et al., 2022).

4.5 Extraction by alkylase

Alkylase or 2.5 g/L alkaline protease is used to extract sericin at 60°C for 90 min at pH 10. Sericin is extracted by trypsin hydrolysis at various temperatures, treatment durations, and concentrations. At 37 and 20°C, respectively, the hydrolysis for 1% trypsin solution is nearly complete in 10 and 34 h. By exposing sericin to a 1 or 8% trypsin solution for 4 h, 26.4 or 28.7% of sericin is produced, respectively. However, the application of this approach for extraction purposes is constrained by the large expanses involved and the enzyme's sensitivity to working conditions (Ahsan et al., 2018).

4.6 Acidic and alkali extraction method

The extraction of sericin can also be carried out using acids such as tartaric and citric acid among others. While applying acidic conditions, the temperature must be kept at boiling. Both alkalis and acids degrade proteins, and because sericin is a protein in nature, it might be destroyed during extraction. Acid, alkali, and hot water degradation of sericin result in various trypsin inhibitory activities (Biswal et al., 2022).

5. Composition

Sericin is a high-molecular-weight, amorphous, and globular protein that accounts for 25%−30% of the protein content of silk. It contains 90% protein in nature, whereas carbohydrates, oils, and wax salts of minerals, colors, and different impurities account for the remaining 10% (Costa et al., 2023). There is a large amount of polar amino acids (such as serine, lysine, and aspartic acid) present in sericin, making it water-soluble. The order of amino acids in a protein dictates its characteristics. The repeating amino acid sequence in sericin structure is [Gly-Ser-Val-Ser-Ser-Thr-Gly-Ser-Ser-Thr-Asp-Ser-Ser-Thr]n, where Gly is glycine, Ser is serine, Thr is threonine, Val is valine, and Asp is aspartic acid, respectively. These amino acids are important in binding and physiochemical change. Sericin is classified into three levels based on its water solubility: inner, middle, and exterior (Khalifa & Ladhari, 2021).

5.1 Amino acid composition

The macromolecular structure of sericin is comprised of 18 different amino acids (Fig. 1.1). The majority of these amino acids have polar side chains that contain carboxyl, hydroxyl, and amino groupings. The polar chemical moieties and structures are the source of its inborn biological properties. Sericin protein has a composition of 12.2% nonpolar amino acids, 45.8% polar amino acids, and 45.8% hydroxy amino acids. The greater predominance of hydroxyl-rich amino acids such as aspartic acid (18%), serine (32%), and glycine (16%) in sericin is important (Bascou et al., 2022; Bhat et al., 2024; Hu et al., 2023). Sericin comprises almost 70% hydrophilic amino acids; therefore, it has the potential to partially dissolve in water and absorb huge

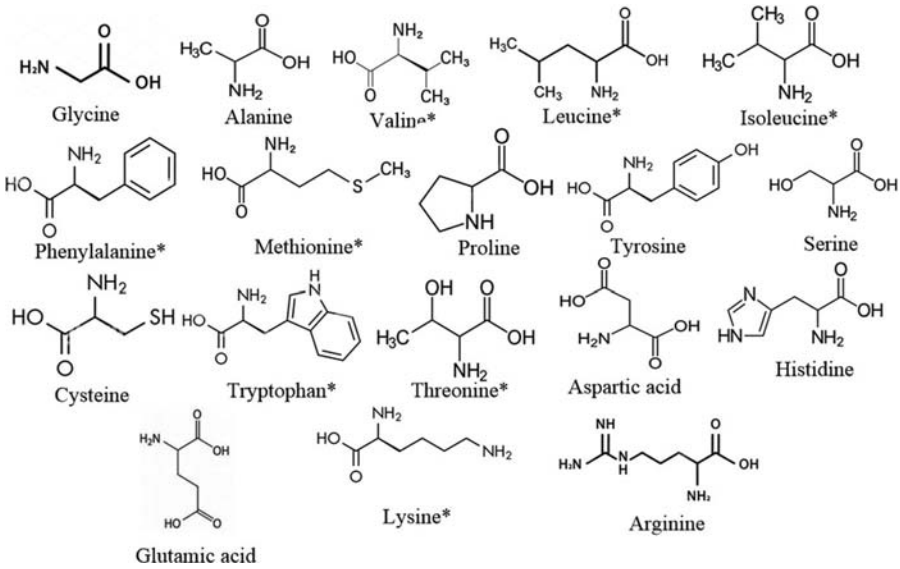


Figure 1.1 The amino acid composition of sericin.

quantities of water. The protein's isoelectric point, which is very near to 4, reflects the fact that it has a greater number of acidic groups in comparison to basic amino acids (Li et al., 2023; Wattanavijitkul et al., 2024, pp. 653−688).

The amino acid content of sericin has always been the same, but the extraction methods have a slight influence on the proportion of amino acids. Serine is the most abundant amino acid in sericin; aspartic acid and glycine are the next most abundant amino acids (Seo et al., 2023). Because of its strong polar hydroxyl groups, serine plays a crucial role in shaping sericin's operational and physiochemical features. Sericin functioning is additionally influenced by aspartic acid and glycine (Saad et al., 2023). In addition, sericin comprises two aromatic amino acids, which are tyrosine and phenylalanine, that contribute to the natural fluorescence of the protein. Sericin also includes hydrophilic protein molecules (approximately 70%), which contribute to its high solubility (Saha et al., 2023). Moreover, aromatic acids, such as phenylalanine (6.6%), are present in significantly lower concentrations. During the extraction of sericin, raising the amount of ethanol causes a rise of amino acids such as serine, threonine, and aspartic acid and a reduction of amino acids such as alanine, leucine, isoleucine, glutamic acid, phenylalanine, and histidine (Seo et al., 2023).

Serine and threonine levels can alter sericin's antioxidant effects, and these hydroxyl amino acids work as a kind of chelating agent for trace metals like copper and iron (Fatahian et al., 2022). In the extraction process, an excessive amount of ethanol raises the number of hydrophilic proteins while reducing the content of hydrophobic proteins in the collected sericin. The methionine nature of sericin is greater when obtained through the thermal treatment method (Silva et al., 2022). Similarly, the amount of

tyrosine component in sericin was much reduced when extracted using the urea extraction method compared to other methods. Sericin extracted with hot water includes the maximum concentration of sulfur-containing amino acids, such as methionine and cysteine, which aid in the creation of double-helical structures. These amino acids are closely related to collagen formation (Seo et al., 2023).

6. Structure

Sericin's functional characteristics are influenced by its structure and molecular weight (Fig. 1.2). Furthermore, the chemical structure and molecular weight of sericin are primarily determined by the method of sericin and fibroin isolation and the process of extracting sericin from degumming fluid. The spherical, amorphous, partially unfolded sericin structure is notable. Sericin is made up of random coils and beta-sheet structures, forming both the amorphous and crystalline portions. Sericin is partially unfolded, with 35% beta-sheet, 63% random coil, and has no alpha helix content. The secondary structure of sericin varies by isolation method (Das, 2022). Sericin I on the cocoon thread is amorphous, while II and III are fragile crystals with poor mechanical strength. Due to the presence of random coils, sericin exhibits amorphous properties when in a dry state. It is possible to improve the mechanical strength of sericin by mixing it with other polymers and then crosslinking and copolymerizing the resulting mixture resulting in a stronger biomaterial (Yang et al., 2023).

High temperatures, in general, trigger the breakdown of beta sheets. Due to decreased coupling and reduced hydrogen bonding between both of the silk proteins, sericin and fibroin, sericin extracted with hot water has less β-sheet structure. The sericin that is most closely bound to fibroin exhibits a higher percentage of the β-sheet structure as compared to other groups of sericin due to its insolubility in warm water (Kumar Dan et al., 2022). Water infiltration into the silk cocoon is made easier by the process of extraction with Na_2CO_3, which also adds to the denaturation of the secondary protein β-sheet structure (Sabarees et al., 2023). Furthermore, ethanol-induced dehydration causes the sericin protein to change from random coils to β-sheets. The temperature of the casting process affects sericin's structure as well. The sericin molecules adopt a β-sheet form rather than a random coil when the casting temperature is lowered (Vidyashree et al., 2024).

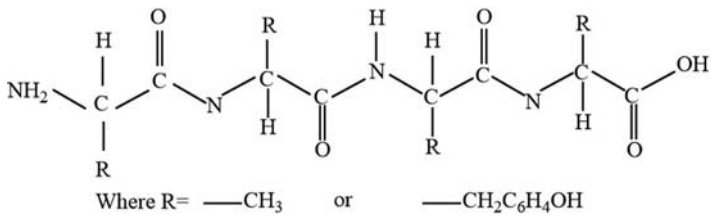


Figure 1.2 The primary structure of silk sericin protein.

The surface appearance of dried sericin powder is observed to be wrinkled, which could be owing to the collapse of hollow spherical structures being abruptly evaporated. When exposed to air, sericin agglomerates due to its hydrophilic nature.

6.1 UV and FTIR

The most useful for determining protein structure is the utilization of the C═O stretching vibration. The highest value at 1540 cm^{-1} was generated by the sericin's random coil structure and belongs to amide II (Rodin & Belton, 2022). The signature peak of sericin at 1400 cm^{-1} can be seen in all samples. A prominent negative band at 198 nm in the Circular Dichroism spectra of the sericin powder sample suggests a random coil configuration. The existence of the sheet is revealed by a small negative band at 218 nm (Kalita et al., 2024; Kanoujia et al., 2023).

An FTIR spectrometer was used to record the FTIR spectra of sericin. The protein molecules may exhibit distinctive peak shapes, which correspond to extending of the C═O group of amide I at 1700 cm^{-1} to 1600 cm^{-1}, stretching of the N−H group of amide II at 1540 cm^{-1} to 1520 cm^{-1}, and extension of the C−N group of amide III at 1270 cm^{-1} to 1230 cm^{-1}(Noosak et al., 2022).

6.2 Molecular weight

Proteins of different molecular properties combine to form sericin. These molecular sizes can range from 10 to 400 kDa (Jo et al., 2020). The difference in molecular size is because of different processing times, extraction methods, pH, and temperature. Sericin with low molecular weight is easily soluble in cold water and can be restored from the early stages of raw silk production, while serine containing higher molecular weight is soluble in hot water and can be obtained from the later stages (Bascou et al., 2022). If the sericin is extracted from an acidic solution, its molecular weight is in the range of 35−150 kDa. On the other hand, an alkaline solution degrades sericin into sericin peptides and thus gives molecular weight in the range of 15−75 kDa (Bai & Hsueh, 2015). Various extraction techniques for sericin can even provide various amino acid compositions. When the serine extracted by alkaline, acidic solution, and heat is analyzed by using sodium dodecyl sulfate-polyacrylamide gel electrophoresis, it shows diverse and broad bands. However, to get diverse bands of serine in the range of 10 to >225 kDa, it is usually treated with urea (Jo et al., 2020).

7. Physical properties of sericin

7.1 Solubility and viscosity

Small sericin proteins with molecular weights of 5−60 kDa dissolve in cold water. The large sericin peptides having molecular weights of 60−300 kDa are soluble in hot water but difficult to dissolve in cold water (Wu et al., 2014). The solubility of sericin is likewise related to its amorphous and crystalline states. The amorphous region is made

up of randomly shaped coils, which is the predominant molecular structure of freely soluble sericin. The crystal area, known as the β-sheet, is more difficult to dissolve. The α-sericin dissolves more easily in boiling water than β-sericin (Shitole et al., 2020). The viscosity of sericin varies slightly, from 1.771 cP to 1.091 cP depending on the degumming process.

7.2 Gelling property

The gelation of sericin happens rapidly at lower temperatures (10°C) with a pH of around 6−7. Hot water can dissolve the random coil patterns, while the low temperature affects the sericin structure by converting the random coil into beta-sheets, which enhances the sericin gel formation capabilities. Sericin gel strength improves as the surface tension is lowered, so the gelation duration decreases with the addition of high quantities of poloxamer gel. This is due to the hydrophilic components of the later gel absorbing the water that surrounds sericin. Sericin exhibits a sol-gel transition ability when heated to 50−60°C in water, and it can gel again when cooled (Shitole et al., 2020).

7.3 Isoelectric pH/point

Isoelectric pH is a point at which the electrical charge of a molecule becomes zero. Isoelectric pH also refers to the concentration of hydrogen or any other ions at which this condition can be detected. As a result, it has become common practice to describe the isoelectric point in the context of the pH scale. Sericin has 4.3 isoelectric pH due to less amount of basic amino acids than acidic amino acids (Razikova et al., 2023).

7.4 Crosslinking and stability

Crosslinking creates bonds between sericin molecules and makes them more resistant to solvents, heat, and mechanical stress. Different crosslinking agents, such as phytic acid, glutaraldehyde, dimethyl urea, or epoxy resin, can be used to modify the properties of sericin and improve the color fastness and durability of silk fabrics. Sericin provides stability through its high affinity for the medicinal substance due to its high biocompatibility and biodegradability. Sericin has been examined for a wide range of pharmaceutical uses such as drug carrier, solubility enhancement, formulation stabilization, and release modifications (Shitole et al., 2020).

8. Biochemical properties of sericin

8.1 Biocompatibility and immunological response

Biocompatibility is the most noticeable feature for biomedical applications of any material. (Cacopardo, 2022) recommended that when sericin-based biomaterials interacts with any person, they do not cause any detrimental effects (immunological reactions).

Initially, it was considered that sericin causes adverse effects such as immunogenicity, allergenicity, and inflammation in silk applications (Liu et al., 2022). Sericin's biomedical applications have been hindered for decades due to concerns about its biosafety. Presently, there is a great deal of evidence indicating that sericin does not elicit a substantial immune response on its own (Aramwit, 2014; Panilaitis et al., 2003). Furthermore, the number of cell lines culture media having sericin as the primary medium that does not cause any cytotoxicity showed sericin is safe and pure to use (Vidyashree et al., 2024). In vitro testing with mouse fibroblasts showed that sericin extracted with urea was mildly harmful at concentrations as low as 60 g/mL and highly toxic at concentrations higher than 100 g/mL (Aramwit et al., 2010). When sericin was extracted using other methods acid, alkaline, or heat, it yielded less toxicity as determined by the proportion of alive fibroblasts. The antioxidant activity of sericin might also be due to its polyphenol and flavonoid contents (Lee et al., 2024).

The sericin-based films/membranes caused a minor increase in the levels of tumor necrosis factor-σ and interleukin-1β in murine macrophages in vitro, which was similar to that caused by polystyrene plates. The inflammatory response showed a significant reduction in the TNF-α and IL-10 when sericin-based cream was applied to the wound-induced in rats (Aramwit et al., 2009). The sericin-derived hydrogel was injected into albino mice to examine inflammatory responses. There was no increase in the number of neutrophils or macrophages in the tissue of the hydrogel deposited site when it contrasted with the fibroin and alginate hydrogel. As compared to fibrinogen, silk sericin did not significantly enhance the levels of antibodies such as IgG and IgE. All of the above findings exhibit that the most efficient biocompatible protein is the sericin protein for various applications (Liu et al., 2022; Song et al., 2016).

8.2 Biodegradability

Sericin is an organic and biodegradable polymer that is degraded in vitro and in vivo by proteolytic enzymes (e.g., proteinase K, protease XIV, collagenase, chymotrypsin, and matrix metalloproteinase) that act at the amorphous hydrophilic portions of both light and heavy chains of silk (Holland et al., 2019). The amino acids are the products of sericin breakdown that get absorbed without provoking an immunological response in the body (Behera et al., 2023). A clear benefit is evident when biodegradable biomaterials are utilized to treat wounds. The use of a biodegradable wound film/dressing eliminates the need to replace or remove it from the wound site, decreasing discomfort and pain for the patient as well as damage to newly developed tissue.

It has been reported that to evaluate the breakdown profile of sericin, the protease XIV enzyme has been used as a reference enzyme (Guo et al., 2020). However, it is important to take into account that the enzymatic degradation rate is affected by various factors including structural and morphological properties of sericin structures (sponge, film, hydrogels, fibers, etc.) biological environmental attributes at the placement site, processing state, and the availability of chemical and mechanical stresses.

8.3 Antioxidant potentials

Reactive oxygen species (ROS) are produced during regular cell metabolism but can be harmful when a large concentration is present. ROS and free radicals are weak, unstable, and react easily with other substances in the body, causing damage to the cell or tissue, which leads to a variety of disorders (ischemia, cancer, reperfusion, cirrhosis, etc.). Sericin is widely recognized for its strong antioxidant properties. Sericin's antioxidant capabilities are due to its ROS scavenging activity, antityrosinase, and antielastase activities, as well as due to suppression of lipid peroxidation. Sericin's antioxidant potentials are linked to its high content of amino acids (serine and threonine), which contain hydroxyl groups that function as chelators for trace metals like iron and copper. The antioxidant enzymes that is, superoxide dismutase, catalase, and glutathione peroxidase may be activated by sericin. Furthermore, the pigmented molecules such as carotenoids and flavonoids collected in the sericin layers could be one of the reasons for sericin's antityrosinase and antioxidant activity. The sericin extracted from cocoons with pigments demonstrates stronger antityrosinase activity than the sericin extracted from cocoons without pigments (Miguel & Álvarez-López, 2020).

8.4 Metabolic activities

Sericin's capacity to reduce lactate production facilitated a marked increase in innate immune response, as it triggered the expression of interferon via the RIG-I-MAVS pathway, which resulted in exceptional activities of anti-RNA in vitro. Therefore, sericin may have potential value in treating metabolic diseases. Sericin has been shown to regulate glycolipid metabolism when used as a dietary additive (Liu et al., 2022). The oral administration of sericin to the type 2 diabetic animal raised liver glycogen levels and factors linked to the insulin signaling pathway while reducing blood glucose levels. It suggests that sericin has the potential to control glucose metabolism through the insulin phosphatidylinositol-3-kinase or protein kinase-B (PI3K/AKT) signaling pathway and can control lipid metabolism in animals that are obese (Kunz et al., 2016). Sericin and its derivatives (such as the F5-SP) sequence of peptides are potential inhibitors of σ-glucosidase that can effectively block cellular glycolysis (Song et al., 2018).

8.5 Photoprotective activity

Sericin also possesses a photoprotective function because it can absorb UV radiation and prevent oxidative damage by retaining redox balance (Parashar et al., 2020). The topical application of sericin shielded female hairless mice from ultraviolet radiations that cause sunburn and tumor induction. Sericin has a variety of amino-based groups enriched in oxygen, hydrogen, and nitrogen allowing for high absorption of UV radiation wavelengths less than 200 nm (Gore et al., 2019).

8.6 Maintenance of cell growth ability

Sericin has the potential to stimulate the growth of cells and maintain cell function across a range of cell types such as tumor cells, insect cells, and mammalian cells. Sericin can serve as a nutrient and replace fetal bovine serum or bovine serum albumin to support cell culture (Cao & Zhang, 2017). Cell adhesion can be supported by sericin. Sericin has been found to have multiple benefits for cell culture, making it an attractive option for tissue engineering. As a result, the biomaterials that are based on sericin are extensively researched and applied in various areas of tissue engineering, including corneal epithelial repair nerve injury repair, bone tissue engineering, skin injury, and adipose tissue engineering (Khosropanah et al., 2022).

9. Sericin is a valuable industrial waste

Sericin has long been ignored in the sericulture industry. The dried cocoons of 400,000 metric tons and 50,000 metric tons of sericin were produced worldwide. The widespread sericin wastewater discharge causes water contamination and an increase in chemical and biological oxygen needs (Ji et al., 2022). The extraction and use of sericin could have major economic, social, and environmental benefits, requiring reevaluation. The scientific research on sericin has been steadily increasing since the last decade (Fig. 1.3). Collecting silk sericin from degumming garbage or cocoons reduces environmental contamination (Fatahian et al., 2021). Complex interactions between amino acid chains, organic content, solubility, and structural arrangement allow sericin to crosslink, co-polymerize, and amalgamate with other polymers. These qualities combine to give sericin its antioxidant, moisturizing, healing, antibacterial, antimicrobial, UV radiation blocking, and anticancer properties. Sericin's environmental, social, and economic benefits as a high-value enhancing material can only be exploited

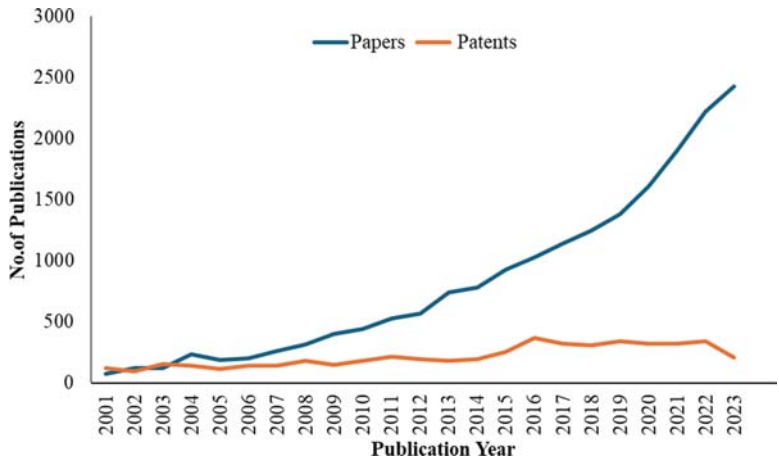


Figure 1.3 The number of publications and patents related to sericin in the last 23 years.

by its extensive use in food, cosmetics, biomedical, and pharmaceutical industries (Seo et al., 2023).

9.1 Industrial applications

Sericin is proving to be an extremely useful biomaterial, thanks to the fact that it can be broken down naturally. It has the potential to be used as a polymer in the manufacturing of functional membranes and other products. By combining sericin with other components, it is feasible to make polymers that are both biodegradable and kind to the environment.

9.2 Antifrosting agent

The naturally occurring antifrosting characteristics of sericin can be beneficial when applied to surface coatings. Antifrosting treatments using sericin-coated films have shown to be successful in a variety of settings, including refrigerators, deep freezers, refrigerated trucks, and ships with onboard refrigeration. In addition, films with sericin added to them that are placed on roads and roofs can be used as a preventative measure against issues that are caused by frost. Notably, studies have demonstrated that improving the functional efficiency of numerous long-lasting materials by treating them with sericin increases their durability (Wankhade, 2020).

9.3 Cosmetics

Sericin and silk fibroin have been extensively utilized as constituents in many skin, hair, and nail care products (El-Sayed et al., 2021). The incorporation of sericin into topical lotions and ointments has demonstrated potential as an effective agent for combating the signs of aging and wrinkles. The incorporation of sericin into cosmetic compositions, such as creams and shampoos, yields a diverse array of advantageous outcomes, encompassing antiaging properties, enhanced skin and nail elasticity, and hydration, as well as safeguarding against chapping and brittleness (Giovannelli et al., 2021). Previous studies have demonstrated that the utilization of gels containing sericin can lead to an elevation in hydroxyproline levels within the stratum corneum, alongside a reduction in skin impedance. These findings provide evidence for the emollient qualities of sericin.

Research has demonstrated that the utilization of sericin at dosages ranging from 0.02% to 2% in hair and bath formulations can effectively diminish hair surface damage (Jogur et al., 2020, pp. 359–395). The use of sericin gels on unblemished skin leads to an augmentation in the inherent moisture of the skin. This effect is achieved by a reduction in skin impedance, an elevation in hydroxyproline levels, and the hydration of epidermal cells. A major portion of sericin is comprised of amino acids with hydrophilic side groups, which are accountable for the observed effects. It is worth mentioning that the exceptional water-absorbing capability of sericin can be attributed, at least in part, to its elevated serine content, which ranges from 30% to 33% (Sarangi et al., 2023). Sericin can form a thin and uniform layer on the surface

of the skin, serving as a protective barrier that prevents excessive water loss (Dash et al., 2023).

9.4 Textile industry

Sericin is an advantageous compound utilized for the surface modification of fibers and fabrics within the textile industry. Cellulose fibers and wool are commonly subjected to coatings, which yield advantageous outcomes across various domains. The use of sericin coating on fabrics has been demonstrated to result in reduced concentrations of free formaldehyde, hence enhancing their safety profile (Ali et al., 2022, pp. 187−220). The likelihood of experiencing skin irritation or allergic reactions upon contact with these materials is reduced, and they also exhibit greater electrical resistance. Furthermore, the application of sericin treatment to textiles results in a marginal reduction in their tensile strength. Additionally, the treated textiles exhibit discernible antibacterial qualities.

Moreover, the use of sericin has been found to mitigate the hydrophobic nature of polyester fibers, hence enhancing their capacity to absorb ultraviolet (UV) radiation. The integration of sericin with other materials in a strategic manner enables the production of nanofibers with antibacterial properties, which can be effectively utilized in the context of wound dressings. Sericin-coated fibers have undergone testing for their suitability in several applications, such as diapers, diaper liners, and medical textiles employed in wound dressings (Saha & Mondal, 2021). Atopic dermatitis, pressure ulcers, and rashes represent a limited selection of skin conditions that get advantages from the administration of this treatment, hence emphasizing its importance in facilitating the process of healing and alleviating abrasive skin lesions in individuals.

10. Biomedical/therapeutic applications

10.1 Anti-inflammatory potential

During inflammation, necrotic tissues and potential contaminants are phagocytosed. At this stage, cytokines and growth factors secreted by inflammatory cells recruit the cells involved in the formation of new tissue. However, this phase needs to be controlled since the unchecked, exuberant production of inflammatory cytokines encourages the expression of metalloproteinase, which further can degrade the extracellular matrix. To reduce skin inflammation and allergic reactions, sericin influences the synthesis of certain anti-inflammatory cytokines (Seyedaghamiri et al., 2021). It starts the healing process by inhibiting the enzyme's activity, that is, COX-2 and iNOS. Significant inflammatory mediators are IL-1 and TNF-α. Additionally, they trigger or stimulate adhesion molecules, which are essential for the proliferative phase. (Arango et al., 2021) described that the adhesion molecules are activated by sericin, which is essential for the proliferative phase. Sericin regulates the release of the inflammatory cytokines (IL-1β and TNF-α) have previously been demonstrated by in vitro and in vivo assays (Behera et al., 2023; Rahimpour et al., 2023).

10.2 Antitumor potential

Sericin exhibits significant anticancer properties. The administration of sericin through oral means demonstrates a capacity to diminish colon malignancies in a dose-dependent manner by suppressing the formation of aberrant crypt foci in the colon. The inclusion of sericin in one's dietary intake has the potential to concurrently mitigate constipation, prevent colon cancer, and enhance mineral absorption (Ahsan et al., 2021). Sericin possesses robust antiproliferative characteristics and is capable of inducing cell cycle arrest (Adamiak et al., 2024).

10.3 Wound-healing activity

The exceptional wound-healing properties of sericin can be attributed to its strong affinity for keratin, a structural protein present in both skin and hair, as well as its notable adhesive capabilities. The utilization of silk threads derived from silkworms in the production of surgical sutures represents a noteworthy medicinal application (Schäfer et al., 2023). The utilization of silk sericin membranes as bandage materials has garnered significant attention due to its notable attributes of exceptional flexibility and outstanding tensile strength (Bakadia et al., 2022).

The capacity of silk protein films to enhance the proliferation of epithelial cells plays a pivotal role in their efficacy to expedite the wound healing process. The utilization of silk films as wound remedies has been associated with enhanced collagen regeneration, reduced inflammation, and diminished lymphocyte infiltration within the wound site (El-Ashram et al., 2021). The regeneration capacity appears to arise from the stimulation of basic fibroblast growth factor (BFGF) synthesis, subsequently triggering the activation of several cells essential for the wound healing mechanism, including fibroblasts and myofibroblasts (Lu et al., 2022). Furthermore, the utilization of silk protein films as biomaterials for wound healing is supported by their notable attributes of great biocompatibility and resistance to infections.

10.4 Antityrosinase potential

Tyrosine as an enzyme substrate can increase oxidative activity. Sericin has antityrosinase properties and inhibits polyphenol oxidase. Accumulated carotenoids and flavonoids in sericin layers are responsible for providing sericin with antityrosinase activity (Liu et al., 2022). Various methods for extraction of sericin are known to play a role in the effective antityrosinase capability of sericin. However, its antityrosinase activity is found to be highest when it is extracted with urea (Aramwit et al., 2020). The possible reason for the high antityrosinase activity of sericin, when it is extracted with urea, is that arginine and valine bound to tyrosinase enzyme in maximum amounts are extracted during this process. Moreover, the antityrosinase activities of sericin biopeptides are due to much serine, threonine, and asparagine residues working as chelators to provide the strongest inhibitory effects (Miguel & Álvarez-López, 2020).

10.5 Antiaging potential

Sericin enhances the synthesis of collagen type I and inhibits apoptosis. It surpasses vitamin C, in terms of antiaging properties, by minimizing oxidative stress. It suppresses tyrosinase activity and the generation of intracellular hydrogen peroxide and regulates nitrite, which produces oxidative stress (Guo et al., 2020; Luo et al., 2023). Along with the antiaging properties of silk sericin peptide fractions, the pluronic and polyacrylic acid found in gels prepared using silk sericin can prevent transepidermal water loss from the skin because skin impedance is reduced and hydroxyproline content in skin and hydration of epidermal cells are enhanced (Seo et al., 2023). Thus, silk sericin could be exploited in cosmeceuticals (lotions, creams, and ointments) due to its antiaging characteristics (Grześkowiak & Lochynska, 2022). It can also be used to treat skin disorders like dermatitis.

10.6 Antiobesity potential

The sericin protein is found to be beneficial for combating obesity and hyperlipidemia because it can reduce weight gain and fat contents, enhance the expression of enzymes involved in β-oxidation with an associated reduction of lipogenic enzymes and triglycerides in the liver, and increase glucose tolerance (Wang et al., 2023). Less digestibility of sericin causes the improvement in plasma lipid profile and increase of triglyceride and cholesterol (Biganeh et al., 2022). It can act as a dietary fiber and can increase the excretion of fecal lipids and reduce their plasmatic concentration (Matran et al., 2023). Sericin can lower cholesterol levels may be due to its high serine content with low methionine levels.

10.7 Drug delivery

For drug delivery (either local or systemic) the scaffolds, hydrogels, films, fibers, spheres, foams, capsules, and microneedles can be used (Florczak et al., 2021). Due to the amphiphilic character of sericin, it is used as a vehicle as it possesses a high affinity for charged therapeutic molecules or hydrophilic and hydrophobic drugs. Sericin is applicable for drug delivery, as it has a long half-life in vivo and high moisture absorption and desorption abilities. Many drug carriers (i.e., microparticles and nanoparticles) can be produced by using sericin because of its chemical reactivity that facilitates the easy interaction of molecules. Hydrogels are sericin-based structures, which can be used for drug delivery purposes (Jo et al., 2020). These are prepared through crosslinking, ethanol precipitation, or mixing with other polymers. A crosslinked sericin injectable hydrogel with efficient drug loading capacity and regulated release of small molecular and macromolecular medicines can be prepared (Jacob et al., 2021).

10.8 Tissue engineering

Mostly, sericin has been investigated for bone, skin, adipose tissues, and cartilage regeneration. Sericin can be used individually for regenerating bone. Osteoblast cells (MC3T3-E1) may proliferate faster as a result (Noosak et al., 2022). Its combination with other biomaterials is essential to produce scaffolds with suitable mechanical properties for bone regeneration since it has poor mechanical characteristics. Sericin in combination with calcium phosphate-based materials or hydroxyapatite (commonly used as a blend of biomaterials) is used to produce scaffolds because these biomaterials can simulate the inorganic and organic bone matrixes, respectively (Silva et al., 2022). Sericin is used as an injectable hydrogel for cardiac tissue regeneration. It minimizes the infarct size and scar formation, promotes neovascularization and the wall's thickness, suppresses the generated inflammatory responses, and prevents apoptosis when it is administered into an acute myocardial infarction area; these effects together lead to significant functional improvement. Additionally, sericin exhibits angiogenic activity by promoting human umbilical artery endothelial cells' migration and tubular development (Zhao et al., 2023).

10.9 Supplement in culture media

Sericin can be used individually as well as in conjugation with bovine serum albumin (BSA) in the culture media of mammalian cell lines like human embryonal kidney 293 cells, human hepatoblastoma HepG2, murine hybridomas 2E3-0, and human epithelial HeLa cells. The sericin stimulated the cell's viability, which became more prominent when it was used in combination with BSA. Sericin with molecular weights ranging between 6 and more than 67 kDa can be used to increase cell proliferation. Positive results were shown at lower concentrations from 0.01% to 0.1%, while higher concentrations (1%) were potentially hazardous. Furthermore, autoclaving did not alter the sericin's action, so, it can be used as a supplement in culture media to enhance cell proliferation (Sharma et al., 2022).

11. Health and safety considerations

11.1 Toxicity and allergenicity

The nontoxic effect of sericin makes it possible to use it in drug delivery, the food industry, cosmetics, and other textile industries. (Smith & Lee, 2022; Wang et al., 2021) supported that sericin had no side effects. It had no momentous toxic effects in both in vivo models and in vitro media. They supported that high concentrations of sericin may cause insignificant mild irritation, but there are no serious lethal effects for long-term use. Sericin protein has a very low potential of allergenic, but with the combination of any other protein, they may cause allergic reactions in people having sensitive skin. A study has reported that sericin allergenicity in cosmetics formulations causes a minute prevalence of allergic reactions among consumers. (Green & Choi, 2023; Patel

& Gupta, 2023; Zhao, 2021, pp. 145−152) proposed that sericin testing should be done before its proper use as it may cause mild sensitization in people.

11.2 Regulatory frameworks

The sericin-based food additives and cosmetics safety is supervised by the U.S. Food and Drug Administration (FDA), while the safety of the workplace from chemical exposure is regulated by Occupational Safety and Health Administration (OSHA). European Chemicals Agency (ECHA) controls the Regulation for Sericin Usage in Consumer Products and ensures that sericin usage meets safety standards for their consumers. FDA (US) also evaluated that sericin usage is safe in food and cosmetics industries and recognized it as Generally Recognized as Safe (GRAS). Various patents have also been filed against the formulation, extraction, and usage of sericin and its several products (Sericin-Based Wound Healing Formulations, 2021).

11.3 Safety assessments and studies

Johnson and Davis (2021) and Liao and Chen (2022) reported that sericin has no adverse effects when it is used as a topical ointment, and it has a nontoxic effect when it is inspected orally at recommended doses (Kumar & Zhang, 2024). It also exhibits protected effects when it is used as an antiaging product and helps to reduce oxidative stress. (Zhang & Lin, 2024; Kim & Roberts, 2022) also demonstrated that sericin promotes wound healing effect having no cytotoxicity and enhances cell sustainability.

12. Challenges and future directions

12.1 Life cycle assessment

The ecological impact of silk sericin production and utilization is assessed by life cycle assessment (LCA). The main challenges of sericin LCA comprise the limited data availability and quality production process of sericin. The absence of standardized methodologies for LCA in silk sericin extraction makes it problematic for cross-study comparisons. After describing the system boundaries, having all relevant factors and processes can also make it challenging (Choudhary & Kumar, 2022; Li & Chen, 2021).

12.2 Technical challenges in sericin utilization

Silk sericin yield from waste to wealth can be enhanced and made profitable by improving its extraction techniques. The functionalization, purity, and compatibility of sericin should be achieved to increase its usage in drug delivery, cosmetics, textile, and food industries. The economical and scalability of sericin extraction make it more valuable to meet its industrial demand (Aramwit, 2021; Kundu et al., 2021).

12.3 Economic and market considerations

The expensive purification technique of silk sericin makes less viable of its commercial demand. The market demand must be understandable in various industries. In healthcare sectors, the regulatory framework should be addressed to get approval for sericin-derived products. Silk sericin must compete with other synthetic and profitable polymers that may have reputable market demand (Park & Kim, 2022; Sharma & Kundu, 2023).

13. Conclusion

The recovery of sericin from waste to wealth is significant for societal, economic, and environmental welfare. Sericin's distinctive properties make it valuable for its pharmacological and biomedical applications. Their unique characteristics help produce biocompatible and biodegradable products. Despite the diverse applications and beneficial properties of sericin, it also possesses certain drawbacks that impede its utilization in biomedicine. The extraction method is crucial for improved biological performance and consistent physiochemical profile. It should be scalable and sustainable for industrial adoption, potentially improving the economic competitiveness of the silk industry. Moreover, due to its rheological characteristics and poor mechanical properties, it is not suitable for drug delivery or tissue engineering. The sericin-based scaffold is often produced with desirable attributes when it incorporates other compounds. Innovative extraction techniques and ongoing research are set to uncheck the full potential of sericin, supporting its ongoing progress and integration into therapeutic solutions and emerging technologies.

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Different extraction routes for degumming

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Jovita Kanoujia and Vikas Pandey
Department of Pharmaceutics, Amity Institute of Pharmacy, Amity University Madhya Pradesh, Gwalior, Madhya Pradesh, India

1. Introduction

Natural polymers known as silk proteins have been extensively investigated for their potential in creating nanomaterials and for various biomedical uses. Specifically, sericin and fibroin, two types of silk proteins, have found applications in drug delivery and biomedical fields due to their exceptional mechanical and physicochemical traits. These traits encompass biocompatibility, gradual biodegradation, and self-assembly capabilities. Notably uncommon among natural polymers, silk proteins possess an exceptional amalgamation of properties. Furthermore, they exhibit favorable attributes such as mild aqueous conditions, heightened biocompatibility and biodegradability, and the capacity to improve the stability of enclosed active pharmaceutical ingredients (APIs), including proteins, pDNA, and small-molecule drugs (Tomeh et al., 2019).

Silk primarily comprises fibroin and sericin, accompanied by minute quantities of waxy compounds, mineral salts, and pigments, constituting its principal elements. These two components, both protein-based, contribute to around 75% and 25% of the overall weight of silk, with fibroin and sericin, respectively (Gupta et al., 2014). Sericin, possessing a predominantly amorphous nature and enhanced water solubility, functions as a binding agent within the cocoon, preserving its structural integrity. The sericin substance encompasses both random coil and β-sheet configurations. The random coil conformation shifts to a β-sheet structure as temperature declines, ultimately forming a gel. When immersed in hot water, the random coil shape dissolves. Demonstrating remarkable gelation capabilities, sericin easily dissolves in water within the temperature range of 50−60°C and reverts to a gel upon cooling. This effectiveness in gelation arises from its chemical composition, rich in hydroxyl groups due to the inclusion of serine (approximately 33%), aspartic acid (16.8%), and glycine (8.8%) (Hossain et al., 2023).

The extensive utilization of silk fibroin in the realm of drug delivery is attributed to its adaptability, potential for chemical modification, and manageable degradability. Systems for drug delivery based on fibroin have the capability to enclose and stabilize a diverse range of small drug molecules, enzymes, vaccines, proteins, and DNA. This encapsulation not only prolongs the viability and effectiveness of these substances but also extends their activity within the body (Pandey, Haider, Chandak et al., 2020). Sericin, a substance with a gummy texture that is extracted along with silk fibroin,

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is presently under exploration for its potential in activities like antimicrobial, antitumor, and anticoagulant functions. The process of degumming sericins from silk cocoon fibers, a process pivotal for multiple industries, involves the elimination of the proteinaceous, gum-like substance known as sericin, which envelops the silk fibers. This strategic procedure is indispensable in the production of top-notch silk fibers. The removal of sericin, which naturally coats the silk fibers, is essential to ensure the superior quality and characteristics of the final silk products. The process, referred to as degumming, encompasses diverse techniques aimed at effectively dissolving or eliminating the sericin layer while safeguarding the structural integrity of the silk fibers (Pandey, Haider, Jain et al., 2020). Sericin finds application in the cosmetic industry, particularly in the formulation of shampoos and creams. Comparative properties have been observed in silk protein derived from various silkworms. Researchers are currently assessing different extraction methods to determine their impact on the activity of silk protein as a biopolymer.

Over the past 20 years, there has been a significant rise in publications (research articles, reviews, books, and book chapters) and patents. The data, compiled from Google Scholar by selecting search results year by year, are summarized in Fig. 2.1. This figure illustrates a continuous increase in publications, highlighting the growing importance of sericin as a valuable material across various fields.

This chapter delves into the innovative and diverse extraction routes for degumming sericin, providing a comprehensive analysis of the latest methodologies and their implications. By examining both traditional and cutting-edge techniques, the chapter offers insights into the efficiency, sustainability, and potential applications of each extraction method. This detailed comparison not only highlights advancements in sericin extraction

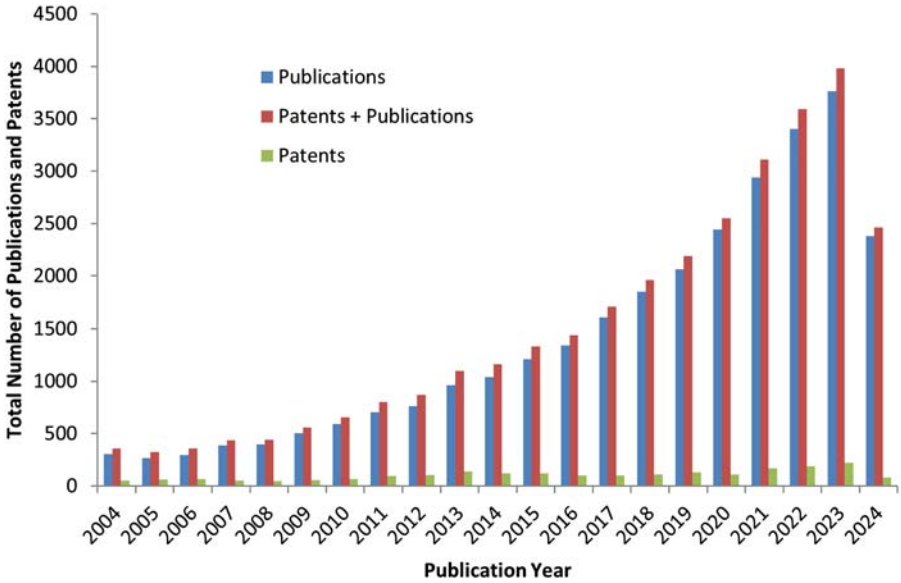


Figure 2.1 The number of publications and patents for the last 20 years in the field of sericin.

but also underscores its growing significance in various industrial and biomedical fields. The novel approaches discussed aim to enhance the quality and yield of sericin, paving the way for new research directions and practical applications.

Fig. 2.1 shows that there is increase in number of publication in the field, representing that the material is gaining interest day by days to perform the various research area. Sericin is becoming an emerging area of interest for researchers. Sericin is transforming from a byproduct of the silk industry into a valuable resource with wide-ranging applications. Its unique properties make it an exciting focus for researchers aiming to develop innovative solutions across biomedical, cosmetic, and environmental fields. As research continues to uncover new uses and improve existing applications, sericin is poised to become a staple in various industries, driving sustainable and health-conscious advancements.

This chapter focuses on the properties and application of silk protein in drug delivery and biomedical applications. Within this chapter, we shall delve into the importance of degumming sericins, its pivotal function within silk manufacturing, and the array of techniques deployed in the degumming progression. Additionally, we will explore the merits of degumming and its influence on the caliber and adaptability of silk fibers intended for a variety of applications, alongside the analysis of the sericin obtained through different methods (Carissimi et al., 2019).

Here are some common extraction routes for degumming sericin from silkworm cocoons:

Boiling water degumming: One of the traditional methods for degumming silk worm cocoons is boiling them in water. The cocoons are immersed in hot water, and the heat helps soften and dissolve the sericin. After boiling, the softened sericin can be easily removed by hand or by using mechanical devices, leaving behind the silk fibers. Extraction can be performed by using two methods: open boiling and autoclaving, at various time intervals of 30, 60, and 90 minutes, as reported by Bhat et al. The crude sericin powder was recovered through hot air drying and freeze-drying (lyophilization). The highest recovery rate of crude sericin powder, $14.12 \pm 0.05\%$, was achieved using the autoclave method followed by lyophilization. Additionally, the autoclave extraction method yielded higher protein content and purity compared to the open boiling method (Bhat et al., 2024).

Enzymatic degumming: Enzymatic degumming is a more modern and gentle method for removing sericins. It involves treating the silk worm cocoons with specific enzymes that selectively break down the sericin without damaging the silk fibers. The enzymes hydrolyze the proteinaceous sericin, making it easier to separate from the silk fibers.

Alkaline degumming: In alkaline degumming, the silk worm cocoons are treated with a dilute alkaline solution, such as sodium carbonate or sodium hydroxide. The alkaline solution helps break down the sericin into water-soluble compounds, which can be washed away, leaving behind the degummed silk fibers.

Mechanical degumming: Mechanical degumming involves physically agitating the silk worm cocoons to loosen and remove the sericin. This can be achieved through various methods, such as rubbing the cocoons against each other or using

mechanical devices to create friction, facilitating the separation of sericin from the silk fibers.

Ultrasonic degumming: Ultrasonic degumming is a noncontact method that uses ultrasonic waves to break down the sericin. The silk worm cocoons are exposed to ultrasonic vibrations, which create cavitation bubbles that help in the disintegration of the sericin, making it easier to remove. Lai et al. have developed an efficient intermittent ultrasonic pretreatment strategy to enhance sericin protein production from *Cassava* silkworm cocoons. The protein yields are influenced by ultrasonic power and duration, with ultrasonic pretreatment significantly increasing yields compared to conventional methods. Electrophoresis and chromatography confirmed the protein as sericin. Morphology and particle size analysis revealed that sonication disrupts the protein's molecular structure, resulting in smaller particle sizes and altering its secondary structure and thermal stability (Lai et al., 2024).

The choice of degumming method depends on factors such as the desired level of degumming, the quality of silk fibers required, and the available equipment and resources. Each extraction route has its advantages and suitability for specific applications in the silk industry.

2. Methods for degumming

Sericin imparts a coarse and rigid texture to silk, causing a decline in desirable traits like shine and purity, and furthermore contributing to uneven dye absorption. The elimination of this sericin is imperative to enhance the subsequent treatment of silk. The procedure involved in eradicating sericin from silk is termed as degumming and is calculated in term of degumming efficiency. The degumming process of silk is essential, and researchers have extensively investigated it to achieve the highest fiber quality. Various methods, including physical, chemical, and enzymatic degumming, have been employed for *Bombyx mori* silk.

Degumming efficiency test: The degumming efficiency of silk is measured by the following formula

$$\text{Degumming Efficiency}(\%) = \frac{W1 - W2}{W1} \times 100$$

where, $W1$ = weight before degumming and $W2$ = weight after degumming.

Various tests are performed on material, which includes tensile strength, water vapor permeability, abrasion, pilling, and crease recovery test of fabric.

Thoroughly examining the extraction conditions holds significance, given their potential impact on the ultimate characteristics of sericin. Particularly concerning sericin, meticulous control over the extraction conditions becomes vital due to its pronounced sensitivity to heat. Factors such as temperature and duration of treatment, constituting extraction parameters, have established roles in influencing both the efficacy and caliber of sericin extraction. The yield assumes importance as it directly dictates the economic viability of the sericin extraction process (Gupta et al., 2014).

2.1 By using deep sea water

Traditional degumming techniques utilizing soap and alkalis effectively eliminate sericin. However, these methods contribute to the breakdown of the sericin chain structure, leading to the loss of potential properties. Moreover, the removal of soap from the sericin solution is both arduous and costly. In light of these challenges, exploring alternative degumming approaches for sericin removal from cocoons and devising methods to recover and recycle sericin by-products generated during the degumming process could yield substantial economic and societal advantages (Seo et al., 2023).

The vast distance from solar radiation results in minimal bacterial activity, if any, while the depth beneath the surface seawater contributes to a high concentration of inorganic substances. Due to the elevated mineral content and reduced bacterial contamination in comparison to other water sources, the utilization of deep sea water (DSW) as an extraction buffer for sericin holds potential in diverse applications such as cosmetics, foods, and biomedical materials (Orcutt et al., 2011).

The assessment of sericin extraction from silkworm cocoons involved the utilization of natural carbonate ions present in DSW, eliminating the need for chemical additives, and conducted at elevated temperatures. The extracted sericin, along with the DSW buffer, underwent a straightforward filtration and lyophilization process to encourage the separation of sericin protein fractions. Subsequently, marine mineral and *Molus alba* extracts were employed to achieve a retentate featuring diverse functional attributes (Hong et al., 2019; Hossain et al., 2023).

Hong et al. introduced an efficient technique for extracting sericin from silk cocoons utilizing DSW. The focus was centered on sericin extraction without the inclusion of chemical additives, aiming to attain a secure, cost-effective sericin powder. The sericin extraction process involved a straightforward high-temperature approach encompassing heating, condensation with *M. alba*, filtration through cotton cloth, cold preservation, and lyophilization. Findings revealed that the sericin yield (26%) achieved through DSW extraction was roughly 2% higher than that yielded by a chemical buffer (0.2 M Na_2CO_3, 24%). The marine mineral-derived sericin from *M. alba* (MSM) exhibited a size distribution of 15−250 kDa, with notable peaks within the range of 75−250 kDa, featuring a galactose chain. Furthermore, this MSM product demonstrated notable antioxidant, skin-whitening, and antibacterial effects while maintaining safe long-term storage. Consequently, our outcomes advocated for the adoption of the eco-friendly DSW extraction approach, resulting in the generation of a proteinaceous, biodegradable biopolymer suitable for sericin preparation (Hong et al., 2019).

2.2 By using a chemical buffer

The traditional method for eliminating sericin from silk, known as degumming, involves the utilization of sodium bicarbonate and Marseille soap or immersion in a boiling alkali solution (Fig. 2.2). The effluent produced after degumming contains sericin along with salts and soap residues. Due to the expense of Marseille soap, alternative agents such as urea, mercaptoethanol, acids, surfactants, or sodium chloride can

be employed for extraction. However, these substances left behind in the residual water render such approaches environmentally unfriendly and hinder the retrieval of high-quality sericin (Bascou et al., 2022).

2.3 By using high temperature high pressure

Degumming was executed within an aqueous environment utilizing two distinct apparatuses: The high-temperature high-pressure (HTHP) beaker dyeing machine and the IR dyeing machine, both set to 100°C for duration of 40 minutes, following the established method. Subsequent extraction procedures varied in terms of time and temperature. The IR dyeing machine was engaged for extraction at temperatures of 90, 100, 110, and 120°C, with time intervals spanning 15, 30, 60, 90, 120, and 150 minutes, each conducted separately. Likewise, the HTHP dyeing machine was utilized for extractions at 100, 110, and 120°C, also employing time spans of 15, 30, 60, 90, 120, and 150 minutes individually. The resulting solution from these extractions underwent both qualitative assessment through spectroscopy and quantitative evaluation by quantifying the protein content. The obtained outcomes were then compared against the established sericin standard for benchmarking purposes (Gupta et al., 2014).

2.4 By using infrared heating

Infrared (IR) heating is becoming popular in process industries as an effective and nonpolluting method of activation because of reportedly higher thermal efficiency and faster heating rate as compared to convective heating. It is recognized as a method with easy control of heating temperature, convenient application, and significant savings of space and energy consumption (Gupta et al., 2013). IR machines work on the principle of direct heating where heat is transferred directly to the center of material in the form of electromagnetic waves, without heating the surrounding air (Ramaswamy et al., 2012). A novel approach has been used to control pollution and minimize waste in wet processing of silk. Process conditions for extraction of sericin from silk waste using IR machine was developed. Complete extraction of sericin from silk waste could be obtained using a lower temperature, lower time of treatment, and lesser water consumption as compared to the conventional HTHP process. The process reduces not only the amount of water and chemicals required in conventional processing but also the pollution load considerably by not allowing any sericin to go into the effluent (Gupta et al., 2023).

2.5 By hydrolytic methods

The process of degumming silk entails breaking down the peptide bonds of sericin, achieved through either hydrolytic or enzymatic means, followed by the removal of sericin from the silk fibroin. Sericin hydrolysis can occur under neutral, alkaline, or acidic conditions, resulting in four distinct fractions with varying properties. Among degumming methods, boiling-off in an alkaline soap solution is the most commonly

employed. There exist numerous qualitative techniques for evaluating the degree of degumming. Typically, degumming occurs in an alkaline solution containing soap, which, although effective, poses a harsh treatment that can also impact the fibrin structure (Gulrajani, 1992).

Utilizing alkali-based methods enhances both labor productivity and machine efficiency by reducing chemical costs and shortening treatment times from 90–120 minutes to 10–30 minutes. However, using alkalis alone for boiling-off silk is not recommended as it leaves the material discolored, thin, and coarse. The optimal approach involves a combination of soap and alkalis to achieve a satisfactory compromise. Recent advancements in synthetic surface-active agents have renewed interest in alkali-based degumming processes and agents. Numerous alkalis have been explored for their potential as degumming agents, including potassium carbonate, sodium hydroxide, sodium silicate, sodium carbonate, sodium pyrophosphate, trisodium phosphate, sodium bicarbonate, ammonia, borax, and salts of weak acids such as boric, silicic, and stannic acid.

It has been determined that the pH range of the boil-off bath in alkaline degumming should be carefully maintained between 9.5 and 10.5. Below pH 9.5, degumming occurs too slowly, posing a risk of mechanical damage, while exceeding 10.5 rapidly escalates the likelihood of chemical damage. Degumming efficacy is notably sluggish and incomplete at pH values below 8.4. To ensure the desired pH level, buffer solutions are recommended. Several buffers have been studied, including potassium carbonate/sodium bicarbonate, sodium carbonate/sodium bicarbonate, sodium hydrogen phosphate/trisodium phosphate, and potassium tetraborate/boric acid. Among these, sodium carbonate/sodium bicarbonate is extensively researched and is sometimes prepared by blending soda ash with a precise quantity of sodium bisulfite. Studies suggest that the degumming rate is influenced not only by pH but also by the overall concentration of electrolytes in the buffer solution (Gulrajani, 1992).

2.6 By enzymatic methods

Traditionally, degumming is achieved through the use of chemical agents such as soda (Na_2CO_3), detergents, and other chemical substances. However, these agents pose environmental risks due to their harmful effects. Therefore, the discovery of alternative components capable of substituting these hazardous agents while yielding comparable or nearly identical results would be of immense value.

An escalating tendency involves the utilization of exceedingly specialized biocatalysts, namely enzymes, for both the chemical treatment and physicochemical alterations of textile fibers. Enzymes, being products of nature, boast full biodegradability and execute their tasks with unobtrusive efficiency, devoid of residual pollutants. This renders enzyme concentrations suitable for effectively conducting the degumming process of mulberry silk yarn (Antony & Chinnammal, 2013).

The study examined various enzymes extracted from natural sources such as papaya skin, pineapple skin, and guava leaf, each at different concentrations (10%, 15%, and 20%) and temperatures (35°C, 45°C, and 55°C), to assess their impact on degumming efficiency. Analysis involved evaluating samples based on degumming efficiency, as

well as conducting additional tests such as tensile strength, water vapor permeability, pilling and abrasion resistance, crease recovery, whiteness, and spot testing using standard methods. Results indicated that the enzyme extracted from papaya skin demonstrated the highest degumming efficiency at 15.9% concentration and 45°C temperature, alongside favorable outcomes in other tests. In comparison, the conventional degumming process achieved a degumming efficiency of 16.6%. These findings suggest that the enzyme extracted from papaya skin could serve as an eco-friendly alternative to conventional degumming methods (Rahman et al., 2020).

Based on the investigation into silk degumming employing dehydrated latex from *Carica papaya* Linn., optimal conditions were identified as follows: utilizing a 4% dry latex solution at 75°C for duration of 30 minutes under neutral conditions. These conditions demonstrated no detrimental impact on the strength or surface of the fibers. The treated fibers retained their glossy, supple, and sleek appearance. Staining tests using direct dyes produced a pink hue, suggesting the presence of a minor residue of sericin. This alternative process holds the potential to replace traditional degumming methods, offering cost-effectiveness and environmental harm reduction (Sasithorn & Luepong, 2009).

An increasing inclination is observed toward employing highly specialized biocatalysts, namely enzymes, for both chemical processing and physio-chemical alterations of textile fibers. Enzymes, being natural products, are fully biodegradable and perform their tasks quietly and effectively, leaving no pollutants behind. Therefore, utilizing enzyme concentration proves to be effective in facilitating the degumming process of mulberry silk yarn. The enzyme derived from papaya skin exhibited optimal outcomes at a concentration of 15% and a temperature of 45°C. In addition to its strong degumming performance, other test outcomes were also deemed satisfactory when compared to the conventional approach. In summation, it can be inferred that eco-friendly degumming surpasses the conventional technique, and this naturally derived method can be adapted to address environmental concerns (Rahman et al., 2020).

Enzymes have emerged as a favorable method for silk degumming due to their reduced energy consumption. The effectiveness of the degumming process relies on factors such as enzyme concentration, treatment duration, pH, and temperature. Silk treated with proteases leads to a sericin with variable chain lengths.

Freddi et al. obtained a range of peptides weighing between 5 and 20 kDa through protease degumming. Different alkaline (3374-L, GC 897-H), neutral (3273-C), and acid (EC 3.4 23.18) proteases were applied to a crêpe silk fabric to assess their efficacy as degumming agents. The proteases were utilized at optimal pH and temperature conditions, while variations in enzyme dosage (0.05−2 U/g fabric) and treatment duration (5−240 minutes) were implemented to analyze sericin removal kinetics. Degumming loss with soap and alkali stood at 27 wt.%. In 1 hour, the maximum sericin removal was 17.6 wt.% for 3374-L (2 U/g fabric), 24 wt.% for GC 897-H (1 U/g fabric), and 19 wt.% for 3273-C (0.1 U/g fabric). However, under the experimental conditions, EC 3.4 23.18 exhibited minimal efficacy as a degumming agent. The degumming loss increased with treatment duration, reaching 25 wt.% with 1 U/g fabric of 3374-L. Morphological analysis revealed complete removal of sericin from the warp yarns of the crêpe fabric, while sericin deposits persisted within the internal portions of

the highly twisted weft yarns. The chromatographic pattern of soluble sericin peptides varied depending on the enzyme type, dosage, and treatment duration, resulting in a mixture of peptides weighing between 5 and 20 kDa, with an average molecular weight of approximately 12 kDa (Freddi et al., 2003).

Suwannaphan et al. assessed the structural integrity of both silk proteins. While the fibers remained undamaged, the sericin was broken down into peptides measuring 10−12 kDa in size. An extracellular serine protease derived from *Bacillus* sp. C4 SS-2013 (C4) demonstrated notable specificity toward sericin substrate. The crude enzyme exhibited the capability to completely remove sericin (with a specific activity of 25.0 U mg^{-1}) without compromising the integrity of the silk fibroin fiber, even during extended incubation periods. It could be readily concentrated and stored for prolonged durations at low temperatures. Following purification, the enzyme displayed a molecular weight of 28 kDa, a 3.1-fold purification, a yield of 6.2%, and a specific activity of 78.0 U mg^{-1}. Its optimal pH and temperature were determined to be 8 and 50°C, respectively, and it maintained stability within a pH range of 5−11 and temperatures between 30°C and 40°C. Additionally, the enzyme's activity was enhanced in the presence of Ca^{2+}. This study marks the first report of kinetic values determined using a sericin substrate. Furthermore, aside from its specificity toward sericin and other adhesive proteins while sparing fibrous proteins, the purified C4 enzyme exhibited impressive capabilities in silk degumming, yellow color bleaching, and sericin degradation. It effectively cleaved sericin substrate into peptides ranging from 10 to 12 kDa in size. Consequently, the C4 protease presents itself as a promising option for industries such as silk production, cosmetics, and detergents, among others.

2.7 Microwave-assisted extraction

Microwave-assisted steam degumming is an innovative and eco-friendly method for removing sericin. Microwave heating significantly reduces the time needed for steam degumming. Microwave degumming is the most efficient method, achieving a 99.8% yield of sericin. The sericin extracts have a composition similar to that of commercial sericin. The extraction methods affect the molecular weight and solubility of sericin in water. When using microwave-steam synergistic degumming (10 minutes microwave, 120°C steam, 30 minutes steam), the degumming efficiency was three times higher and energy consumption was half that of the traditional Na_2CO_3 method. Additionally, the novel method took only 0.75 hours compared to 2.75 hours for the traditional method. Microwave-steam synergistic degumming, a clean technology, offer a short processing time, high sericin degumming rate, chemical-free operation, and low energy consumption. This method supports better and faster sustainable development (Fig. 2.2).

2.8 Aqueous ionic liquid solutions as green solvents

Protein extraction from silk is a unique area of research focused on efficiently extracting the silk proteins, fibroin, and sericin, from silk fibers, typically done using chemicals. In a study by Kalita et al., ionic liquids (ILs) were used as a green and alternative method for degumming sericin from both mulberry (*B. mori*) and nonmulberry

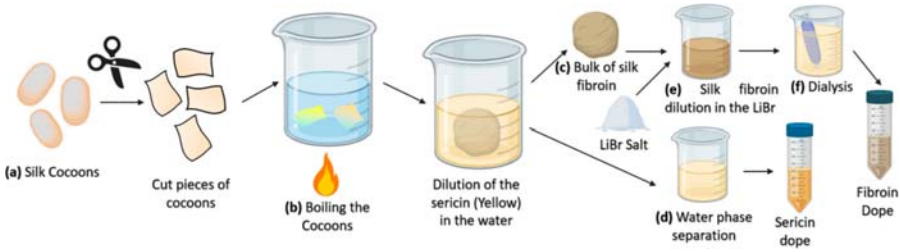


Figure 2.2 Extraction of sericin in the laboratory (degumming process) by cutting the cocoons into small pieces.
Reprinted under the Creative Commons Attribution (CC BY) license from Yonesi, M., Garcia-Nieto, M., Guinea, G. V., Panetsos, F., Pérez-Rigueiro, J., & González-Nieto, D. (2021). Silk fibroin: An ancient material for repairing the injured nervous system. *Pharmaceutics, 13*, 429.

(*A. assamensis* and *P. ricini*) silk. The study evaluated six ILs with varying tail lengths for their degumming efficiencies. The interaction between silk proteins and IL ions involves a complex ionic disruption of nonpolar interactions, hydrogen bonds, and electrostatic effects. The study found that 1-butyl-3-methylimidazolium chloride (BMIM.Cl), 1-ethyl-3-methylimidazolium tetrafluoroborate (EMIM.BF4), and tetraethylammonium bromide (TEAB) resulted in higher weight loss percentages in silk fibers compared to other ILs, indicating their effectiveness in sericin removal without significant damage to the silk fiber. TEAB emerged as a particularly promising candidate for sericin extraction due to its ability to promote protein destabilization. Additionally, the structure of the extracted silk protein sericin remained largely unchanged, as confirmed by FTIR spectra and SEM images. This study is the first to use ILs for extracting nonmulberry silk sericin and demonstrates that ILs can be a potential green solvent for sericin extraction (Kalita et al., 2024). Comparison of the various degumming methods of sericin has been summarized in Table 2.1.

3. Characterization of the sericin extracted from various degumming methods

Sericin can be characterized by instrumental methods include techniques like mass spectrometry, separation (chromatography, electrophoresis), thermal analysis (calorimetry, thermogravimetric analysis), hybrid methods (gas chromatography combined with mass spectrometry, gas chromatography combined with IR spectroscopy), and spectroscopy (ultraviolet-visible spectroscopy, nuclear magnetic resonance [NMR] spectroscopy, X-ray spectroscopy) (Figs. 2.3 and 2.4).

3.1 Ultraviolet-visible (UV) spectroscopy

A distinctive peak was found at 275.40 nm in the case of a standard sericin solution to assess the quality of proteins because they contain peptide and aromatic bonds, which

Table 2.1 Comparison of the main degumming methods of silk.

Degumming methods	Material used	Pros and cons
Alkaline degumming	Sodium carbonate Sodium bicarbonate Urea Electrolysis of water	• Improved productivity • Damage silk fibroin • Introduce chemicals
Acidic degumming	Tartaric acid Malic acid Citric acid	• Fast degumming • The process is not easy to handle • Introduce chemicals
Soap degumming	Marseille soap Neutral soap	• Low efficiency • Introduce chemicals
Enzymatic degumming	Papain Trypsin	• Fast and efficient • High cost
High temperature high pressure		• Damage silk fibroin • Free of chemicals
Carbon dioxide supercritical fluid degumming		• No contamination • High cost

Reprinted under the Creative Commons Attribution (CC BY) license from Pan, M., Jin, Y., Ye, Y., Jiang, W., Zhu, L., & Lu, W. (2024). An efficient and eco-friendly method for removing sericin using microwave-assisted steam degumming. *Environmental Technology & Innovation*, 35, 103674.

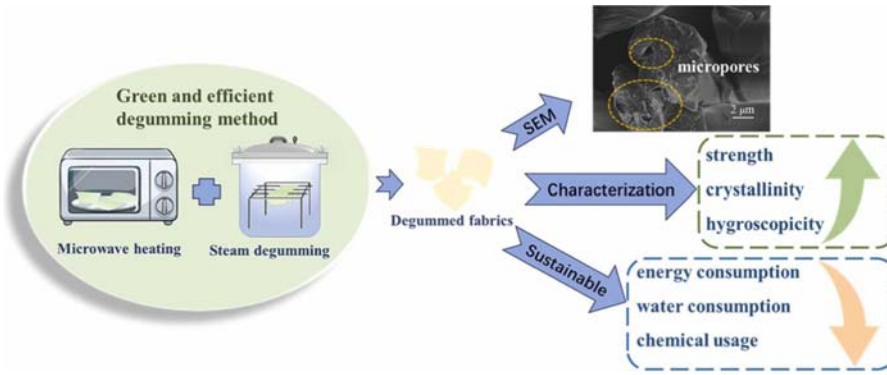


Figure 2.3 Microwave-assisted steam degumming method.
Reprinted under the Creative Commons Attribution (CC BY) license from Pan, M., Jin, Y., Ye, Y., Jiang, W., Zhu, L., & Lu, W. (2024). An efficient and eco-friendly method for removing sericin using microwave-assisted steam degumming. *Environmental Technology & Innovation*, *35*, 103674.

are significantly absorbed in the UV area. When comparing the extracted samples to the standard sample (275.4 nm), there was a shift in peak that indicated a modification in the fundamental properties of the proteins. Consequently, UV-visible spectra are unique and can be used for thumbprinting. In a different investigation, the UV

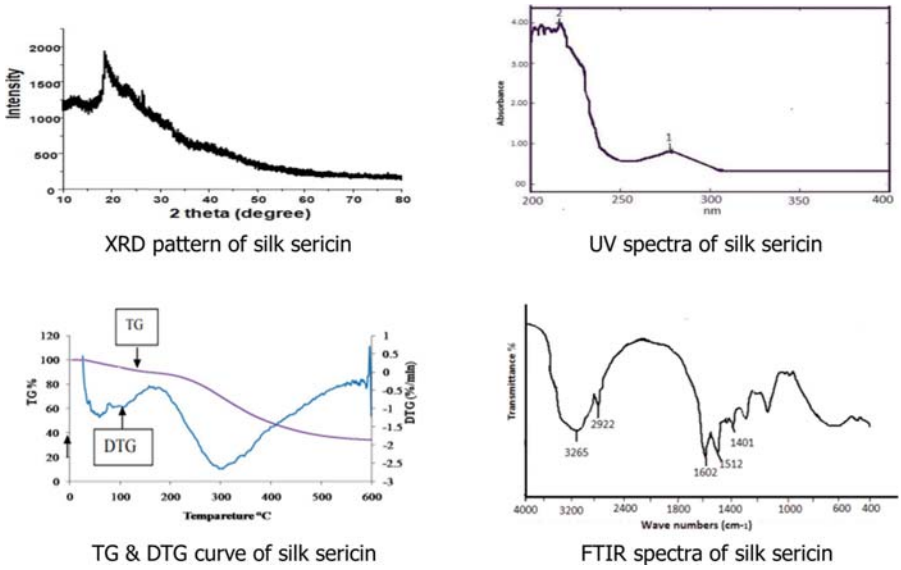


Figure 2.4 Characterization of extracted sericin for XRD, UV spectra, TG and DTG analysis, and FTIR spectra.
Reprinted from the Saha, J. M. M., Sheikh, M. K., Habib, M. A. (2019). Extraction, structural and functional properties of silk sericin biopolymer from Bombyx mori silk cocoon waste. *Journal of Textile Science and Engineering, 9*, 1000390.

absorption spectra of the sericin solution were ascertained using Biochrom 4060 software and a Pharmacia LKB UV spectrophotometer (Uppsala, Sweden). In the UV absorption spectrum, a distinctive peak for sericin was found about 275 nm. Due to its ability to absorb ultraviolet radiation, sericin is a good UV protection agent. The sericin fabric demonstrated UV absorption properties; as a result, it can be employed as a UV-protective agent (Gulrajani et al., 2008). The absorbance peak of sericin was measured in the UV visible spectrum, and it was found to be between 218 and 276 nm. It was silk sericin at its most distinctive. Because of the amino acid peptide linkages, the pure sericin's UV-vis spectrum was detected at 218 nm. There may be sericin present in the extract because the absorption peak at 276 nm is related to the absorption of aromatic amino acids (phenylalanine, tryptophan, and tyrosine) (Karthick et al., 2023).

3.2 Fourier transform infrared spectroscopy

Using the Fourier transform infrared spectroscopy (FTIR) system (Waltham, MA), a different study group examined the sericin generated from the salting out procedure and represented the comparable amide I, amide II, and amide III bands. Amide I, which is located in the 1600−1700 cm-1 range, is the strongest absorption band of sericin proteins out of all of these. Amide I peaks are caused by stretching vibrations of C═O that range from 70% to 85% and C−N groups that range from 10% to 20%.

The usual cause of amide II is in-plane N−H bending, which produces absorption peaks between 1510 and 1580 cm^{-1}. Stretching vibrations of C−N and C−N−H indicate residual potential energy. FTIR-attenuated total reflection spectroscopy (FTIR-ATR) of sericin and silk sericin−embedded silver nanoparticles was utilized for characterization in another study conducted by Masud et al., in 2021 (Al Masud et al., 2021). The sericin protein's usual bands of absorption, such as amide I, amide II, etc., were found. The 3 mM $AgNO_3$ solution's absorption band was detected at 735, 788, 1290, and 2010 cm^{-1}. SS-AgNPs were used to represent the band of amide I (1625 and 1640 cm^{-1}) and the stretching vibration of amine N−H (3365−3385 cm^{-1}) at ratios of 1:6 and 1:8, respectively. Furthermore, the synthesis of AgNPs was unable to alter the structure of sericin (Al Masud et al., 2021). In one study, alkaline degumming is the method used to produce silk sericin protein. The vibrational stretching of the C═O bond is confirmed by the peak in sericin 1656 cm^{-1}, which also suggests the presence of the amide I group (Karthick et al., 2023).

In one study, the cocoons were under went high temperature high pressure treatment to investigate the effect of temperature (90, 110°C) and autoclaving time (15 and 30 minutes) on quality of sericin. The presence of the C═O group of the amide linkage is likely indicated by the overlapping peaks at 1645 and 1616 cm^{-1}, which validate the structure of the protein in all four samples, including its beta-sheet structure for the primary amide and random coil structure. For various silkworm races, with varying temperatures and extraction times, no discernible variations were found (Hossain et al., 2023).

The use of sericin in formulations yielded consistent characteristic peaks in FTIR analysis, as documented by multiple research efforts. In two case studies where sericin was used to prepare nanoparticles, showed characteristic peaks of amides I and amide II (Bahremand et al., 2024; Gagliardi et al., 2024).

3.3 Sodium dodecyl sulfate-polyacrylamide gel electrophoresis

The relative molecular mass of sericin varies greatly on sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) because of variations in extraction techniques and purifying procedures. A dispersed band in the molecular weight range of 15−250 kDa was seen in sericin derived from different species. The protein's core structure's peptide linkages were compromised by the thermal treatment of the cocoon suspensions. Because the samples contained a combination of polypeptides with varying molecular weights, the bands were broader. The molecular weight distribution of sericin is reported by different researchers to span from 20 to 400 kDa. This investigation's use of electrophoresis analysis at various temperatures and times showed that sericin was broken up into peptides with a wide variety of molecular weights (15−250 kDa) and lengths. A high molecular weight was obtained from the extraction of sericin using high-temperature and high-pressure techniques, demonstrating its crystalline form and the presence of a large amount of β-sheet structure (Hossain et al., 2023).

The current study investigates an appropriate extraction procedure for sericin extraction from Nistari cocoons (traditional race) and analyze the molecular mass of

the extracted material using SDS-PAGE. In this work, sericin was extracted using various buffers, urea, NaOH, Na_2CO_3, Triton X-100, LiBr, and $CaCl_2$ concentrations. Out of all of them, the extraction of sericin using sodium hydroxide solution yielded the highest yield, followed by sodium carbonate solution. On the other hand, the extract showed streaks on an SDS-PAGE, indicating that the sericin had degraded. Comparatively, it was discovered that urea and Triton X-100 treatments were the most successful in terms of both quantity and quality. Sericin extracted with 6 M urea and Triton X-100 showed a distinct SDS-PAGE profile (Kurmi et al., 2023).

In a different SDS-PAGE investigation, sericin recovered from fabric showed a diffused band with a molecular mass between 6.5 and 205 kDa, while standard sericin B (20 mg/mL) and C (60 mg/mL) showed low range bands with a molecular weight between 3.5 and 43 kDa. Standard sericin, with a molecular mass of less than 50 kDa, could dissolve easily in cold water, whereas extracted sericin, with a molecular mass of between 50 and 200 kDa, was only soluble in hot water (90°C). This enormous disparity in molecular mass may have a profound effect on the characteristics and uses of sericin. It is possible to conclude that the peduncle of a plant contains 200 kDa of sericin, which is thought to represent a substantial fraction (Gupta et al., 2014).

3.4 Thermogravimetric analysis

The silkworm race-1 [BSRB 01(P) (Bivoltine)] sericin had the greatest thermal stability at 90°C (15 minutes) and 110°C (15 minutes) for each of the four silkworm species. It was determined from the TG curves above that the extraction temperature and time with the lowest value (R1T1) demonstrated the maximum thermal stability. According to the findings made by the other, the decomposition temperature of all the sericin samples fell between 470 and 580°C (5). The plot obtained as a result of a change in weight against temperature is known as a thermogravimetric curve/thermogram. In one study, the thermogravimetric analysis (TGA) and DTG analysis of sericin revealed that thermal degeneration (fast weight loss) took place in the temperature range of 210°C−400°C. The sericin extracted from cocoons showed two degradation peaks (315°C and 370°C), which may be due to molecular flowing and scission (Martínez et al., 2017). Another studies also reported similar results, the decomposition temperature of sericin was 300°C. It can be observed that the mass loss of sericin is 6% respectively at 100°C due to loss of moisture, low-molecular-weight solvent, and gas (Saha et al., 2023).

3.5 Matrix-assisted laser desorption/ionization-time of flight

In one investigation, the sericin hydrolysate was further examined using matrix-assisted laser desorption/ionization-time of flight (MALDI-TOF) after the researcher used an enzyme to hydrolyze the sericin. The analysis revealed that a molecular mass (sharp peak) at 4169 Da was present in the enzyme-free control sample. Peptide distribution showed a prominent peak at 1139.7 Da, which fell within the molecular mass range of 1124.5−1345.8 Da when one unit of enzyme was present. The MALDI spectrum of the hydrolysate, when both enzyme units were present for hydrolysis, was

spread within the range of 525−616.25 Da, with the largest peak occurring at 616.2 (More et al., 2018). A high temperature-high pressure approach was used to extract sericin, and it was done for 1 hour at 130°C and 2.1 MPa. Multiple peaks in the mass spectrum that corresponded to LMW-sericin were exhibited by MALDI-TOF, indicating that the MW ranged from 26 kDa (Cherng et al., 2022).

3.6 High-performance liquid chromatography analysis

Bombyx mori cocoon sericin was prepared by heating a 0.2% sodium carbonate solution with 100 g of cocoon for 2 hours and filtering through a glass microfiber filter to remove fibroin. The state of sericin was also revealed through high-performance liquid chromatography (HPLC) analysis. The absorbance at 275 nm of a Superdex 75 HR column (Pharmacia, U.S.A.) was measured after sericin was put into a buffer containing 0.2 M NaCl and 0.05 M Tris HCl (pH 7.0). The hydrolyzed sericin's molecular weight ranged from 6 kD to more than 67 kD, according to HPLC analysis (Terada et al., 2002).

In an experiment, HPLC on the gel permeation column was used to determine the dispersion of the molecular sizes profile of silk sericin hydrolysates. Eleven hours of hydrolysis were conducted at 37°C−65°C. Moreover, it was discovered that alcalase hydrolysate had strong antioxidant properties. Additionally, the study showed that peptides with molecular masses between 200 and 3000 Da were effective antioxidants. Consequently, it was determined that the pharmaceutical and medical industries may find usage for silk sericin hydrolysate (SSH) (Wu et al., 2010). Various analytical methods for analysis and characterization of sericin have been summarized in Table 2.2.

3.7 X-ray diffraction

In one study, beaker dyeing machines and IR dyeing machines connected with HTHP were used to degumming sericin samples obtained from different sources. Since the structure of the extracted sericin is so important, X-ray diffraction (XRD) was performed at room temperature using the X'pert PRO XRD (PANalytical, Netherlands) to examine the crystallinity of these collected samples. When silk was glandular and not yet crystallized, its diffraction peaks were $2\theta = 12.2$ degrees and 28.2 degrees. Spun silk with a secondary β-sheet structure displays a diffraction peak at $2\theta = 18.9$ degrees and 20.7 degrees. The standard sericin solution's XRD curve was around $2\theta = 20.5$ degrees. Examining the peaks revealed that they were wide, which supports the theory that the powders were amorphous. Researcher conducted an XRD investigation on sericin in order to use the XRD method to look into the molecular conformation. The crystalline structure of sericin obtained from wild silk and that of sericin isolated from *Bombyx mori* is almost the same. The solubility of the two types of silk is the only physiological distinction; the chemical reaction between the silk sericin, and the tannins found in wild silk makes it relatively insoluble.

Saha et al. extracted sericin using HPHT method and evaluated by XRD. The result revealed that crystal diameter and crystallinity index of silk sericin was 0.47 nm was

39.66%. These results indicate that sericin is more amorphous (Saha et al., 2023). Various characterization parameters of extracted sericin such as XRD, UV spectra, TG and DTG analysis, and FTIR spectra are shown in Fig. 2.2.

3.8 Gel filtration chromatography

In one investigation, crude powder comprising 75% (v/v) ethanol and gel filtration chromatography was used to recover sericin from effluent from the silk industry and analyze its relative molecular mass. The collected sericin was ground into a powder and used to make a solution containing roughly 20 mg/mL using a Sepharose CL-6B column. The solution was tested using a pH 7.0 sodium phosphate buffer solution against 20 mM. Analysis was done on the absorbance value at 220 nm wavelength. Following elution analysis, the chromatogram revealed the two peaks. The protein fraction that eluted had a high molecular mass and ranged in molecular mass from 1652 kDa to 1209 kDa. A significant peak representing a low-molecular-mass protein fraction was discovered; its molecular mass ranged from 476 to 124 kDa.

The tropical tasar silkworm, *Antheraea mylitta*, has a strong thread called a cocoon peduncle that connects the cocoons to the tree branches with a ring. This thread is known to contain sericin, a high-molecular-weight water-soluble adhesive protein. 1% sodium chloride or 8 M urea with 1% sodium dodecyl sulfate and 2% beta-mercaptoethanol were used to isolate the sericin. Utilizing gel filtration chromatography, the protein was refined. A single, roughly 200 kDa band was seen in SDS-PAGE under both reducing and nonreducing circumstances (Dash et al., 2006). Cocoon sericin was extracted at 80°C for varying incubation durations of 2−60 minuts in 8 M urea with 5% ME. The sericin solutions were then examined using gel filtration chromatography. The degradation of the polypeptides was shown to escalate as the incubation period increased, reaching a notable level after 20 minutes or more (Takasu et al., 2002).

3.9 Amino acid analysis

The content of protein can be ascertained using an amino acid analyzer. According to published research, out of the 18 amino acids, serine makes up the majority of sericin (ranging from 27.3% to 32.74%) shown in Table 2.2. Besides serine, the other two major amino acids found in sericin are glycine and aspartic acid. Different sources and extraction techniques for sericin can result in variations in its composition. The proportion of hydrophilic amino acids affects sericin's solubility (Kambhampati et al., 2019; Sothornvit et al., 2010).

3.10 Liquid chromatography−mass spectrometry analysis

A brief centrifugation was performed on the sample in preparation for liquid chromatography−mass spectrometry (LC/MS) analysis. The Q-Exactive mass spectrometer utilized for the analysis was equipped with an Accela HPLC system in Mithra Biotechnology, and it was controlled by the Xcalibur 3.0. In addition, low-molecular-

Table 2.2 Analytical methods for analysis and characterization of sericin.

S. No.	Analytical method	Source of sericin	Extraction method of sericin	Observation	Discussion	References
1	UV-visible spectroscopy	*Bombyx mori*	Infrared heating	The absorption peak at 275.40 nm	Due to the presence of peptide bonds and aromatic structure in amino acids	Gupta et al. (2013)
		–	Salting-out with ammonium sulfate	275 nm		Gulrajani et al. (2008)
		Bombyx mori	Alkali degumming method	276 nm		Karthick et al. (2023)
2	FTIR spectroscopy	–	Salting-out with ammonium sulfate	1600−1700 cm^{-1}, C═O stretching 1510 and 1580 cm^{-1}, N−H bending	Amide I, Amide-II	Gulrajani et al. (2008)
		Bombyx mori	Boiling of cocoons	1625 and 1640 cm^{-1}	Amide I	Al Masud et al. (2021)
		Bombyx mori	Alkali degumming method	1656 cm^{-1}	Amide-I	Karthick et al. (2023)
		Race-1: BSRB 01(P) [Bivoltine] Race-2: BSR 92/2. [Multivoltine] Race-3: Nistari [Multivoltine] Race-4: Urboshi [Multivoltine]	High temperature high pressure	1616−1645 cm^{-1}	Amide I	Hossain et al. (2023)

Continued

Table 2.2 Analytical methods for analysis and characterization of sericin.—cont'd

S. No.	Analytical method	Source of sericin	Extraction method of sericin	Observation	Discussion	References
3	SDS-PAGE	Race-1: BSRB 01(P) [Bivoltine] Race-2: BSR 92/2. [Multivoltine] Race-3: Nistari [Multivoltine]	High temperature high pressure	15−250 kDa	Sericin obtained from races 1, 2, and 3 showed a diffused band	Hossain et al. (2023)
		Bombyx mori (race-Nistari)	6M urea, triton X-100	10−225 kDa (urea) 25−75 kDa (triton X-100)	Sericin extracted from triton X-100 showed better quantity and quality	Kurmi et al. (2023)
		–	High-temperature high-pressure, infrared heating	50−200 kDa (extracted sericin), Less than 50 kDa (standard sericin)	Soluble in hot water, soluble in cold water	Gupta et al. (2014)
4	TGA	Race-1: BSRB 01(P) [Bivoltine] Race-2: BSR 92/2. [Multivoltine] Race-3: Nistari [Multivoltine]	High temperature high pressure	Thermal stability at 90°C. (15 min) and 110°C (15 min)	Race-1 derived sericin showed highest thermal stability. Low extraction temperature and time gives higher thermal stability	Hossain et al. (2023)
		–	Autoclave	Degradation peaks at 315°C and 370°C	Decomposition due to scission and molecular flowing	Martínez et al. (2017)
		Bombyx mori	High temperature high pressure	DSC curve at 330°C	Less thermal stable	

5	MALDI-TOF	*Beauveria* sp. (MTCC 5184)	Degumming by alkaline protease	The peak at 4169 Da (without enzyme) The peak at 1139.7 Da (with one unit enzyme)	Mass of sericin hydrolysate	More et al. (2018)
		Bombyx mori	High temperature high pressure	Sericin mass is 2.6 kDa	Low-molecular-weight sericin	Cherng et al. (2022)
6	HPLC	*Bombyx mori*	Extraction using calcium carbonate (0.2%)	6−67 kD	Sericin hydrolysate molecular mass distribution	Terada et al. (2002)
		Bombyx mori	Extraction using NaCl	200−3000 kD	Sericin hydrolysate molecular mass distribution	Wu et al. (2010)
7	XRD	–	High temperature high pressure	Glandular silk $2\theta = 12.2$ degrees, 28.2 degrees Spun silk $2\theta = 18.9$ degrees, 20.7 degrees	Amorphous nature with broad peak	Gupta et al. (2013)
		–	Hot water extraction	Sericin from wild silk Sericin from Bombyx mori at $2\theta = 19.2$ degrees	Crystalline nature with sharp peak	Tsukada (1983)
		Bombyx mori	High-pressure high-temperature method	Crystal diameter and crystallinity index of silk sericin was 0.47 nm was 39.66%.	Amorphous	Saha et al. (2023)

Continued

Table 2.2 Analytical methods for analysis and characterization of sericin.—cont'd

S. No.	Analytical method	Source of sericin	Extraction method of sericin	Observation	Discussion	References
8	Gel filtration chromatography	–	Hot water treatment	Peak 1 = High molecular mass protein fraction (1652 kDa to 1209 kDa) Peak 2 = Low molecular mass protein fraction (476–124 kDa)	High- and low-molecular-weight fraction	Jo and Um (2015)
		Antheraea mylitta	1% Sodium chloride or 8M urea with 1% sodium dodecyl sulfate and 2% beta-mercaptoethanol	200 kDa	High-molecular-weight sericin	Dash et al. (2006)
		Bombyx mori	Extraction at 80°C for varying incubation durations of 2–60 minutes in 8 M urea with 5% ME	Sharpness index = 1.021	The degradation of the polypeptides was shown to escalate as the incubation period increased	Takasu et al. (2002)
9	Liquid chromatography–mass spectrometry analysis	*Bombyx mori*	High temperature high pressure	2–7 kDa	Low molecular weight sericin	Cherng et al., (2022)
10	NMR spectroscopy	–	Autoclaving	Peaks at 6.68 and 6.96 ppm	Presence of tyrosine residue in sericin	Cho et al. (2003)

weight sericin's (obtained by HTHP) molecular weight ranges from 2 to 7 kDa when measured by LC-MS (Cherng et al., 2022).

3.11 Nuclear magnetic resonance spectroscopy

The method known as nuclear magnetic resonance (NMR) is used to examine how electrically charged molecule nuclei interact with radiofrequency electromagnetic radiation. This method is useful for quantifying and identifying the structure of molecules. According to the findings, the proton peaks of the sericin tyrosine residue at 6.68 and 6.96 ppm moved downfield to 7.09 and 7.26 ppm ^{1}H NMR spectra (Cho et al., 2003; Diehl, 2008; Zhang, 2002) (Table 2.3).

4. Technical challenges in sericin utilization, economic and market considerations

The biggest technical challenge lies in extracting and purifying sericin from silk cocoons. Different methods offer advantages and disadvantages. They can affect the amount of sericin obtained (yield) and also alter its physical properties and potential pharmacological activities. The selection of efficient extraction method and transformation of sericin into a product is another challenge. Extracting sericin can be a

Table 2.3 Amino acid composition of sericin.

Amino acid	Percentage of a total amino acid (%) (Sothornvit et al., 2010)	Percentage of a total amino acid (%) (Zhang, 2002)
Serine	32.74	28
Aspartic acid	17.64	17.97
Glycine	9.89	16.29
Glutamic acid	7.31	6.25
Arginine	6.16	3.52
Threonine	5.51	7.78
Tyrosine	4.63	2.87
Alanine	3.86	5.20
Valine	3.14	3.77
Lysine	3.05	1.21
Histidine	1.81	1.32
Leucine	1.44	1.21
Isoleucine	1.04	0.64
Phenylalanine	1.08	0.64
Proline	0.59	–
Methionine	0.11	0.79
Cystine	–	0.69

complex and costly process, requiring specialized equipment and expertise. The price of sericin fluctuates based on its physical properties and level of purity. Food- or cosmetic-grade sericin typically falls within a certain price range (Fabiani et al., 1996). An additional technical challenge lies in ensuring the stability and bioactivity of sericin across various applications. Researchers and industry professionals are actively working to overcome these limitations. Considering the economics, the cost of extracting and processing sericin can be a barrier to its widespread commercial use. Previously several researchers reported extraction, characterization, and further transformation into product. Nowadays, it is easily available in the market and can be directly used for various purposes. Commercialization of sericin solely depends upon the extraction, characterization cost, and market demand of sericin-based products. Consumers are increasingly drawn to sustainable and natural ingredients. Businesses that understand this trend and navigate the regulations related to sericin use will be well-positioned to succeed with strategically marketed sericin products (Capar & Pilevneli, 2024; Capar et al., 2022).

4.1 Quality/purity, environmental impact, cost-effectiveness

The quality of sericin depends upon the grade of sericin such as cosmetic-grade, food-grade sericin, ISO-certified sericin, etc. It can be available in powder as well as solution. Physical characteristics such as amino acid profiling, nitrogen content, loss on drying, pH value, residue on ignition, ash value, and total protein content are the main evaluation parameters that need to be studied before commercialization. Heavy metal contents and microbial testing are also part of quality testing. The food-grade sericin is useful as an additive and packaging material. For the food industry to fully embrace sericin's potential, it needs to be both affordable and high-quality. Additionally, sericin must deliver consistent and powerful biological effects (Chao et al., 2023). A comprehensive safety evaluation, including understanding how sericin is processed by the body (its metabolic pathway), is also crucial. From an environmental standpoint, recycling wastewater from the silk industry is essential. Fortunately, this waste also holds promise for producing high-quality sericin in a cost-effective and eco-friendly way. The yield of sericin extracted from silk cocoons typically falls within the range of 10%−25%, depending on the extraction method (traditional extraction and newer method), silkworm cocoon quality, and processing conditions (cold water, hot water, chemical extraction, high pressure, and enzyme-mediated extraction) (Shree et al., 2023; Sone et al., 2023).

Conclusion: Historically, sericin has been regarded as a by-product and typically discarded. However, ongoing endeavors have been made to salvage and utilize it as a natural biopolymer in diverse applications. When extracting sericin, precise control of extraction conditions is essential due to its high sensitivity to heat. Factors such as temperature and duration of treatment during extraction are recognized to influence both the efficiency and quality of sericin extraction. The yield holds significance as it directly impacts the economic viability of the sericin extraction process. The process of degumming sericins holds a crucial significance in the conversion of raw silk cocoons into refined silk fibers, rendering them appropriate for utilization in textiles,

fabrics, and assorted silk-based commodities. By comprehending the intricacies of the degumming procedure and its consequences, we can acquire invaluable insights into the generation of premium-grade silk materials, as well as the diverse methodologies harnessed to attain heightened silk excellence. Selecting an extraction method that efficiently provides the desired structure and imparts the appropriate biological activity to sericin is crucial for its intended applications. This could encourage the commercialization of sericin for biomedical uses. In the future, additional comparative studies on how different extraction methods affect sericin's biological activity will be necessary.

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Chemical, physical, and enzymatic modifications of sericin to produce new functional materials with improved properties

3

Hafiz Muhammad Tahir, Aamir Ali, Eisha Malik and Ayesha Muzamil
Department of Zoology, Government College University Lahore, Lahore, Pakistan

1. Introduction

Biomaterials, with their intrinsic property of interfacing with the human body (biocompatibility), play a pivotal role in revealing the causes and effects of various medical interventions. These innovative materials are stepping up to tackle the challenges of our time. From regenerating damaged tissues to delivering targeted medications, biomaterials are driving advancements in medical science and technology, offering hope for a healthier future (Kalirajan et al., 2021). Silk is a wondrous biomaterial in this intricate world of natural polymers. This luxurious fiber, spun by humble creatures, boasts unmatched strength and biocompatibility. For centuries, scientists and artisans have been enthralled by this unique material. Sericin is therefore a testament to the marvels, nature can create (Ghalei & Handa, 2022; Schäfer et al., 2023). This protein is derived from silkworm cocoons, notably those of *Bombyx mori* L., and mainly consists of amino acids such as glycine, serine, aspartic acid, and threonine.

Beyond the well-known fibroin (65%−85%) that forms its structural core, silk is blessed with another intriguing component sericin (15%−35%) (Ghalei & Handa, 2022; Saad et al., 2023). Sericin was considered a waste product for decades and thus remained useless for centuries until the researchers had made it purposely intentional (El-Sayed et al., 2021). Consequently, recent studies are paying more attention to sericin in various applications of biomedical, pharmaceutics, food, and cosmetic industries (Arango et al., 2021a). Besides its well-known wound healing and anti-inflammatory properties, silk sericin (SS) accounts for greater biocompatibility and biodegradability (Fig. 3.1). Researchers are utilizing these properties to develop innovative solutions like tissue engineering scaffolds, which provide a supportive structure for damaged tissues to regrow. Additionally, sericin's biocompatibility makes it a promising candidate for targeted drug delivery systems, where it can encapsulate medications and deliver them directly to diseased areas, minimizing side effects on healthy tissues (Das et al., 2021; Ghensi et al., 2019; Jo et al., 2020; Tao et al., 2019; Veiga et al., 2020).

The field of silk sericin research has changed, recognizing that modifying it does not make natural sericin useless; instead, it is about unfolding its full potential

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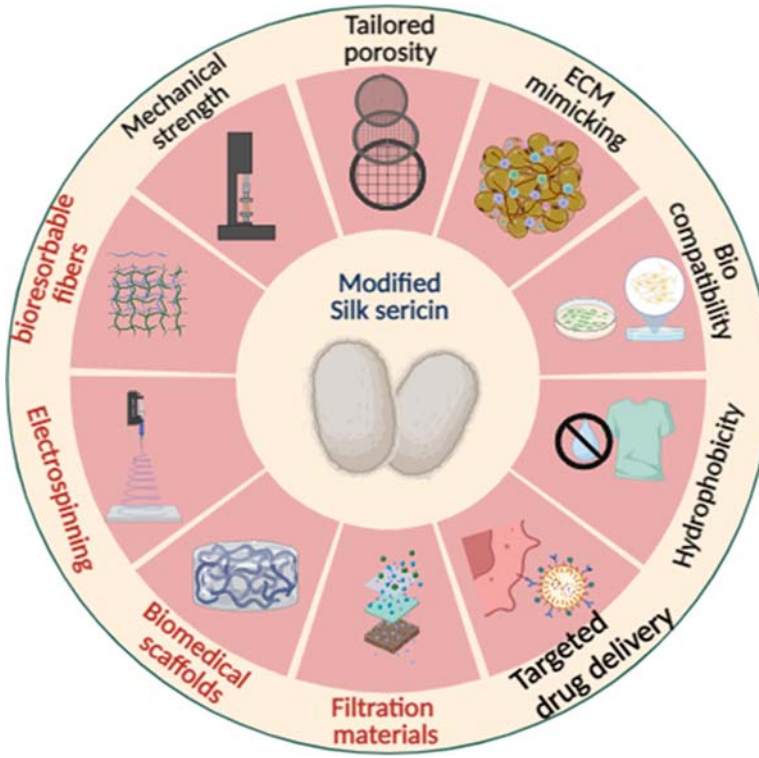


Figure 3.1 Various biomedical applications of modified silk sericin.

(Saad et al., 2023). It is now fascinating the scientists and researchers with its wonders. The scientific research on the modification of sericin has been steadily increasing since the last decade (Fig. 3.2). This emerging field concentrates on intentional modifications to sericin using chemical (crosslinking or grafting), physical (changes in temperature, pressures, or addition of solvents), and enzymatic processes, hydrolysis, physical cross-linking, and biological modifications (Aramwit et al., 2023). These precise adjustments aim to induce specific changes in the protein's structure, ultimately enhancing its adaptability and effectiveness across a diverse range of medical applications (Ghalei & Handa, 2022; Kim et al., 2016; Saad et al., 2023). Researchers are delving deeper, unlocking a diverse spectrum of innovative functional materials derived from this remarkable protein. From biocompatible medical implants to high-performance textiles, sericin's unique properties are being harnessed to create a new generation of materials that are both functional and sustainable. This exploration promises to revolutionize various fields, pushing the boundaries of what is possible with this wonder material (Arango et al., 2021b; Yang et al., 2023).

This review will thoroughly examine each avenue of modification, delving into the methodologies utilized, the characterization techniques employed, and the extensive

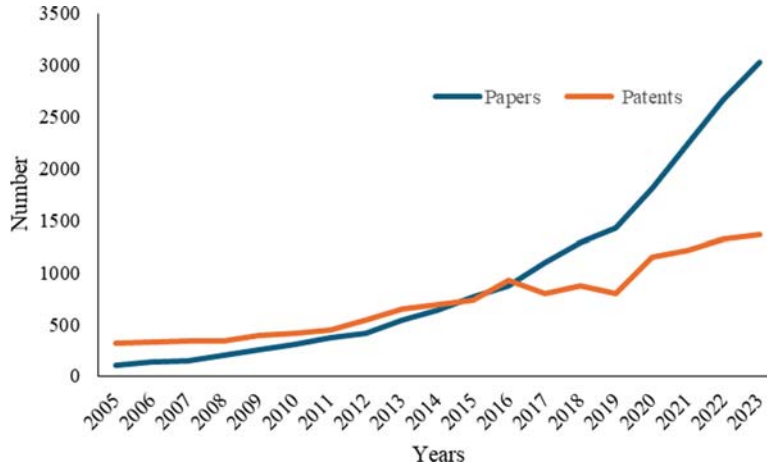


Figure 3.2 The yearly increase in the number of publications and patents related to modified silk sericin.

array of functional materials that have been generated as a consequence (Liu et al., 2022; Yang et al., 2023).

2. Modification of silk sericin

Sericin in silk acts as a gel-layer surrounding the fibroin, but it is weakly soluble in its unmodified form. It can be cross-linked with various polymers to overcome the weaker and poor solubility (Aramwit et al., 2023; Liu et al., 2022). The modifications are categorized as physical, chemical, and enzymatic modifications (Fig. 3.3).

3. Physical methods

The physical blending is done by the appropriate techniques like electrospinning (Mathew et al., 2024), in which the sericin is converted into a mesh of super-thin nanofibers, under an electric field. This wondrous, nonwoven mat has wide applications in nanotechnology, biotechnology, and biomedical fields. The blending can also be done by the extrusion method in which the sericin and other materials are mixed in their molten forms (Zhu et al., 2024). The resulting polymers like sericin-based biomedical scaffolds, filtration materials, functional films, and bioresorbable fibers are created. Researchers tailor the sericin concentration to specific application needs, which allow the new biomaterials to achieve enhanced functionalities.

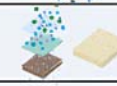
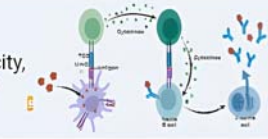
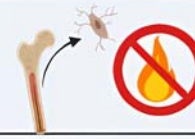
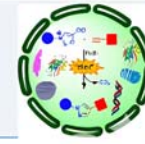
various sericin modifications	Biomedical and other applications
sericin + chitosan or collagen	cell growth and regeneration 
sericin + metalic\ ceramic nanoparticles	targeted drug delivery 
sericin + porous materials	improve water efficiency and selectivity 
sericin + hydrogels	making cosmetics and moisturizers 
sericin + PVA	to make wound healing dressings 
sericin + polyurethane	make flexible electric sensors like sweat sensors etc. 
sericin + -CH3CO	enhance stability, resilience, elasticity and strength of sericin 
sericin + -CH2-CH3	reduce immunogenicity, improves cell growth 
sericin + -PO4	accelerates bone cell growth, enhance fire resistance 
sericin + sugars	enhance biocompatibility, improves mechanical strength 
sericin+ -C4H5O2	allows "click chemistry reactions" 

Figure 3.3 Sericin modifications and applications.

3.1 Irradiation

In the process of irradiation, the samples are introduced by the various radiations according to the need of the application under the safety protocols. The radiations may be of three types following the need of the sample. The gamma radiations are prioritized for deeper penetration even if there is a thick sample of sericin (Kim et al., 2020). The high-energy photons in the gamma rays are responsible for more thorough permeation, allowing the uniform modification of sericin material. It is highly suggestive for biomedical applications due to the effective sterilization against the microbes and their spores.

After the modified samples are cooled down, the new sericin is analyzed and characterized properly to compare its physical, chemical, and biological properties with unmodified samples. We may observe the higher biocompatibility with raised mechanical strength and improved degradation rate, but the high-energy photons emitted during this method can reduce the bioactivity of the sericin. Besides these, the process generates a large amount of free radicals, which require the presence of antioxidants for their eradication. Thus, the controlled doses and target standardizations are crucial to have minimal damage and risk and reproducible results. Moreover, there should be strictly shielded facilities to overcome direct hazardous exposure to radiation.

A general method of irradiation is illustrated in Fig. 3.4 in which a clean composite of silk sericin is taken (like the sericin film in the illustration), and a radioactive isotope (cobalt-60) is introduced from a radioactive source inside a closed chamber. The doses are calculated according to the type of composite used, and the exposure time is set in accordance. The irradiated sericin is hence cooled down, and the radioactive waste is disposed of in a separate can.

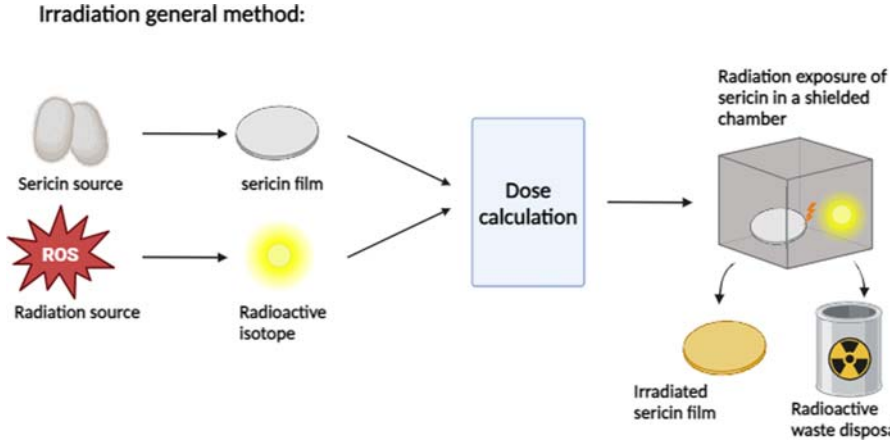


Figure 3.4 General method of irradiation.

3.2 Electro-spinning

The traditional way of spinning was by using a spinning wheel by hand, and the spinners could produce 200g of silk per day (Belbéoch et al., 2021).

Electrospinning is the formation of tiny fibers by an electric spark as a potential, which results in three-dimensional, highly porous, bioresorbable scaffolds with increased surface area (Rahmati et al., 2021; Yao et al., 2019). The sericin made an exceptionally modified polymer when spun with the eminent technique of electrospinning (Chachlioutaki et al., 2022). This versatile technique utilizes a high-voltage electric field to modify the polymer solution, which ends up with extremely thin fibers after stretching and splitting. These microscopic fibers range from 2 nm to several micrometers in diameter. The nonwoven mats as a result of electrospinning processes interlinked the nanoworld to the silk's natural properties. They have both the increased surface area as a desirable feature at the nanometric scale and the silk's inherent properties such as biocompatibility, strength, better draping ability, and elasticity (Babu, 2018). The higher surface area, high aspect ratio, and better tunable properties combined to value these nanofibers in diverse scientific and technological applications, such as filtration systems, drug delivery mechanisms, and tissue engineering advancements.

Sericin-renowned blend with PVA (sericin-PVA) modifies its rheological properties to make it suitable to spin in the apparatus otherwise it comparts very weak mechanical properties ultimately making it less effective for industrial field applications (Khan & Tsukada, 2014; Mowafi & El-Sayed, 2023). The schematic diagram (Fig. 3.5) represents a general method of electrospinning of that modified sericin. The setup contains a syringe filled with a spinnable polymer solution. The injection pump provides an adequate flow rate forming a droplet at the tip of the needle (Mitchell & Tojeira, 2013; Shin et al., 2012). It operates under a high voltage, which generates a cone-shaped structure called a Tylor cone at the tip of the needle where the electric spark creates a requisite tension to generate an aerial river on the collector. While jetting is in progress, the solvent present in the solution rapidly evaporates causing a decrease in diameter to nanometric scale and solidification of the polymer. The spun fibers are collected as they dry out randomly in the form of a mat. It is now a synergistic biomaterial where sericin enhances the biocompatibility and cell adhesion of PVA, while PVA reinforces the sericin, leading to improved structural integrity.

3.3 Stretching

The remarkable mechanical properties of silk fiber lie in its unique structure. It mainly contains amorphous random coils and α helixes, which account for greater flexibility and extensibility, as well as the crystalline β-sheets for impressive tensile strength. Scientists have now successfully created hot-stretched silk fibers (HSSFs), which magnify the mechanical properties of the original silk by boosting the amount of specific crystalline structure (β-β-sheet nanocrystals) as well as its overall content in fibers (Ashby, 2008; Lu et al., 2022). The improved mechanical performance as a result of the new crystalline orientation has made the silk a perfect candidate for tough fibers against

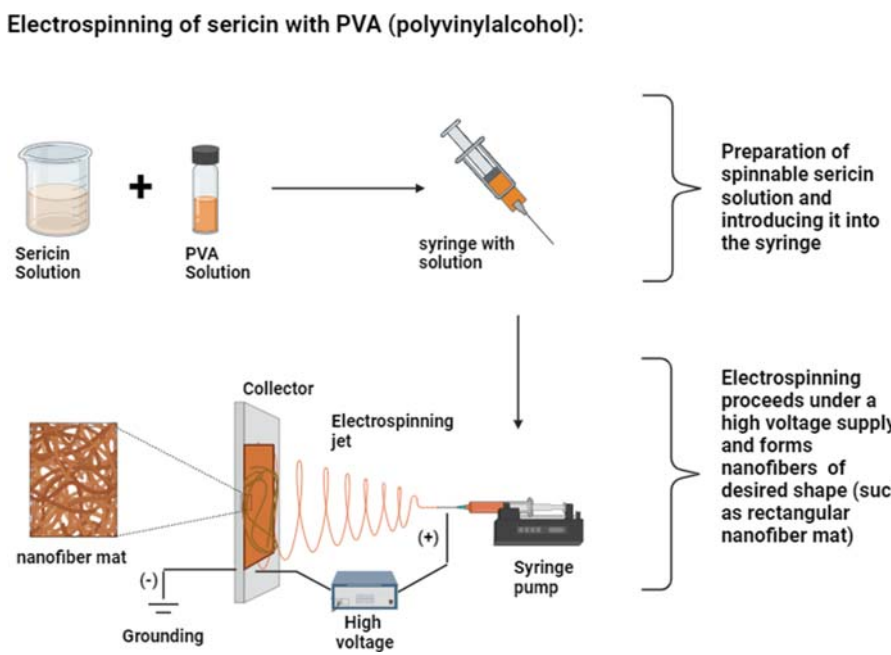


Figure 3.5 The electrospinning of sericin-PVA solution.

Kelver or spider silk (Bourzac, 2015). More precisely, stretching cause a physical change in the structure and properties of desired sericin forms (films, plates, fibers, etc.) by applying the tensile forces in one direction (uniaxial stretching) as well as in both directions of that material (biaxial stretching) (Chen et al., 2017; Lu et al., 2022). The final steps during stretching result in stiffer and more strengthened silk fibers with lesser weight and better organized insoluble crystalline structure (Fig. 3.6). The physical shear is caused by the shear forces within the globular micelles due to the little hydrophobic interactions in its structure (Keten et al., 2010; Zhou et al., 2000). It enhances the mechanical strength of a polymer by aligning the sericin molecules and improving the porosity and elasticity. However, the risk of structural damage is very high, like the possibility of the uncontrolled rate of stretching at the different aspects. The directional stretching induces the anisotropic properties to the materials, which allow the designation of these polymers to a specific functionality rather than the multiple aspects.

4. Chemical methods

The presence of 18 cationic, anionic, polar, nonpolar, and aromatic amino acids, engrossed the scientists toward the chemical modifications of sericin to improve its applications (Veiga et al., 2020). Mostly, the food industries are taking a variety of

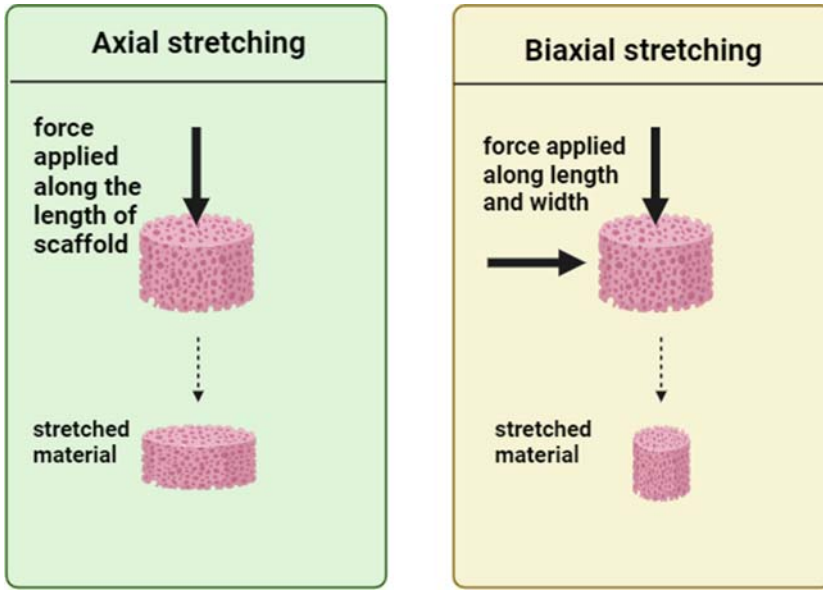


Figure 3.6 The difference between axial and biaxial stretching of sericin material.

advantages from the chemically modified properties of sericin. The low-molecular-weight sericin (<20 kDa) is mainly important for medication purposes, cosmetic industries, health sciences, and the production of various biomaterials; meanwhile, the high-molecular-weight sericin (>20 kDa) is usually used in the formation of advanced biomaterials such as membranes, hydrogels, and huge composites.

During chemical modification, sericin allows the formation of covalent or noncovalent bonds due to the presence of many hydroxyls (-OH) amino groups or carbonyl groups in its structure. This not only overcomes the sericin's natural limitations (weaker solubility and potential) but also enhances its functionalities. There are highly reactive groups on the SS such as hydroxyl (-OH), carboxyl (-CO), amino ($-NH_3$), and the double bonds, which make it more amenable to various chemical alterations (Hu et al., 2023; Liu et al., 2022). The hydroxyl and carbonyl groups are the polar chemical groups that allow for the formation of copolymers, crosslinks, and various blends with different polymers (Das et al., 2021; Seo et al., 2023b). These reactive groups when reacts with acetyl ($-CH_3CHO$), alkyl ($-CH_2-CH_3$), phosphate ($-PO_4$), sugars or methacrylate ($C_4H_5O_2$) groups, the hydrophobicity, biocompatibility, biodegradability, and other efficacies in sericin multiplies at some extent (Hu et al., 2023).

4.1 Acylation/acetylation

Acylation is the introduction of acyl (-RCO) or acetyl ($-CH_3CO$) groups in the hydroxyl (-OH) groups at the side chain in silk sericin to improve its hydrophobicity, stability, resilience, and biodegradability (Ogino et al., 2006; Yan et al., 2021). However, these

modifications to the protein structure may introduce cytotoxicity and compromise the inherently biocompatible nature of sericin. A study shows that acetylated sericin has improved emulsifying properties by surpassing the salty environment (0.5M NaCl), thus ensuring a higher solubility extent compared to those of original form sericin (Ogino et al., 2006).

4.2 Glycosylation

Glycosylation, also known as Millard reaction, is the chemical attachment of sugar molecules (saccharides) with the side chain amino (-NH_2) groups in the sericin (Fig. 3.7). It is a recent advancement in food industries (Gerrard et al., 2003), which can alter the protein nature, as well as its texture by renewing its functionalities (Wang & Zhang, 2023). The limited solubility and pupal odor of natural sericin can be overcome by the introduction of sugars into it. Regardless of the type of sugar added, it has been observed by Zhao's team that the solubility is enhanced by 2−3 times, and the antioxidant capacity is increased by 3.5−5.5 times as compared to the original sericin (Zhao et al., 2018). Despite these profound facts, glycosylation is still a complex and expensive process that utilizes the expertise and proper optimization of this process for successful gains or applications.

4.3 Crosslinking

It is a process of formation of covalent bonds between the individual sericin molecules to multiply their durability, elasticity, stability, and biodegradability (Das et al., 2021). Chemical agents like glutaraldehyde, carbodiimides, and other chemicals like epichlorohydrin or genipin are the most common inducers of cross-linking in the silk sericin

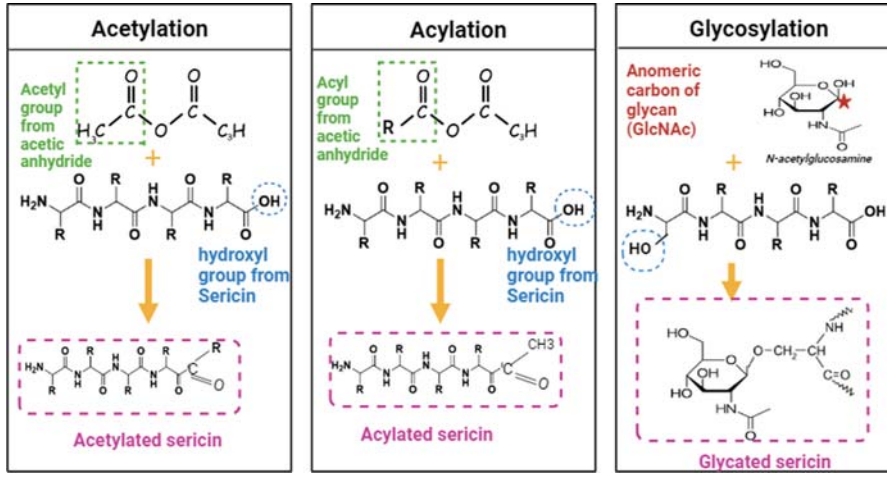


Figure 3.7 The illustration shows the formation of acetylated, acylated, and glycosylated sericin by different types of reactions.

(Freitas et al., 2021). It strengthens the sericin network by enhancing the tear resistance, rigidity, and modulus of the natural sericin. Besides all this, crosslinking can limit flexibility and enhance potential cytotoxicity by altering the protein's texture and introducing the reactive groups in the polymer (Khalifa et al., 2017).

5. Enzymatic modifications

With the addition of enzymes, the sericin is chemically modified in a controlled and definite way. For a safer and milder modification process, the enzymatic crosslinking is a gentler approach as compared to the chemical cross-linkers (Hu et al., 2023). Specific enzymes act on their respective sites in the sericin molecules, thus aiding in the physical crosslinking process like transglutaminase catalyzes the covalent bond formation as well as in the chemical reactions like hydrolysis, deamination, oxidation, etc. (Guo et al., 2020a). Other commonly used enzymes are tyrosinase (Anghileri et al., 2007), laccase, and horseradish peroxidase (HRP).

5.1 Enzymatic hydrolysis

The breakdown of sericin molecules into smaller pieces (peptides), by the use of water molecules as a shear which cleaves the linkage between the sericin molecules with the help of enzymes. The enzymes like proteases (trypsin, papain, or alcalase) are widely used in this method. The peptides as a result of this modification now retain higher solubility and biocompatibility.

5.2 Enzymatic polymerization

A fascinating technique of linking sericin molecules together (making polymers of proteins) by connecting the specific amino acids via even stronger covalent bonds with the help of enzymes is called enzymatic polymerization. The specific enzyme called Transglutaminase (TGase) is responsible for the cross-linking of the specialized amino acids (lysine and glutamine) in the sericin side chains (Cui et al., 2017). It imparts higher formability and biocompatibility to the sericin (Guo et al., 2020b).

5.3 Enzymatic oxidation

Enzymes like laccase, HRP, or tyrosinase are used to introduce the oxygen molecules from water into the sericin molecule, and this process is termed as enzymatic oxidation of sericin (Guo et al., 2020a). The involvement of oxygen atoms can create new functional groups such as carbonyls, carboxyls, or quinolines and alter the overall chemical nature of the molecule. It achieves the same results as the chemical methods but without any danger or harm. Imagine modifying SS without the danger of harsh chemicals (Zhang et al., 2018). Biocatalysis makes it possible, creating a safer and more sustainable process. Thus, it is the most accepted method to modify the SS.

6. Silk sericin–based materials

By itself, silk sericin is blessed with enormous qualities, but its real potential shines by the various modifications. Following are the notable examples of SS-based materials with their potential applications in various fields of life.

6.1 Fibers and scaffolds

Fibers are thread-like, thin structures that are formed by techniques like electrospinning. Sericin in this form provides higher flexibility and durability. In tissue engineering, these fibers enhance cell attachment and migration, which aids in the effective drug delivery systems with a controlled release of therapeutic agents to a specific target. The ultrathin nanofibers are designed to mimic the natural tissues, which prove its higher biocompatibility. They are used as scaffolds for tissue regeneration like bone, tendons, nerves, and cartilage. The three-dimensional structures with desired porosity are the scaffolds of modified sericin, which mimics the extracellular matrix (ECM) in the living tissues.

6.2 Films and hydrogels

When sericin and water mixture is formed into a viscous solution under controlled parameters, it is then cast onto a flat surface to form thin films and membranes. Different crosslinking techniques (physical, chemical, or enzymatic) can further improve the stability and strength of the materials. By forming films and membranes, the sericin's natural abilities multiply and these properties unlock a world of possibilities in various fields like biomedical and pharmaceutical applications such as the formation of wound healing dressings, food packaging, tissue engineering scaffolds, and medicinal electronics, and the encapsulation of drugs and medicines.

6.3 Biosensors and bioelectronics

The sericin-based biosensors are sensitive to the detection of biomarkers for different diseases in medicinal diagnostics. These degradable and sustainable sensors have a long operational life span. These bioelectronics are also known as green electronics (which are responsible for the reduction of environmental wastes) (Irimia-Vladu, 2014; Xu et al., 2019).

6.4 Nanoparticles

Sericin-based nanoparticles are altered to attach specialized molecules like drugs, imaging agents, and different cell moieties, in tissue engineering they are responsible for the targeted delivery of drugs to the specific sites on the living cells.

6.5 Composites

Composites are mixtures of two different materials that show macroscopic homogeneity but are heterogeneous at the microscopic scale (Sharma, 2021). The modified sericin is mixed with other materials to create composites of diverse functionalities that have potential applications in various fields of life. For example, Choa's research team has developed sericin\graphene oxide composite materials that effectively guide stem cells toward bone regeneration (Qi et al., 2020).

6.6 Cosmetics

Sericin is a silk-driven protein that is well known for its moisture-retaining and anti-inflammatory properties, which make it a demanding material for its use in cosmetics such as hair care, skincare, and nail care (Saha et al., 2019). It not only induces the hydrating power of moisturizers but is also an organic replacement for harsh chemical antiaging creams. It promotes the skin elasticity and gives it a fine appearance.

7. Challenges and future directions

The high production cost of sericin is a significant challenge for scientists, which can limit its potential applications and hinder the real prospects of sericin. Despite the presence of modification techniques, many sides of sericin are still discoverable. There is a need to conduct advanced in-vivo evaluations to understand the precise behavior and immunological responses of sericin-based biomaterials.

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Sericin-based nanospheres and other nanoformulations for various applications

4

Lei Zhang
Department of Chemical Engineering, Waterloo Institute for Nanotechnology, University of Waterloo, Waterloo, ON, Canada

1. Introduction

Natural silk primarily consists of two proteins: silk fibroin (SF), making up about 65−85%, and silk sericin (SS), accounting for 15−30% (Sahoo et al., 2023; Yang et al., 2023). The structure of natural silk features a core of two SF filaments encased in SS, which closely surrounds SF, providing protection and adhesion (Hu et al., 2018). The distinct amino acid compositions and molecular weights of SF and SS contribute to their unique physicochemical and biological characteristics (Lamboni et al., 2015). SF is renowned for its exceptional mechanical strength, biocompatibility, and biodegradability, making it a popular choice in biomedical applications (Hu et al., 2023; Jia Liu et al., 2022; Sahoo et al., 2023; Yang et al., 2023). Historically, SS was overlooked due to its inferior mechanical properties and potential allergenic effects (Park et al., 2018). However, advancements in modification techniques and a better understanding of its biosafety have brought to light SS's unique biological functions, such as antioxidant properties, pH responsiveness, and biocompatibility, garnering global research interest (Hu et al., 2023; Xu et al., 2022; Das et al., 2021).

SS is recognized for its biocompatibility, biodegradability, and nutritional value, finding applications in food additives and packaging. Its standout features include FDA approval and superior initial physicochemical and biological properties compared to other proteins or protein derivatives (Das et al., 2021). SS-based biomaterials can be easily synthesized through methods like cross-linking, copolymerization, and blending with other polymers. These materials exhibit specialized functions such as targeting, pH sensitivity, and photoluminescence, making SS a versatile component for various applications (Hu et al., 2023; Jia Liu et al., 2022; Sahoo et al., 2023; Yang et al., 2023). This study thoroughly examines the characteristics, functionalities, and applications of SS, see Table 4.1, especially in food additives, packaging, biomedical imaging, drug delivery, wound healing, and more, highlighting its potential in developing new biomaterials for various sectors, including cosmetics, 3D cell culture matrices, corneal repair, bone disease treatment, and even electronic devices, thereby providing a comprehensive overview of SS's versatility and its emerging role in advancing material science.

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Table 4.1 A summary of the biomedical applications of SS-based biomaterials.

Biomedical applications		Source of silk	Forms	Research stage	References
Monitoring		–	Hydrogel	In vivo	Jiang et al. (2021)
		Bombyx mori, *Baiyu*	Hydrogel	In vivo	Liu et al. (2016)
		Bombyx mori, 140 Nd-s	Hydrogel	In vivo	Qi et al. (2018)
		Bombyx mori, 185 Nd-s	Hydrogel scaffold	In vivo	Chen et al. (2018)
Drug delivery	Small molecule compounds	*Bombyx mori*, *Baiyu*	Nanoparticle	In vivo	Huang et al. (2016)
		–	Nanoparticle	In vivo	Hu et al. (2018)
		The rhLF transgenic silkworm strain (D9L-rhLF)	Nanosphere	In vivo	Xu et al. (2022)
		–	Nanoparticle	In vitro	Suktham et al. (2018)
		–	Nanoparticle	In vitro	Zhu et al. (2022)
		Bombyx mori, *Baiyu*	Hydrogel	In vivo	Liu et al. (2016)
		–	Hydrogel	In vitro	Al-Tabakha et al. (2021)
		Bombyx mori, 185 Nd-s	Hydrogel	In vivo	Zhang et al. (2015)
		–	Hydrogel	In vitro	Yan et al. (2021)
		J108 strain	Hydrogel	In vitro	Kanpipit et al. (2022)
	SiRNA	–	Nanoparticle	In vitro	Yalcin et al. (2019)
		Bombyx mori	Nanoparticle	In vivo	Kara et al. (2021)
		–	Hydrogel	In vivo	Kanazawa et al. (2015)
	Functional protein/ peptide	*Antheraea mylitta*	Hydrogel	In vivo	Sapru et al. (2021)
		Bombyx mori, 140 Nd-s	Hydrogel	In vivo	Wang et al. (2015)
		Bombyx mori	Film	In vivo	Nishida et al. (2011)

Skin wound healing	–	Hydrogel	In vivo	Tao et al. (2019)
	Bombyx mori, 140 Nd-s	Hydrogel	In vitro	Zhang et al. (2020)
	–	Hydrogel	In vivo	Tao et al. (2021)
	–	Film	In vitro	He et al. (2017)
	–	Film	In vivo	Shah et al. (2019)
	–	Nanogel	In vivo	Zhang et al. (2023)
	Silkworm cocoons, 140 Nd-s	Microneedle	In vivo	Deng et al. (2022)
Others	*Silkworm cocoons, 140 Nd-s*	Scaffold	In vivo	Qi et al. (2020/2020)
	–	Scaffold	In vitro	Dinescu et al. (2013)
	Bombyx mori	Scaffold	In vivo	Chachlioutaki et al. (2022)

2. SS-based biomaterials

2.1 Extraction and biological activity of SS

Silk sericin, a vital silk protein component, is derived primarily from *Bombyx mori* and *Antheraea mylitta* silkworms, making up 15%−35% of silk's total mass (Suryawanshi et al., 2020). SS extraction from cocoons has evolved to include various methods (Fig. 6.1) like high-temperature baths and ultrasonic degumming, which maintain the integrity of SF while efficiently separating SS (Saad et al., 2023). Chemical treatments, such as the sodium carbonate method, have improved SS yield significantly, albeit with potential alterations to its structure. Innovations in degumming, like using less salt and water or incorporating eco-friendly ionic liquids, have made the process more sustainable. Biological approaches using specific proteases offer an environmentally benign alternative, effectively breaking down SS into small peptides (Bascou et al., 2022; Yang et al., 2023).

SS's antioxidant properties (Fig. 6.1), highlighted by its ability to inhibit lipid peroxidation and tyrosinase activity, are linked to its amino acid composition, particularly serine and threonine. These amino acids, along with SS's polyphenol and flavonoid content, contribute to its antioxidant capability (Lei Zhang et al., 2023; Yang et al., 2023). SS's pH-responsive nature, changing its charge based on the pH level, allows for novel biomaterial applications, including drug delivery systems that enhance cellular uptake (Hu et al., 2017; Xu et al., 2022). Its rich content of hydrophilic amino acids also enhances SS's water solubility, further broadening its application in biomaterials (Zhang et al., 2023).

Beyond its chemical properties, SS promotes cell proliferation (Lamboni et al., 2015), aids in wound healing (Zhang et al., 2023), and could serve as a substitute for bovine serum in cell culture media, attributed to its molecular structure rich in functional groups that can reduce oxidative stress and support early cell adhesion (Sasaki et al., 2005). The versatility of SS, from its role in biomedical applications to its potential in developing novel biomaterials, underscores its growing importance in scientific research and industrial applications (Saad et al., 2023; Sahoo et al., 2023).

2.2 Classification and fabrication of SS-based biomaterials

Various SS-based biomaterials (Fig. 6.1), such as nanoparticles, hydrogels, membranes, and microneedles, (MNs) have been developed. The desolvation method, known for its mildness and ease of implementation, is predominantly used to create protein-based nanoparticles (Tarhini et al., 2017). This process dehydrates the protein, altering its structure from stretched to coiled by adding a desolvating agent like alcohol or acetone to the protein solution while stirring (Elzoghby et al., 2015). To enhance the density and stability of the nanoparticles, SS's amino groups are cross-linked (Das et al., 2021). For instance, SS nanoparticles have been effectively produced using ethanol desolvation at room temperature and stabilized with glutaraldehyde, allowing them to remain stable for 5 days at 4°C with a diameter of around 120 nm and a zeta potential of 25.6 mV (Das et al., 2014). SS nanoparticles crosslinked with genipin have

been developed for biomedical uses, demonstrating high encapsulation efficiency and controlled release properties for drugs like atorvastatin (Kanoujia et al., 2016).

When protein levels surpass the critical micelle concentration (CMC), they naturally form nano-sized aggregates through self-assembly (Tarhini et al., 2017). The addition of other molecules can lower the CMC, facilitating the formation of protein nanocomposites. By reacting SS with activated polyethylene glycol (PEG), self-assembled SS nanoparticles are produced, transitioning SS's structure from a random coil to a beta-sheet configuration (Cho et al., 2003). This structural change, driven primarily by hydrophobic forces, enables the creation of versatile nanoparticles. Mandal and colleagues developed SS/poloxamer nanoparticles capable of carrying both hydrophobic (FITC-inulin) and hydrophilic (paclitaxel) drugs (Mandal & Kundu, 2009). These nanoparticles demonstrated enhanced effectiveness against paclitaxel alone in vitro and triggered apoptosis in MCF-7 cancer cells, showcasing their potential to deliver a range of therapeutic agents to specific sites.

Designing and preparing SS-based biomaterials like hydrogels, scaffolds, and films is straightforward due to SS's abundance of polar groups, which facilitate cross-linking (Takasu et al., 2007). Glutaraldehyde, a common cross-linker, is often used to form protein networks by connecting free amino groups (Elzoghby et al., 2015). For instance, Wang and colleagues created a hydrogel by blending SS with sodium alginate in varying ratios, using glutaraldehyde and calcium ions as cross-linkers (Das et al., 2021; Zhang et al., 2015). However, due to concerns about glutaraldehyde's toxicity, researchers have explored natural cross-linking agents (Das et al., 2021; Jain et al., 2018). Zhang et al. employed genipin to produce a highly hydrophilic hydrogel with adjustable properties such as pore size and adhesion by altering the genipin-to-SS ratio.

SS scaffolds represent another versatile application, produced through 3D printing techniques that combine SS with methacrylated gelatin (GelMA) (Chen et al., 2018). This combination, confirmed by FTIR analysis, allows the scaffold to become transparent in PBS, facilitating under-scaffold visibility and enabling real-time wound monitoring.

Additionally, SS can form transparent films without needing a cross-linking agent, with their mechanical properties tunable through solvent modification or material blending (Jang & Um, 2017; Teramoto et al., 2008). SS-based MNs are crafted by casting SS solutions into PDMS molds, followed by reinforcing with a PVA base layer (Deng et al., 2022). Deng and team developed SS MNs with antibacterial qualities for treating infected wounds, showcasing their utility in piercing the skin's outer layer and administering therapeutic substances.

3. SS-based biomaterials for cosmetics applications

Silk sericin—based biomaterials have emerged as a revolutionary component in the cosmetics industry, leveraging their intrinsic hydrating, antioxidant, and biocompatible qualities. Recent studies have highlighted SS's efficacy in enhancing skin

moisture and elasticity, making it a potent ingredient in antiaging skincare products (Kitisin et al., 2013; Padamwar et al., 2005). Its antioxidant properties offer a protective shield against environmental aggressors, establishing SS as a crucial element in formulations aimed at skin defense, such as sunscreens and antipollution serums (Aramwit et al., 2012; Orlandi et al., 2020).

Furthermore, the unique film-forming capability of SS ensures effective hydration for hair without residue, contributing to improved hair texture and shine, as evidenced in contemporary hair care solutions (Cao & Zhang, 2016). The gentle nature of SS aligns with the needs of sensitive skin, minimizing irritation and promoting soothing effects, thus widening its applicability in dermatological care (Cao & Zhang, 2016).

Innovative applications of SS in bioactive cosmetic patches and transdermal films have been explored, enabling targeted delivery of active compounds to the skin, enhancing the performance of cosmetic treatments (Zhang et al., 2023). The adaptability of SS with various formulating agents allows for diverse cosmetic textures, from lightweight hydrating gels to rich, emollient creams, catering to a broad spectrum of consumer preferences.

The advancements in SS-based biomaterials underscore the shift toward sustainable, effective, and science-backed ingredients in cosmetics. The integration of SS in future formulations is anticipated to redefine skincare and beauty regimens, emphasizing natural-origin ingredients and multifunctional benefits for holistic skin health and aesthetics.

4. SS-based biomaterials for food additives and food packaging

The excellent safety profile, biocompatibility, oxidation resistance, and ease of degradation make SS a promising additive for food applications (Barajas-Gamboa et al., 2016/2016). Its inclusion in the U.S. Food and Drug Administration's Generally Recognized As Safe (GRAS) list highlights its potential for enhancing the bioavailability of essential minerals such as zinc, iron, magnesium, and calcium without altering their serum concentrations (Ghosh et al., 2017; Sasaki et al., 2000). This could be attributed to the improved solubility of these minerals due to the chelating capabilities of SS's polar groups. Additionally, dietary SS may contribute to atherosclerosis prevention by managing triglyceride levels and low-density lipoprotein (VLDL) in the bloodstream (Ghosh et al., 2017; Kato & Iwami, 2002).

Although the health benefits of SS are well-documented, its application in food products is still largely experimental (Takechi & Takamura, 2014). Research by Takechi et al. explored incorporating SS into bread to investigate its effects on the food's color, texture, and palatability, with findings suggesting a preference for bread containing SS (Dong et al., 2020; Ghosh et al., 2017). This points to SS's potential in enhancing food products, aiding in digestion and absorption. Similarly, its addition to salad dressings has been studied for its emulsifying and antioxidant properties,

indicating its utility in maintaining emulsion stability and preventing lipid oxidation (Takechi et al., 2011). However, the application of SS in food is contingent upon the degumming methods used, as traditional methods involving sodium carbonate can introduce unwanted byproducts and excessive salt, rendering SS unsuitable for food use (Rani et al., 2018; Wang & Zhang, 2017; Yakul et al., 2021).

In packaging, SS shows promise as a biodegradable and safe material for creating protein-based films and coatings (Seo et al., 2021/2021). Enhancements to SS films through the addition of polymers like nanocellulose have been observed to improve their mechanical properties, with the potential to also enhance antioxidant, antibacterial, and UV-shielding properties (Kwak et al., 2018). The Maillard reaction, involving glucose and SS, has been utilized to create films with improved moisture resistance, oxidation resistance, and UV protection, making them suitable for food packaging applications (Oh et al., 2021). Composite films incorporating SS, chitosan, and carbon dots have shown improved flexibility, antimicrobial, and antioxidant properties, with the added benefit of potential use as anticounterfeiting labels due to the fluorescent properties of carbon dots (Mei et al., 2022).

Furthermore, SS coatings have demonstrated protective effects in food packaging, such as inhibiting browning in cut fruits and enhancing the viability of probiotic cells in freeze-dried microcapsules, thereby protecting them during digestion (Apiwattanasiri et al., 2022; Chimvaree et al., 2019). This underscores the diverse potential of SS in food technology, from enhancing food products to innovative packaging solutions that safeguard food quality and extend shelf life.

5. SS-based biomaterials for in vitro/vivo monitoring

Leveraging the transparency and inherent fluorescence of SS, SS-based biomaterials have emerged as powerful tools for both in vitro and in vivo monitoring applications (Table 4.1). Beyond their role in wound dressing, these biomaterials are now being explored for their potential as injectable therapeutic agents. Jiang et al. (2021) developed an injectable hydrogel composed of alginate, sericin, and graphene oxide (Alg/Ser/GO), which has shown promise in promoting macrophage M2 polarization and enhancing bone regeneration. Similarly, Song et al. (Song et al., 2016) formulated injectable SS hydrogels aimed at cardiac tissue engineering, demonstrating their ability to mitigate inflammation, reduce apoptosis, and improve cardiac function in a mouse model of myocardial infarction, with a noted increase in microvessel density in the affected hearts.

The unique in situ fluorescence of SS enables real-time, noninvasive tracking within the body, offering new perspectives in monitoring the release and degradation of drugs in vivo. Liu et al. (Liu et al., 2016) synthesized a sericin/dextran hydrogel through hydrazone crosslinking, which not only exhibits excellent biocompatibility and biodegradability but also retains the photoluminescent properties of SS, showing fluorescence under specific light excitation wavelengths, see Fig. 4.1a–c.

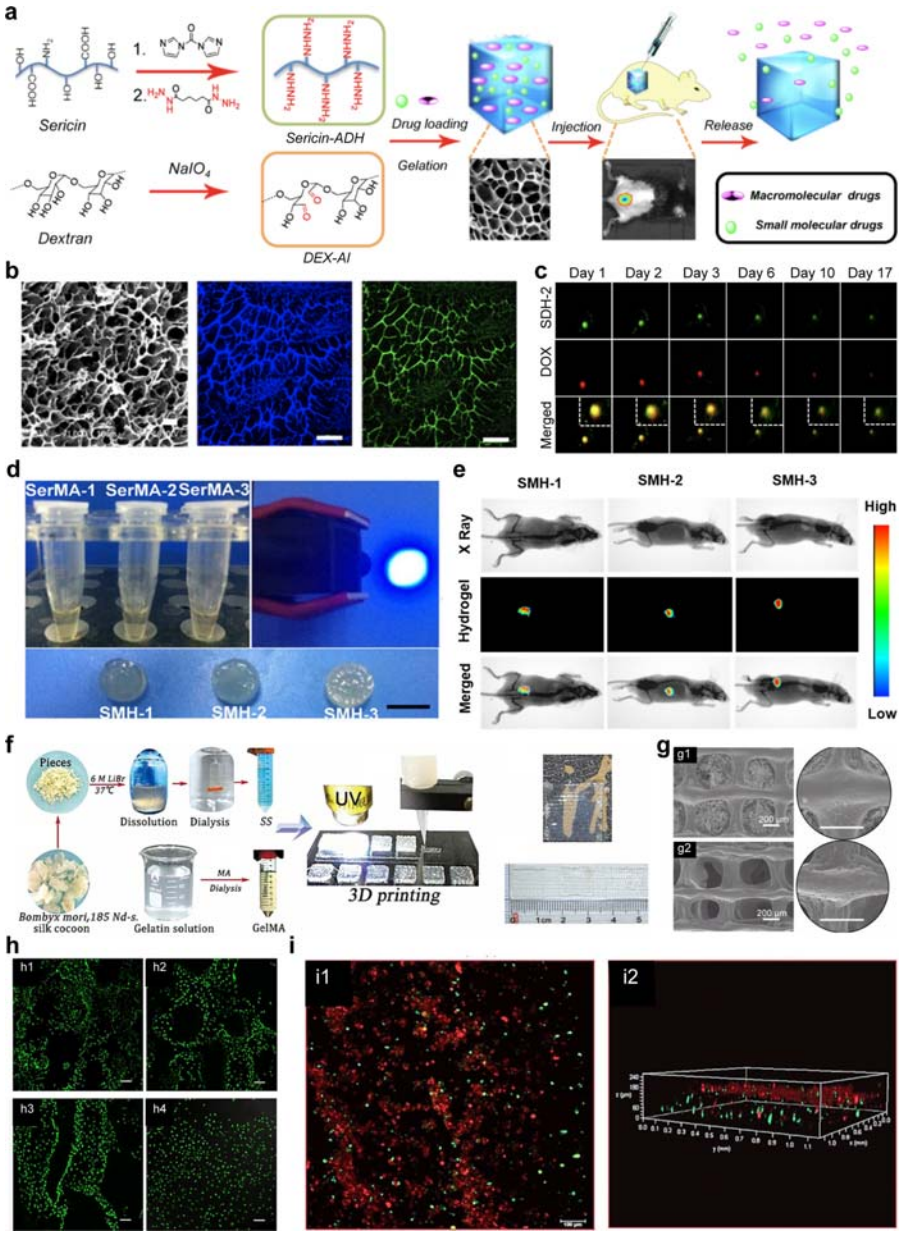


Figure 4.1 (a) Schematic of synthesis of sericin/dextran crosslinked hydrogel (SDH) and utilization of this hydrogel for an injectable and photoluminescence-trackable drug delivery. (b) Scanning electron micrographs of SDH, scale bar = 10 μm. Photoluminescent property of SDH under light with the excitation wavelength of 405 and 488 nm, scale bar = 100 μm. (c) Images of SDH loaded with DOX were measured using a small animal imaging device. The images outlined by white dotted lines in the upper right corner are the enlargement of the merged images. (a−c) Reproduced with permission from reference (Liu et al., 2016). Copyright 2016, American Chemical Society. (d) Gelation of SMHs upon UV light irradiation at

Expanding the utility of SS in tissue engineering, Qi et al. (2018) developed a photo-cross-linkable sericin hydrogel designed for minimally invasive cartilage repair, mimicking the extracellular matrix. By introducing methacrylate groups to sericin, they achieved a hydrogel that solidifies under UV light exposure, with its porosity and mechanical properties adjustable to fit various applications, as depicted in Figs. 6.2d and e. This hydrogel, characterized by its fluorescence, enables in vivo visualization and real-time monitoring of its degradation and the formation of artificial cartilage.

In the realm of wound care, Chen et al. (2018) created an SS scaffold using 3D printing, combining SS with methacrylic anhydride-modified gelatin (GelMA), for real-time wound monitoring. The scaffold's macro-porous design, visible in SEM images (Fig. 6.2f and g), along with its swelling properties and microporous structure, supports efficient wound healing. Confocal microscopy revealed the proliferation of L929 cells within the scaffold (Fig. 6.2h), and coculture experiments with HSF and HaCaT cells demonstrated the scaffold's ability to support rapid cellular proliferation, as shown in Fig. 6.2i. These studies underscore the versatility and potential of SS-based biomaterials in medical and therapeutic applications, leveraging their biocompatibility, biodegradability, and unique optical properties for innovative solutions in tissue engineering and drug delivery systems.

6. SS-based biomaterials for drug delivery

The advancements in drug delivery systems are pivotal for enhancing the efficacy of therapeutic agents by ensuring targeted delivery, optimal cell membrane penetration, and effective endosomal escape (Lv et al., 2021; Yu Song et al., 2022; Zhang, Xu, et al., 2019; Zhang, Sheng, et al., 2019). SS-based biomaterials have emerged as promising carriers in this domain, owing to their biocompatibility and versatility. The applications of SS in drug delivery are diverse, encompassing carriers for small molecule drugs, small-interfering RNA (siRNA), and functional proteins or peptides. This classification underscores the adaptability of SS biomaterials in addressing various therapeutic needs and their potential in facilitating precision medicine (Table 4.1). For more

365 nm, scale bar = 1 cm. (e) Photoluminescent property of SMH in vivo. (d–e) Reproduced with permission from reference (Qi et al., 2018). Copyright 2018, Elsevier. (f) Schematic of fabrication of SS/GelMA scaffolds via 3D printing. (g) SEM images for SS/GelMA scaffolds. Surface morphology of (g1) SS/GelMA 0.5 scaffold and (g2) SS/GelMA0.33 scaffold. (h) Live–dead staining for L929 cells on different matrices at day 7, h1: SS/GelMA 0.5, h2: SS/GelMA 0.33, h3: 20%GelMA, h4: B-SS/GelMA 0.33. (i) (i1) Photographs and (i2) three-dimensional screenshot of bilayer co-culture model. Green plots represent the HSF cells, and red plots represent the HaCaT cells. (f–i) Reproduced with permission from reference (Chen et al., 2018). Copyright 2018, American Chemical Society.

detailed insights into these applications and the mechanisms by which SS-based systems enhance drug delivery, exploring specific studies and reviews in this field can provide a comprehensive understanding.

6.1 SS-based biomaterials for small-molecule drugs delivery

The clinical effectiveness of small-molecule drugs can be hindered by issues such as instability, poor solubility, and the absence of targeted delivery mechanisms (Xiao et al., 2022; Zhang, Xu, et al., 2019). Advances in nanotechnology, including the use of micelles, nanoparticles, and dendrimers, have emerged as promising strategies for enhancing targeted drug delivery (Xiao et al., 2022; Zhang, Xu, et al., 2019). For instance, anthocyanin, a natural pigment known for its biological activities, faces stability challenges and is sensitive to environmental conditions (Li et al., 2021; Yao, Xu, Zhang, Liu, & Zhang, 2021; Yao, Xu, Zhang, Zheng, et al., 2021). A sericin nanogel incorporating anthocyanin has been developed, demonstrating the nanogel's capability to stabilize anthocyanin and prolong its release, while maintaining stability under varying temperatures (Zhang et al., 2023).

Despite the potential of nanoparticles in drug delivery systems, they are prone to aggregation and thermodynamic instability (Xiao et al., 2022; Zhang, Xu, et al., 2019). To counteract this, nanoparticles are often modified or coated with agents like SS, which offers abundant side-chain groups such as hydroxyl, carboxyl, and amino groups, enhancing the stabilization and modification of nanoparticles (Wang et al., 2013). SS-modified nanoparticles can encapsulate hydrophilic drugs, providing them with targeted and pH-responsive delivery capabilities. Huang et al. introduced a sericin−DOX nanoparticle, see Fig. 4.2a, showcasing its effective release in acidic conditions due to pH-sensitive bonds between SS and DOX, and targeted delivery facilitated by folic acid linkage (Huang et al., 2016). This innovative approach was further illustrated through confocal microscopy (Fig. 6.3b). Moreover, SS's pH-responsive nature has been leveraged to create SS nanoparticles modified with chitosan (CS), which exhibits a charge change in acidic tumor environments, enhancing cancer cell uptake. This strategy effectively reduces the biodistribution of drugs in nontarget areas, minimizing side effects (Hu et al., 2018).

SS nanoparticles have demonstrated their efficacy in delivering therapeutic molecules like resveratrol (RSV), known for its antioxidant and antiinflammatory properties but plagued by poor solubility (Suktham et al., 2018). The encapsulation of RSV in SS nanoparticles has shown stability over 4 months, with a significant inhibitory effect on Caco-2 cell growth in vitro. Curcumin (Cur), another phytochemical with therapeutic potential, was encapsulated in zein-SS (ZHS) nanoparticles, showing enhanced stability and dermal penetration, thus offering potential for antidermatitis applications with minimal side effects (Zhu et al., 2022). The unique core−shell structure of ZHS nanoparticles facilitates the release of Cur upon dermal penetration, improving its bioavailability and therapeutic efficacy (Fig. 6.3c).

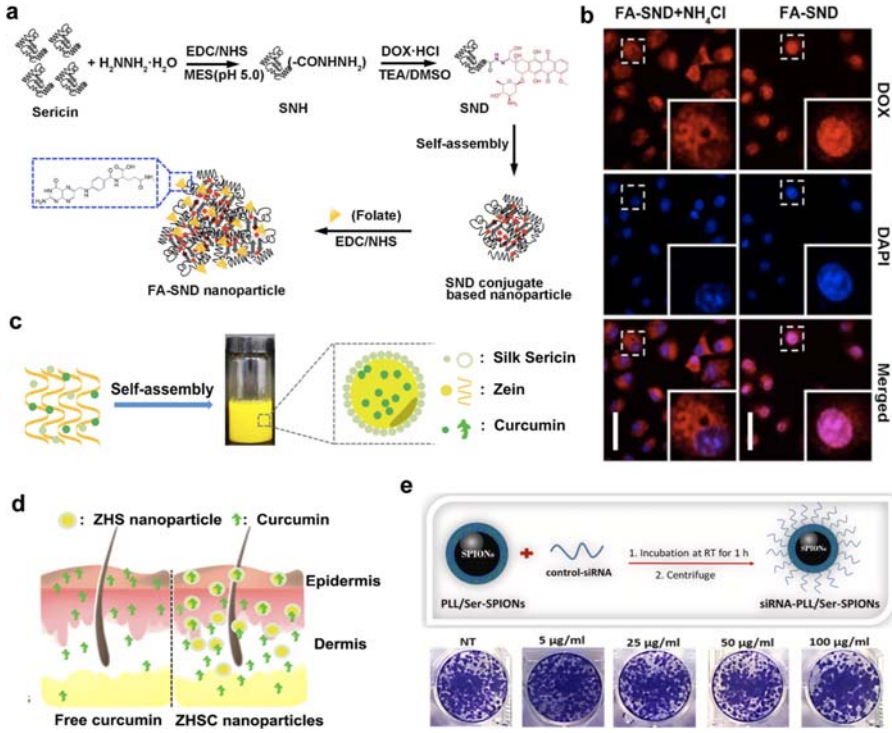


Figure 4.2 Schematic of (a) fabrication of FA-SND (folate-conjugated sericin covalently linked with DOX, FA-SND) nanoparticles and (b) Confocal images of pH-responsive drug release behavior of FA-SND nanoparticles at a cellular level, scare bar is = 50 μm. (a−b) Reproduced with permission from reference (Huang et al., 2016). Copyright 2016, American Chemical Society. (c) Preparation of ZHSCs (zein−SS composite nanoparticles loaded with curcumin) assembly. (d) Possible mechanism of ZHSCs penetrating the skin. (c−d) Reproduced with permission from reference (Zhu et al., 2022). Copyright 2022, Elsevier. (e) Preparation of siRNA-loaded PLL/Ser-SPIONs. Effect of PLL/Ser-SPIONs at various concentrations on the clonogenicity of TNBC cells MDA-MB-231. (e) Reproduced with permission from reference (Kara et al., 2021). Copyright 2021, Elsevier.

Beyond nanoparticles, SS-based hydrogels have been utilized for the efficient loading and release of both macromolecular and small molecular drugs, showcasing superior tumor growth inhibition in cases where DOX was incorporated (Liu et al., 2016). The sustained release of DOX from SS hydrogels resulted in increased apoptosis in tumor tissues, highlighting the potential of SS hydrogels in cancer therapy. Acyclovir, an antiviral drug with limitations like poor water solubility and low bioavailability, has been incorporated into SS hydrogels, demonstrating a pH-responsive release that aligns with the swelling behavior of the hydrogel (Al-Tabakha et al., 2021; Bhandare et al., 2020).

At high pH levels, the carboxylic groups in SS undergo deprotonation, leading to a negative charge on the COO− groups. Conversely, when the pH is lowered, these groups can become protonated. This interplay between protonation and deprotonation in response to pH changes affects the electrostatic interactions within the hydrogel matrix, causing it to swell as the negatively charged COO− groups repel each other in the presence of OH− ions from the surrounding medium (Hu, 2011). This pH-responsive behavior is a key feature of SS-based hydrogels, enabling them to adjust their swelling degree and, consequently, control the release of encapsulated agents in a pH-dependent manner. This pH-responsive mechanism facilitates the targeted release of acyclovir, enhancing its therapeutic potential. Furthermore, the sustained release capabilities of SS hydrogels have been proven with other model drugs, indicating the versatility and potential of SS-based materials in drug delivery applications (Yan et al., 2021; Zhang et al., 2015).

6.2 SS-based biomaterials for small-interfering RNA delivery

Small-interfering RNA (siRNA) holds great promise for therapeutic interventions but faces challenges in delivery due to the need for safe and efficient carriers. Nanoparticle-based delivery systems, particularly those modified with polylysine (PLL) and incorporated into SS structures, have shown potential in addressing these challenges, especially for targeting liver cancer. The incorporation of hyaluronic acid (HA) into these nanoparticles has enhanced siRNA-binding efficiency significantly. Furthermore, the integration of SS into these delivery systems has been noted to improve the pH-dependent stability of the nanoparticles, facilitating effective gene knockdown in targeted cells such as Hep-2 (Kataki et al., 2015; Zhang et al., 2018; Zhang, Sheng, et al., 2019; Yalcin et al., 2019).

Additionally, SS has been employed as a protective coating for other nanoparticle types, such as superparamagnetic iron oxide nanoparticles (SPIONs), to mitigate their inherent toxicity while preserving their superparamagnetic properties. The SS coating on SPIONs, modified with PLL (Fig. 6.3e), has demonstrated high siRNA-binding efficiencies and pH-responsive release, highlighting the potential of SS in enhancing the safety and functionality of siRNA nanocarriers (Fig. 6.3e) (Kara et al., 2021).

Beyond nanoparticles, SS hydrogels have emerged as versatile carriers for siRNA, capable of delivering these therapeutic molecules directly to the site of action. This has been exemplified in studies where siRNA, complexed with cell-penetrating peptides like TAT and junction-opening peptides like AT1002, was encapsulated in SS hydrogels for topical application. Such systems have shown promising results in reducing inflammation and symptoms in dermatitis models, underscoring the synergistic benefits of combining siRNA's silencing effects with the moisturizing, antioxidant, and UV-protective properties of SS hydrogels (Kanazawa et al., 2015; Kim et al., 2013; Wang & Burdick, 2017).

These advancements highlight the multifaceted role of SS in enhancing the delivery and efficacy of siRNA therapies, offering new avenues for the treatment of various diseases.

6.3 SS-based biomaterials for functional protein/peptide delivery

SS-based biomaterials have shown promise in delivering functional proteins and peptides, such as growth factors and neurons, due to their biocompatible and bioactive properties (Kim et al., 2022; Sapru et al., 2021; Wang, Wang, et al., 2022; Wang et al., 2015). A study utilized a combination of SS, CS, and glycosaminoglycans to create a hydrogel that leverages the unique benefits of each component: SS for its antibacterial and antioxidant properties, CS for structural support and antibacterial effects, and glycosaminoglycans as components mimicking the extracellular matrix. This hydrogel was further functionalized with vascular endothelial growth factor and transforming growth factor-β, demonstrating enhanced skin tissue repair and angiogenesis upon transplantation into skin tissues, with notable cell migration and infiltration observed within a week of implantation (Sapru et al., 2021).

Additionally, a genipin-crosslinked SS hydrogel (GSH) with a porous structure was developed to support neuron attachment and growth, showcasing SS's neurotropic and neuroprotective capabilities, including axon extension and hypoxia-induced cell death prevention. This hydrogel's inherent properties could potentially eliminate the need for adding costly cytokines, showing promising in vivo results in terms of cell survival and proliferation (Wang et al., 2015).

Recent advancements have also explored SS films as carriers for controlled release of growth factors. For instance, fibroblast growth factor-2 (FGF-2) was successfully incorporated into SS films, utilizing the ionic interactions between SS's polar side chains and the charged protein drugs. The release rate of FGF-2 from these films was found to be influenced by trypsin concentration, demonstrating a sustained release in trypsin's absence and supporting tissue growth around wounds (Nishida et al., 2011).

These findings highlight the versatility and potential of SS-based biomaterials in regenerative medicine and wound healing applications, offering new avenues for the delivery of therapeutic proteins and peptides.

7. SS-based biomaterials for wound healing

Silk sericin plays a pivotal role in tissue engineering, particularly in promoting wound healing and tissue regeneration. Its utility is evident in the development of hydrogels, which are three-dimensional, hydrophilic networks praised for their optimal dressing characteristics. These include favorable permeability, exceptional biocompatibility,

and the provision of a moist environment conducive to wound repair [13, 83-87]. The inherent hydrophilic and biodegradable qualities of SS, combined with its ease of forming hydrogels either independently or with other polymers, underscore its value in medical and biotechnological applications, fostering advancements in tissue healing processes (Baptista-Silva et al., 2021; Lamboni et al., 2015; Tao et al., 2019; Zhang, Zhao, et al., 2019).

Tao et al. innovated with SS to create a novel hydrogel, termed SA/Se hydrogel, which features injectable and moldable properties enhanced by the addition of silver nanoparticles (AgNPs) to boost its antibacterial activity (Tao et al., 2021). This hydrogel showcased excellent injectability, moldability, and hydrophilicity, supported by its porous structure, leading to significant wound healing acceleration as demonstrated in animal studies (Tao et al., 2021). Zhang et al. contributed to the field by developing a highly transparent SS hydrogel using a sericin−polyacrylamide interpenetrating network. This hydrogel stands out for its clarity and potential as a visual dressing material, which can be further functionalized for a range of clinical applications (Zhang et al., 2020).

SS films are recognized for their utility in dressings for skin conditions and wounds, thanks to their adhesion properties, capability for targeted delivery, prolonged drug release, and enhanced therapeutic effects (Bruneau et al., 2019; Kim et al., 2019; Manesa et al., 2022; Patel et al., 2018; Tran & Tran, 2019). Cai et al. enhanced these films by incorporating polydopamine (PDA)-coated sericin/PVA composites with AgNPs, synthesized in situ. This modification endowed the films with improved hydrophilicity, moisture absorption, and mechanical strength, alongside a significant antibacterial action against Gram-negative and Gram-positive bacteria (Cai et al., 2017). Further extending the versatility of SS films, Shah et al. developed a triple-component nanocomposite film combining CS, AgNPs, and sericin, noted for its antibacterial properties. The incorporation of moxifloxacin HCl (Mox) into the film showed considerable antibacterial activity against various strains and facilitated key healing processes such as fibrosis and collagen reorganization, underscoring the film's potential in wound healing applications (Shah et al., 2019).

Besides the hydrogel, Zhang and colleagues innovatively designed a sericin nanogel for delivering anthocyanin, aimed at enhancing wound healing (Zhang et al., 2023). This approach utilized the bioactive properties of SS to encapsulate anthocyanins, thereby improving their stability and bioactivity. The sericin-based hydrogel formulation demonstrated superior encapsulation efficiency and maintained stability under various conditions such as changes in pH, presence of metals, and temperature fluctuations. Molecular studies suggested that specific amino acids in sericin, particularly phenylalanine and tyrosine, played a crucial role in forming stable nanocomposites with anthocyanins, see Fig. 4.3a. The encapsulated anthocyanins in the nanogel showed an increased ability to scavenge reactive oxygen species (ROS), attributing to the combined antioxidant effects of sericin and anthocyanins. This ROS-scavenging capability was integral to the wound healing process, as it influenced various healing factors like TGF-β, IL-1β, TNF-α, IL-10, and VEGF (Fig. 6.4b−c) (Zhang et al., 2023). The study underscored the synergy between sericin and anthocyanins, both

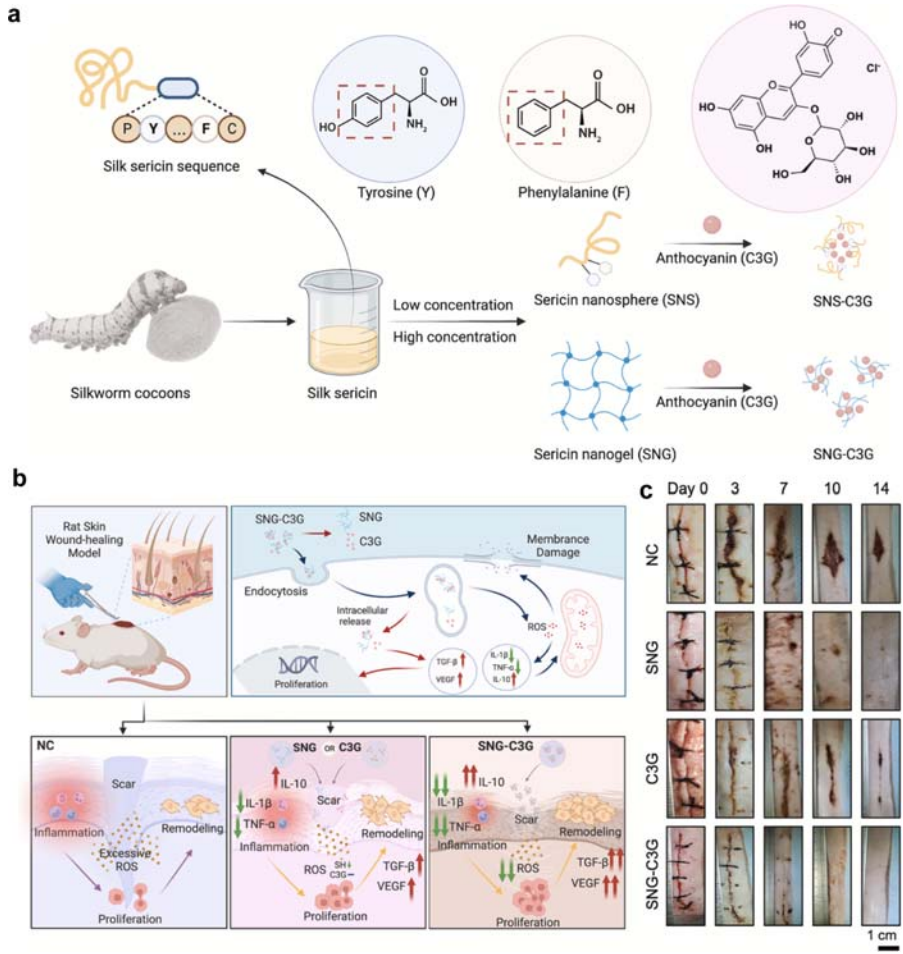


Figure 4.3 Schematic of (a) the formation of silk sericin-anthocyanin nanocomposites. Silk sericin binds anthocyanins in two forms: sericin nanosphere (SNS) and silk hydrogel (SNG), with tyrosine (Y) and phenylalanine (F) amino acids as the main binding sites. (b) Proposed mechanism of the effects of normal saline, sericin nanogel (SNG), C3G and sericin nanogel-anthocyanin (SNG-C3G) on the rat skin wound healing. (c) Photographs of wounds in mice on days 0, 3, 7, 10, and 14 after treatments with normal saline, SNG, C3G, and SNG-C3G (Zhang et al., 2023). Copyright 2023, Elsevier.

derived from silkworms, in creating a stable and bioactive formulation for potential applications in tissue engineering and wound healing.

Exudate and necrotic tissue often obstruct the delivery of therapeutic agents to deeper tissues in skin wounds, making conventional systems like hydrogels, films, and creams less effective (Arshad et al., 2021; Feng et al., 2021). MNs present a minimally invasive solution, capable of bypassing the stratum corneum to reach deeper

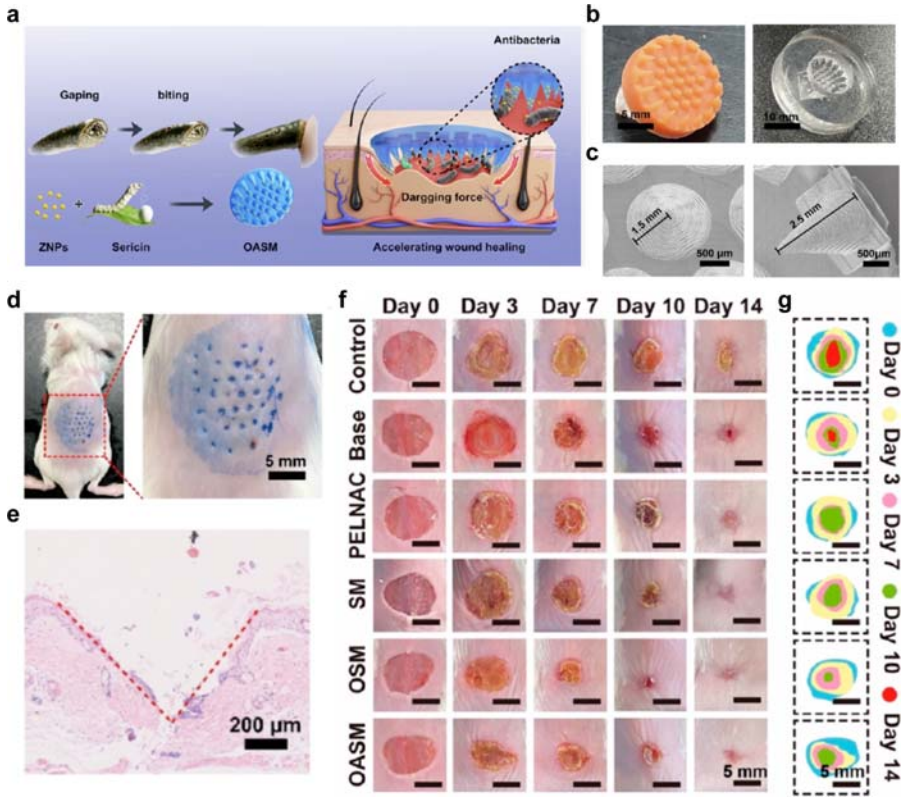


Figure 4.4 (a) Schematic of design and fabrication of bioinspired oriented antibacterial sericin MNs (OASM) for infected wound healing. (b) Optical image of the printed positive master mold and negative PDMS mold produced from the master mold. (c) SEM images of short needles and orientated long needles. (d) Photographs of mouse skin treated with OASM after trypan blue staining. (e) H&E staining of sectioned mouse skin after applying OASM. (f) Photographs of wounds in mice on days 0, 3, 7, 10, and 14. (g) The simulated wound area from different time points overlapped together. (a−f) Reproduced with permission from reference (Deng et al., 2022). Copyright 2022, American Chemical Society.

tissues (Jamaledin et al., 2020; Waghule et al., 2019). The effectiveness of MNs is largely influenced by their polymer composition (Wang & Wang, 2015; Zhang et al., 2017). Deng et al. employed SS in the creation of MNs designed to enhance skin repair. These SS-based MNs successfully formed microchannel arrays on the dorsal skin of mice, demonstrating their ability to penetrate the outer skin layer, see Fig. 4.4 (Deng et al., 2022). The application of these MNs showed a significant improvement in the healing process, as indicated by reductions in wound area (Fig. 6.5f−g). This enhanced healing can be attributed to the regenerative properties of SS, which supports hair follicle growth and angiogenesis, and the antibacterial properties provided by zinc oxide nanoparticles within the MN formulation. Together,

these components synergistically accelerated the healing of infectious wounds, highlighting the potential of SS-based MNs in advanced wound care.

8. SS-based biomaterials for bone diseases and culture matrix

Bone diseases such as bone infection, bone tumors, and bone loss have become a global problem with increasing incidences (Dimitriou et al., 2011; Yea et al., 2015). While traditional therapies have significant limitations, biomaterials provide new strategies for bone regeneration (McMahon et al., 2013; Yea et al., 2015). Porous SS scaffolds are suitable architectures that can provide bone tissues with an environment that promotes cell infiltration, migration, vascularization, nutrient and oxygen flow, and waste material removal (Abbasi et al., 2020; Limmahakhun et al., 2017). It is also important for the scaffold to be able to withstand external loading stress (Abbasi et al., 2020). Qi et al. designed and fabricated a scaffold made of SS and graphene oxide (GO) for bone tissue regeneration (Qi et al., 2020/2020). SS in scaffolds can promote cell adhesion and proliferation (Zhang et al., 2015/2015), while GO in scaffolds can provide tunable mechanical strength and osteogenic induction ability (Kinloch et al., 2018; Lu et al., 2016; Novoselov et al., 2012). The addition of SS significantly improved the mechanical properties and biocompatibility of the scaffold. The in vivo testing showed that the scaffold helped new muscle fibers grow and form.

SS scaffolds mixed with collagen can also be used to repair cartilage tissues (Dinescu et al., 2013). SS scaffolds enriched with hyaluronic acid (HA) and chondroitin sulfate significantly improved the viability, proliferation, adhesion, and spreading of stem cells. A recently reported periodontal tissue engineering scaffold made of silk glue demonstrated good hydrophilicity, biocompatibility, in vitro antiinflammatory effects, and promotion of cell adhesion and proliferation (Chachlioutaki et al., 2022). The scaffold also had a good drug retardation and was able to maintain drug release for up to 15 days.

Silk sericin is known for its antioxidant properties, which play a crucial role in protecting corneal cells from oxidative stress, a key factor in corneal diseases and injuries (Ahearne et al., 2020; Long et al., 2015). Research, such as that by Singh et al. , has explored combining SS with other polymers like hyaluronic acid to enhance the mechanical properties and durability of corneal implants. This adaptability of SS-based materials for various eye-related applications, including drug delivery systems and artificial corneas, highlights the significant potential of this natural silk protein in ophthalmology.

9. SS-based biomaterials for electronic applications

Expanding SS applications into the electronics sector offer a broader perspective on its utility. In electronics, SS's potential in batteries and memristors could lead to advancements in energy storage and computing.

9.1 SS-based biomaterials for battery and supercapacitor

Researchers are developing SS-based batteries that utilize the natural properties of sericin to enhance battery performance. Sericin is a biocompatible and biodegradable material that offers an eco-friendly alternative for battery components. Recent progress involves integrating sericin into electrodes or electrolytes to improve conductivity and stability, aiming for higher efficiency and longer life cycles.

Recently, researchers found that silk has been used in li-ion battery (Pereira et al., 2018; Wu et al., 2019; Zhao et al., 2021). Wu et al. (2019) found that applying sericin as a protective coating on Li metal anodes offers a promising approach to overcoming the challenges of Li dendrite formation in high-energy-density Li metal batteries. By enhancing Li-ion transference and promoting uniform Li deposition, sericin-coated anodes achieve long cycle life and high Coulombic efficiency, even under high current densities. This innovative solution not only advances the performance of Li−S batteries but also paves the way for the commercialization of next-generation Li batteries.

Moreover, the incorporation of silk peptide in ZnSO4-based electrolytes significantly enhances the performance of aqueous Zn-ion batteries by mitigating side reactions at the Zn anode-electrolyte interface, see Fig. 4.5 (Wang et al., 2022). This low-cost, eco-friendly additive leverages its strong polar groups to regulate solvation and provide electrostatic shielding, resulting in a remarkable improvement in cycle life and Coulombic efficiency, indicating the potential for widespread application in reversible zinc-ion batteries.

Developing a hydrogel-based supercapacitor (SC) for implantable power sources using SS presents a promising solution, addressing high performance, biocompatibility, and biodegradability. SS has been applied to hydrogel electrodes (Fig. 6.6c) (Lv et al., 2023), taking advantage of its biological properties. This SC features a conductive multinetwork electrode, demonstrating significant energy storage capacity and durability, even under physiological conditions. Its potential for medical implant applications, such as temporary pacemakers, is underscored by its ability to electrically stimulate cardiac activity, along with its superior biocompatibility and degradation profile postimplantation.

9.2 SS-based biomaterials for memristors

Memristive devices with threshold switching characteristics can be effectively utilized to mimic biological neurons acting as one of the key building blocks for constructing advanced hardware neural networks. He et al. (He, Yan, Zhang, Qin, et al., 2023) demonstrates the successful emulation of a leaky integrate-and-fire memristive neuron

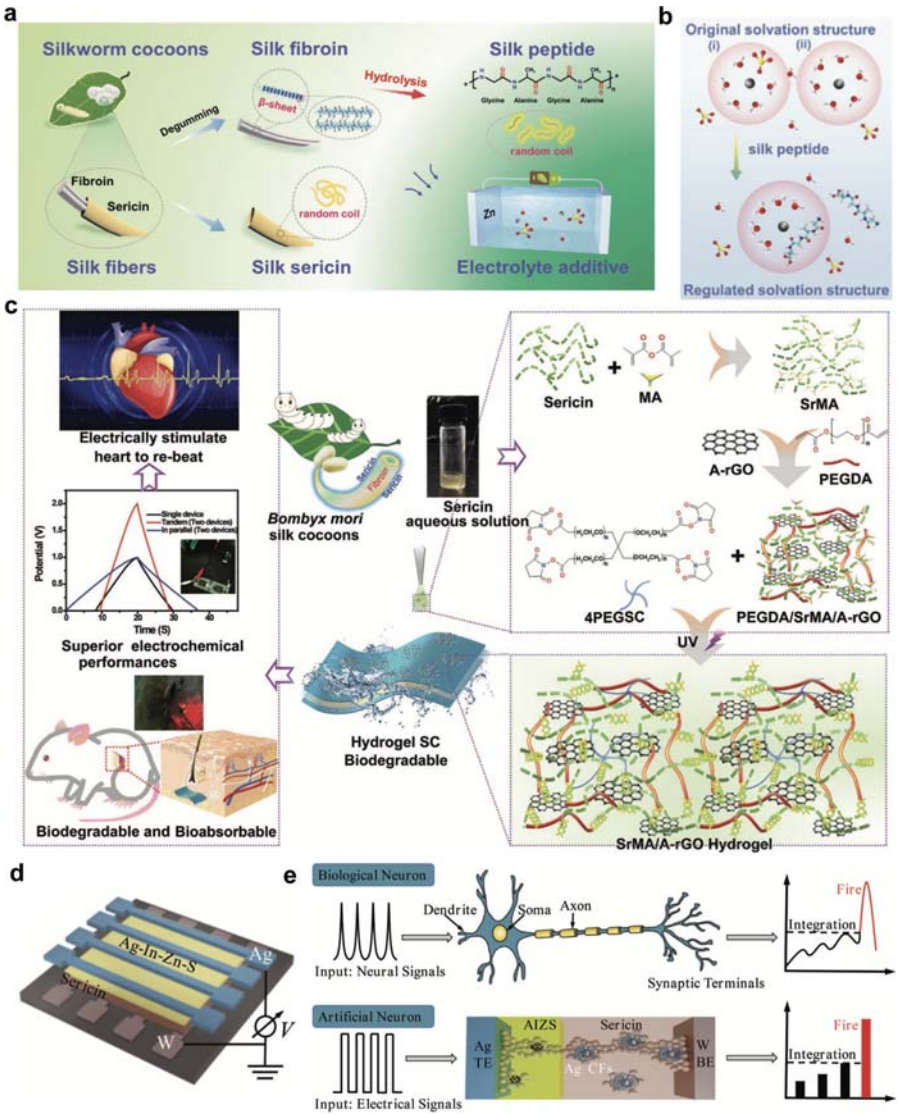


Figure 4.5 (a) Schematic illustration of the relationship among silk sericin, fibroin, and peptide molecules with diverse conformations and polar groups, and their applications as electrolyte additives in ZIBs. (b) Schematic illustration of Zn2+ solvation structure with/without silk peptide (Wang et al., 2022); Copyright 2022, Wiley. (c) Schematic illustration of the fabrication process and application of the supercapacitor based on SrMA/A-rGO hydrogel electrode (Lv et al., 2023); Copyright 20,223 Wiley. (d) The structural schematic diagram of the investigated sericin-based device. (e) Schematic representation of integrate-and-fire function in a biological neuron (above) and schematic representation of integrate-and-fire characteristics simulated by a sericin-based artificial neuron (below) (He, Yan, Zhang, Qin, et al., 2023); Copyright 2023, Wiley.

using a single cell with an Ag/Ag−In−Zn−S/SS/W architecture, eliminating the need for extra circuits (Fig. 6.6d). The device shows excellent electrical performance, including stable threshold switching and low-voltage variation. It effectively mimics neural functions like spike frequency modulation, attributed to a controllable Ag filament mechanism. Additionally, a spiking neural network utilizing this device achieved a high accuracy in pattern recognition tasks, highlighting sericin's potential in neuromorphic computing (Fig. 6.6e).

Also, memristive devices have been fabricated with a specific two-terminal device structure: Ag/Ag−In−Zn−S/SS/W. Their work demonstrates the potential of SS-based memristors in neuromorphic computing, showcasing dual functionality with low switching voltages and rapid speeds (He, Yan, Zhang, Ye, et al., 2023). The devices, capable of mimicking fundamental synaptic behaviors, highlight the feasibility of using eco-friendly materials for advanced neuromorphic systems. These studies (He, Yan, Zhang, Qin, et al., 2023; He, Yan, Zhang, Ye, et al., 2023; Rong et al., 2023) demonstrates the potential of SS-based memristors in bioinspired neuromorphic systems, highlighting their dual functionality in threshold and memory switching. The devices exhibit low voltage requirements, rapid switching speeds, and the ability to mimic synaptic behaviors, underscoring their viability for neuromorphic computing applications.

10. SS-based biomaterials for environmental applications

Environmentally, SS's biodegradability positions it as a green alternative for pollution reduction and resource recovery. These explorations necessitate advanced research to optimize SS's properties for specific applications, ensuring safety and understanding its biological interactions, thereby broadening SS's impact beyond food and biomedicine.

Silk sericin, with its water-soluble amino acids and polar functional groups, exhibits strong hydrophilicity and metal ion chelation capabilities, as demonstrated by Koley et al. in their study on sericin's ability to adsorb heavy metals (Koley et al., 2016). However, determining sericin's saturation point and its effectiveness in filtering metal ions remains a challenge, highlighting the need for a reliable, low-cost method to accurately assess its binding capacity.

Recently, Yao et al. (Yao et al., 2022) developed an SS−anthocyanin (SC) nanocomplex for an intelligent metal ion filter screen, which signals its saturation through color change, see Fig. 4.6a and b. This research introduces an innovative SS filter film incorporating an anthocyanin (C3G) indicator for metal ion chelation, particularly targeting Zn^{2+} and Al^{3+} (Fig. 6.7a). The SS's chelating capability is visually indicated by C3G's color change (Fig. 6.7c), facilitating real-time saturation monitoring. The

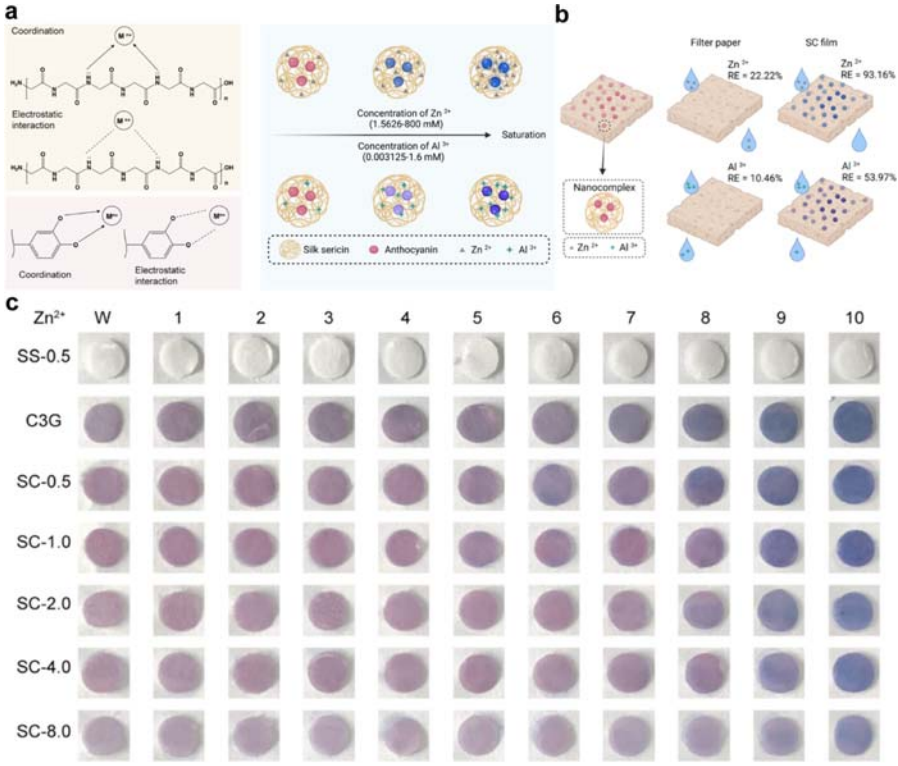


Figure 4.6 (a) The primary interaction process between metal ions and active amino groups of silk sericin (SS). The primary interaction process between metal ions and anthocyanin. Schematic representation of the anthocyanin as an indicator agent to detect the saturation of SS binding metal ions. Metal ions bind with SS first, and when SS is saturated, metal ions bind with anthocyanin, resulting in color changes of anthocyanin. (b) Schematic of filter paper and silk sericin−anthocyanin (SC) film filter metal ions (Zn^{2+} and Al^{3+}). The color of the SC film changes when the SC nanocomplex is saturated. The removal efficiency (RE) of metal ions (Zn^{2+} and Al^{3+}) of filter paper and SC film was presented. (c) Images of C3G and SS−C3G nanocomplex films after mixing with different concentrations of Zn^{2+} (1.5626, 3.125, 6.25, 12.5, 25, 50, 100, 200, 400, and 800 mM) (Yao et al., 2022). Copyright 2022, Royal Society of Chemistry.

physisorption adsorption and chemisorption adsorption are mainly contributed by filter paper and SC nanocoating, respectively. The film demonstrated high removal rates for Zn^{2+} and Al^{3+} (Fig. 6.7b), showcasing its potential for practical applications in metal ion filtration with the added benefit of saturation visualization. In the future, by discovering more ions interaction with SS, this innovative approach offers promising applications in environmental science for real-time monitoring of filtration efficiency.

11. Conclusions and outlook

Silk sericin, once merely considered a byproduct of silk production, has emerged as a substance of interest due to its unique biological properties, uncovered through deepening research. Enriched with 18 essential amino acids, SS fosters rapid cell adhesion and proliferation, showcasing its potential as a versatile biomaterial in food additives, packaging, and biomedical applications. Its biocompatibility, gelation, water solubility, and biodegradability further emphasize SS as a sustainable protein resource. Despite its growing recognition in the food and biomedical sectors, SS applications remain underexplored. Advancing SS's utility involves refining its preparation process, stabilizing its biological activity, rigorously testing its safety, particularly its immunogenicity, and investigating its metabolic pathways and bodily impacts. The exploration of SS in electronics, such as batteries and memristors, alongside environmental applications, underscores its broad potential. This expansion into new sectors necessitates comprehensive research to tailor SS's properties for specific uses, ensuring safety and elucidating its biological interactions, thereby widening its scope beyond conventional domains.

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Sericin-based hydrogels

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Seema Kumari [1,2], *Kashama Sharma* [1,2], *Asha Kumari* [1,2] *and Rahul Sharma* [1,2]
[1]Department of Chemistry, Career Point University, Hamirpur, Himachal Pradesh, India; [2]Centre for Nano-Science & Technology, Career Point University, Hamirpur, Himachal Pradesh, India

1. Introduction

Sericin, a natural protein generated from silk, has received a lot of interest in recent years because of its unique features and numerous uses. Hydrogels, which are three-dimensional networks of cross-linked polymers, have emerged as potential biomaterials in a variety of biological and industrial applications (Mohite & Adhav, 2017). Combining the extraordinary properties of sericin with the structural advantages of hydrogels has resulted in the creation of sericin-based hydrogels with several potential applications and benefits (Yang et al., 2023). Sericin is a protein that is found in silk fibers that are generally eliminated during the silk processing process for textile manufacture. Scientists, on the other hand, have noticed its useful features, making it an appealing option for bioengineering applications. Sericin is bioactive, biocompatible, and biodegradable, making it ideal for biomedical and tissue engineering applications, drug/gene delivery, and the future smart wearable electronics (Saad et al., 2023).

Silk is made up of two major components: fibroin and sericin. Fibroin, in example, has been used not just to make biomedical devices such as surgical sutures but also as a viable choice for tissue engineering and drug delivery systems. This is due to fibroin's desired properties such as appropriate elasticity, mechanical strength, regulated degradation, and biocompatibility. Silk sericin (SS), on the other hand, has been disregarded and abandoned as a waste product in the textile business for a long time, resulting in environmental contamination and the waste of rich natural resources for thousands of years (Hu et al., 2023). Nonetheless, advances in sericin research have revealed that discarded sericin contains extraordinary biological qualities akin to fibroin. Sericin has been shown to support cell adhesion and proliferation, as well as drive cell differentiation. Furthermore, sericin has good moisture retention and antioxidant properties. Sericin can be turned into stable and tunable biomaterials by undergoing alterations such as precipitation or cross-linking with other polymers (Seo et al., 2023). The shape, size, and characteristics of these modified biomaterials, such as elasticity, strength, and biodegradability, may be carefully adjusted. As a result, sericin has piqued the interest of researchers in a variety of sectors, including cosmeceuticals, cell culture, and tissue engineering. Not only would the extraction and application of sericin alleviate environmental problems, but it would also uncover significant potential value in biological research and medicinal applications (Fatahian et al., 2022).

Science and Technology of Silkworm Sericin. https://doi.org/10.1016/B978-0-443-21736-4.00005-2
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Sericin-based hydrogels are gel materials made from sericin, a protein found in silk fibers. When sericin molecules self-assemble and entangle, a three-dimensional network structure capable of holding a substantial amount of water is created (Gamo et al., 1977). Sericin-based hydrogels has gained interest in a variety of biological applications due to its biocompatibility and biodegradability (Jaramillo-Quiceno et al., 2023). The hydrogels unique features, such as configurable mechanical strength and controlled degradation, make it appropriate for a variety of biomedical applications, including drug delivery systems, tissue engineering scaffolds, wound dressings, and regenerative medicine (Nam et al., 2021). Furthermore, the capacity of sericin-based hydrogels to stimulate cell adhesion, proliferation, and differentiation increases their potential for fostering tissue regeneration and wound healing. Furthermore, using sericin in hydrogels preparation is an environmentally benign strategy since it repurposes a by-product of the silk industry that was previously considered waste, minimizing environmental contamination. Overall, sericin-based hydrogels show promise as a flexible biomaterial with important applications in biomedical research and medicine (Dan et al., 2022).

2. Synthesis and characteristics of sericin based hydrogels

2.1 Synthesis of sericin-based hydrogels

2.1.1 Extraction of sericin

Sericin may be extracted from silk fibers using a variety of processes, including boiling, enzyme treatment, and solvent extraction. The recovered sericin can subsequently be processed to eliminate contaminants and other silk-related components (Gulrez et al., 2011).

2.1.2 Cross-linking

Using either physical or chemical means, sericin can be cross-linked to generate hydrogels. In physical cross-linking, external cues like as temperature, pH, or ionic strength are employed to initiate gel formation. Chemical cross-linking, on the other hand, entails using cross-linking chemicals such as glutaraldehyde or genipin to form stable covalent links between sericin molecules (Gulrez et al., 2011).

2.2 Characteristics of sericin-based hydrogels

2.2.1 Biocompatibility

Sericin is biocompatible, which means it is tolerated well by live tissues and cells. Because of this feature, sericin-based hydrogels can be used in a variety of biological applications without eliciting adverse responses or inflammation (Wang et al., 2023).

2.2.2 Biodegradability

Sericin-based hydrogels have the ability to disintegrate over time, allowing for the controlled release of encapsulated medicines or growth hormones. This property is very beneficial in medication delivery systems and tissue regeneration applications (Fatahian et al., 2022).

2.2.3 Water retention capacity

The high water content of hydrogels replicates the natural environment of many tissues and cells. Sericin-based hydrogels may hold a substantial quantity of water, making them useful as wound moisturizers or scaffolds for tissue engineering (Jaramillo-Quiceno et al., 2023).

2.2.4 Mechanical properties

The mechanical characteristics of hydrogels may be modified by varying the sericin content, cross-linking density, and cross-linking technique. Because of this tunability, researchers may build hydrogels with varied stiffness and elasticity to meet the unique needs of various tissues (Nam et al., 2021).

2.2.5 Drug delivery potential

Because of their capacity to encapsulate pharmaceuticals and release them in a regulated manner, sericin-based hydrogels have showed promise as drug delivery vehicles. This regulated release can improve treatment efficacy and lessen negative effects associated with some medications (Dan et al., 2022).

2.2.6 Cell adhesion and proliferation

Sericin-based hydrogels can increase cell adhesion and proliferation, making them ideal for tissue engineering. The inclusion of sericin in hydrogels can promote cell proliferation and tissue regeneration by creating a favorable microenvironment (Chachlioutaki et al., 2022).

3. Synthesis routes for sericin-based hydrogels

Sericin is a natural protein derived from silk that has been investigated for a variety of purposes, including hydrogels production. Crosslinked hydrogels are hydrogels that have chemical or physical cross-links that hold them together and provide stability and strength. There are two common synthesis routes for the sericin-based hydrogels, chemical cross-linking or physical cross-linking using cross-linking agents and temperature or pH, respectively (Khan et al., 2022).

3.1 Cross-linked hydrogels

The current era sees a growing fascination with chemically cross-linked hydrogels mainly because of their excellent mechanical properties and strength. There are different methods to synthesize chemical cross-linking hydrogels.

3.1.1 Chemical cross-linking through complementary reactions in hydrogels

Chemical cross-linking with complimentary reactions results in stable hydrogels with increased mechanical strength. Hydrophilic polymers containing NH2, COOH, and OH functional groups react to produce covalent connections between polymer chains, resulting in the three-dimensional structure of the hydrogels that can hold water. This approach is useful in biomedicine, drug delivery, and tissue engineering because it allows for exact control of hydrogels characteristics for customization (Akhtar et al., 2016).

3.1.2 Cross-linking with aldehydes

Cross-linking with aldehydes is a chemical process that involves the formation of covalent connections between aldehydes molecules and other molecules, often proteins or polymers, culminating in the formation of a cross-linked network. This procedure improves the material's stability and mechanical strength and is extensively employed in the production of hydrogels, biomaterials, and other structured materials. For example: In tissue engineering, glutaraldehyde is commonly used to cross-link collagen in hydrogels. It combines with the amino groups of collagen, generating stable covalent connections that increase the mechanical characteristics and stability of the hydrogels. These cross-linked hydrogels have potential in tissue regeneration as biocompatible scaffolds (Bouhadir et al., 1999).

3.1.3 By addition reactions

Hydrophilic polymers can be cross-linked using bis or higher functional cross-linkers through addition reactions. Polysaccharides, for instance, can undergo cross-linking using compounds like 1,6-hexamethylenediisocyanate, divinylsulfone, or 1,6-hexanedibromide, as reported by Brondsted et al. (1995), Gehrke et al. (1998) and Coviello et al. (1999) respectively.

3.1.4 By condensation reaction

Cross-linked hydrogels can be created via the condensation process, in which functional groups react and water is released as a by-product. For example, silica-based precursors such as TEOS can react with hydrophilic polymers such as PVA or chitosan to form stable cross-linked networks. This approach allows for fine control of hydrogels characteristics as well as the insertion of various functional groups, making it useful for applications such as drug delivery, tissue engineering, and biosensors (Kuijpers et al., 2000).

3.1.5 Cross-linking by high energy radiation

The technique of creating covalent connections between polymer chains using ionizing radiation, such as gamma rays or electron beams, is referred to as cross-linking by high-energy radiation. This approach causes cross-links to develop in the polymer structure, resulting in the establishment of a stable network, which is extensively employed in applications such as polymer modification, sterilization, and the manufacturing of hydrogels and other advanced materials (AbdAlla et al., 2012; Amin et al., 2012).

3.2 Fictionalized cross-linking with chemicals

Cross-linking by free radical polymerization is a chemical process in which reactive molecules known as free radicals begin monomer polymerization, resulting in the production of a three-dimensional network structure. The free radicals establish covalent connections between the monomers during this process, resulting in the production of a cross-linked polymer with increased mechanical strength and stability (Martin et al., 1998; Patil et al., 1996).

3.2.1 Cross-linking using enzymes

The process of forming covalent connections between biomolecules utilizing enzymes is referred to as cross-linking. Enzymes operate as catalysts to promote cross-link formation, resulting in the development of stable and regulated networks such as hydrogels or protein aggregates. This technology provides a biocompatible and specific way for cross-linking biomaterials, making it useful for a wide range of biomedical applications (Akhtar et al., 2016).

3.3 Polymer network modification/linking

3.3.1 Physically cross-linked hydrogels

In the current era, there is growing interest in physically cross-linked hydrogels because they do not require the use of chemical cross-linkers during the synthesis process. There are different methods to synthesize physically cross-linked hydrogels.

3.3.2 By hydrogen bonds

Hydrophilic polymer networks are kept together by reversible hydrogen bonding interactions in physically cross-linked hydrogels generated by hydrogen bonds. These interactions result in a stable three-dimensional structure in the hydrogels, which gives it unique qualities including self-healing and shear-thinning behavior (Song et al., 2013).

3.3.3 By amphiphilic graft and block polymer

Polymers containing both hydrophilic and hydrophobic segments are used in the manufacture of physically cross-linked hydrogels from amphiphilic graft and block polymers. Without the need of chemical cross-linkers, these polymers self-assemble

into three-dimensional networks by noncovalent interactions such as hydrogen bonding or hydrophobic interactions. The resultant hydrogels have unique characteristics and are sensitive to external stimuli, making them useful in drug delivery, tissue engineering, and other biomedical disciplines (Zheng et al., 2017).

3.3.4 Cross-linking by crystallization

Cross-linking via crystallization is the process of creating physically cross-linked hydrogels by forming crystalline domains inside the hydrogels matrix. The hydrogels components self-assemble and crystallize in this process, resulting in a network of linked crystals that offer structural stability to the hydrogels. This physical cross-linking method gives the hydrogels exceptional mechanical characteristics, making it appropriate for use in tissue engineering, drug delivery, and biomaterials (Baptista-Silva et al., 2021).

3.3.5 Cross-linking by ionic interaction

Calcium ions may cross-link alginate. At physiological pH and room temperature, cross-linking occurs. Alginate gels can be employed as a matrix for protein release and for the encapsulation of live cells (Akhtar et al., 2016).

3.3.6 Cross-linking by protein interaction

Physically cross-linked hydrogels use natural proteins or biopolymers to form a stable 3D network through noncovalent interactions, like hydrogen bonding and electrostatic interactions. No chemical cross-linkers are used, making it biocompatible and adaptable for biomedicine and tissue engineering (Gombotz & Wee, 2012; Xu et al., 2017).

4. Applications of sericin-based hydrogels

In recent years, the hydrogels of silk protein with excellent mechanical strength have various other functions such as good swelling features, high pH, cell compatibility, degradation with pH alteration, ability for targeted drug delivery, etc. The multiple functionalities of sericin hydrogels make it feasible to establish new applications. It is found that multiple functional sericin-based hydrogels are presently utilized in various applications of biomedical field such as delivery of drugs, tissue engineering, wound healing, disease treatment, pharmaceutical applications, biosensors, bioprinting, etc. The most progressive applications of sericin-based hydrogels in these fields have been discussed in the succeeding paragraph.

4.1 Delivery of drugs

The sericin-based hydrogels have the features of biocompatibility, nontoxicity, requisite swelling variations, auspicious drug storing ability, resistance toward enzymes,

and biodegradability (Al-Tabakha et al., 2021; Ubaid et al., 2018). Development of biocompatible, decomposable, as well as harmless hydrogels from natural polymers is one of the most prominent areas of research. So, the sericin-based hydrogels have fascinated remarkable attention in the area of drug delivery. Al-Tabakha et al. (2021) developed a sericin-based hydrogels using free radical polymerization technique, in which sericin and acrylic acid were chemically interconnected. The interlinking by acrylic acid provides pH receptivity to the modified system. The initiator ammonium persulfate was used to initiate the polymerization process and cross-linker N′,N′-methylene bis-acrylamide was utilized for interlinking of polymeric chains. This ingredient of hydrogels can change water polymer into insoluble form. They investigated the pH responsive release of drug as well as its safety measurements using sericin-based hydrogels. They found considerable release of drug at pH 7.4, and also, there was no difference in histopathological micrographs of control as well as tissues of rabbit under treatment such as heart, lungs, liver, kidney, and intestines. In another study, Liu et al. (2016) developed a drug delivery approach for effectual cancer treatment within *vivo* along with optical monitoring strategy. These injectable hydrogels of sericin have effective targeted drug system. Fig. 5.1 shows that hydrogels play a significant role in drug delivery system. In this study, sericin fused hydrogels were synthesized using dextran sericin (biocompatible constituents) and hydroze (cross-linking agent). Sericin possesses inherent photo luminescent features (Wang et al., 2014). This feature was utilized to check both in vivo deterioration as well as the quantity of drug lasting within the sericin hydrogels. So, incorporation of targeting components such as peptides (proteins) into hydrogels led to the delivery of drug at a particular site inside the body and reduces side effects as well as systematic revelation (Porter et al., 2007).

4.2 Tissue engineering

In current years, the studies on the utilization of sericin-based hydrogels in the field of tissue engineering have received rising attentiveness due to its nontoxic, sustainable, as well as eco-friendly properties. Pankongadisak et al. (Pankongadisak & Suwantong, 2018) synthesized an injectable chitosan/β-glycerophosphate (CS/β-GP) as well as CS/sericin silk/β-GP hydrogels stuffed with Logan Seeds Extract (LE). The CS/β-GP hydrogels were changed from its sol form to gel at 37°C within few minutes. The inclusion of SS into CS/β-GP suspension resulted in a reduction in gelation time as well as enhancement on porosity. Also, the cumulative quantity of polyphenolic compounds (acids such as gallic acid [GA] as well as ellagic acid [EA]) discharged from the synthesized hydrogels loaded with logan seeds enhanced with the increment in SS content. These hydrogels were found to be nontoxic for both fibroblast as well as osteoblast cell line of mouse. These hydrogels could be a promising material for tissue engineering of bones. In another study, Zhang et al. (2023) fabricated an injectable hydrogels obtained from transgenic platelet derived growth factors (PDGF)-BB SS. This hydrogels provides a sustainable release of GFs for regeneration of bones. It was found that the PDGF-BB transgenic silk hydrogels effectually amplified osteogenesis generated through BMP9 (bone morphological protein)-stimulated

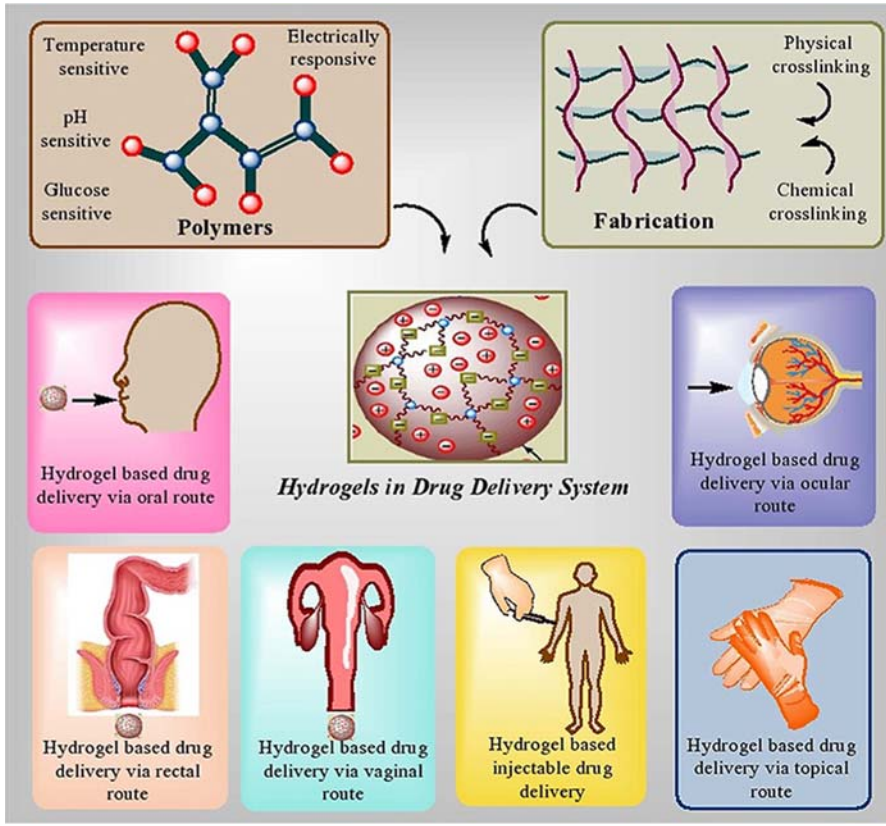


Figure 5.1 Representation of hydrogels in drug delivery system.
Reprinted with the permission of Elsevier (License number−5603520599084). Kesharwani, P., Bisht, A., Alexander, A., Dave, V. and Sharma, S., 2021. Biomedical applications of hydrogels in drug delivery system: An update. *Journal of Drug Delivery Science and Technology*, *66*, p. 102914.

mesenchymal stem cells (MSCs) in vivo and in vitro, at the time of restraining apidogenic distinction. Kim et al. (2022) developed an injectable gellan gum/SS (GG/SS) hydrogels for cell recovery in retina tissue engineering.

4.3 Wound healing

Surgery as well as burns can prompt damage of skin. Some of the wounds that are failed to in the recovery process over a long period of time are termed as chronic wounds (in accordance to American Wound Healing Society). The treatment process of these wounds involve pain, infection, and in extreme cases amputation. Presently, 1%−2% of total population experienced these kinds of wounds in developed countries (Järbrink et al., 2017). The tissue regeneration process required longer time for

repairing and risk of infection as well as septicemias. There is a need of such kind of dressing material/hydrogels which has water consumption ability, antioxidant properties, high transparency degree (for wound visualization), biodegradability, low cost, biocompatibility, antibacterial nature, etc. In this regard, Biptista-Silva et al. (Baptista-Silva et al., 2021) synthesized sericin based hydrogels using a cross-linking promoter, that is, horseradish peroxidase and hydrogen peroxide in different ratios. These hydrogels possess auspicious in vivo outputs when assessed on diabetic mice model. Sericin-based hydrogels are filled in the entire wound area, and this area shows operable contraction or tension (Fig. 5.2 images 1 and 2). These hydrogels hindered the pathogenic bacteria and enhances the healing prophecy. There was shortening of wound area (Fig. 5.2 images 3 and 4), depletion in wound depth, and scar tissues (Fig. 5.2 images 5 and 6) observed within 21 days treatment. In another study, Qi et al. (2018) synthesized photo cross-bindable sericin-based methacryloyl hydrogels by altering sericin's hydroxyl group and amine's methacryloxy groups and tested to heal severe skin injury along with effectual regeneration of hair sacs of mice. Photo-crosslinking improves hydrogels biocompatibility as well as allowing direct implanting of living cells. To compare the regenerative effects of sericin-based hydrogels on

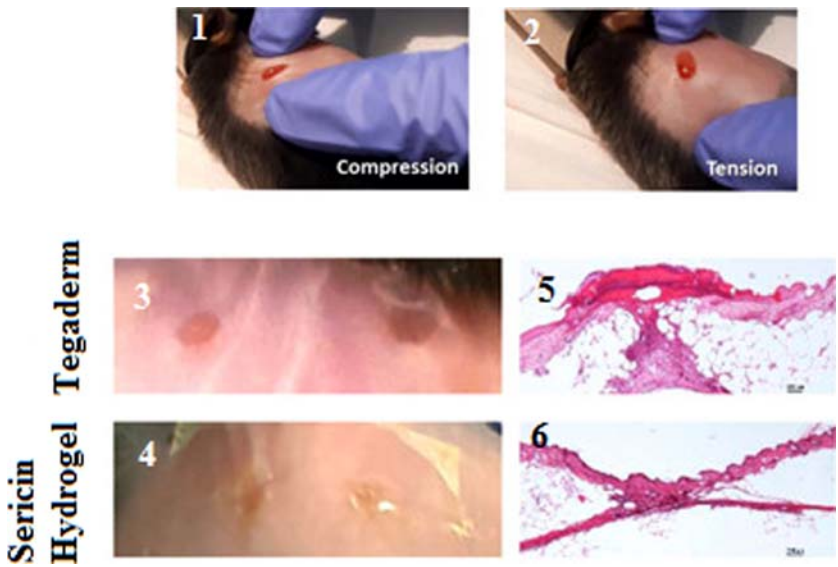


Figure 5.2 In vivo evaluation of sericin hydrogels through a skin wound healing assay in the diabetic mice model. Images of the sericin hydrogels after the first few minutes of in situ application in the wound bed, in compression (1), tension (2), representative images of wounded area at 21 days postwounding (3,4), and histological analyses of skin (5,6). Reprinted with the permission from Baptista-Silva, S., Borges, S., Costa-Pinto, A.R., Costa, R., Amorim, M., Dias, J.R., Ramos, O., Alves, P., Granja, P.L., Soares, R. and Pintado, M., 2021. In situ forming silk sericin-based hydrogels: A novel wound healing biomaterial. *ACS Biomaterials Science & Engineering*, *7*(4), pp. 1573−1586. https://doi.org/10.1021/acs_biomaterials.0c01745. Copyright (2021) American Chemical Society.

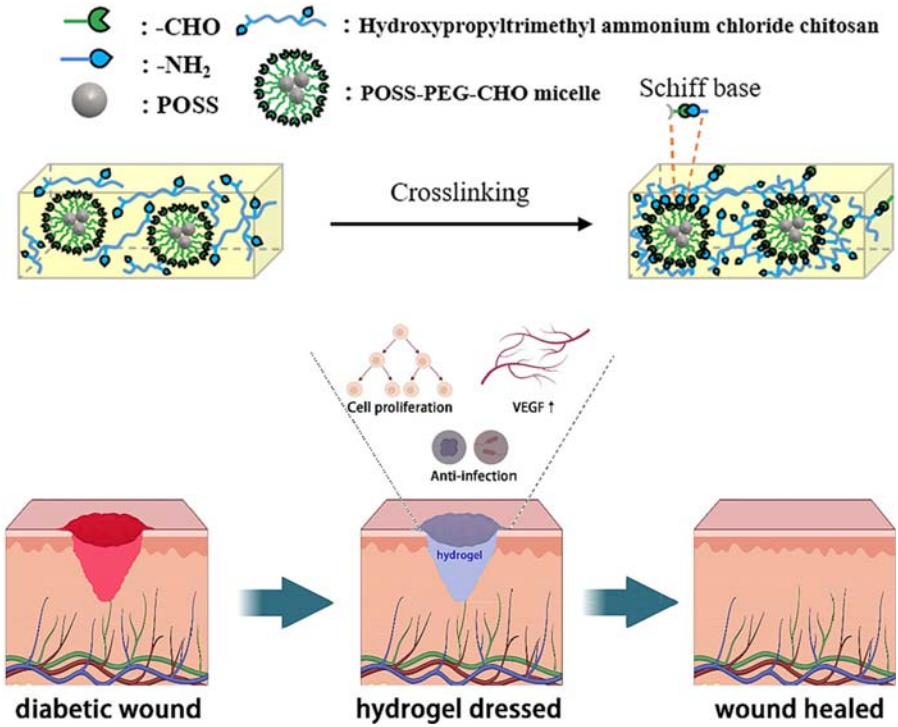


Figure 5.3 Representation of hydrogels in wound healing system.
Reprinted with the permission of Elsevier (License number−5603550649697). Li, C., Jiang, T., Zhou, C., Jiang, A., Lu, C., Yang, G., Nie, J., Wang, F., Yang, X. and Chen, Z., 2023. Injectable self-healing chitosan-based POSS-PEG hybrid hydrogel as wound dressing to promote diabetic wound healing. *Carbohydrate Polymers*, *299*, p. 120198.

skin full thickness injury, PELNAC (artificial dermal based on collagen) is chosen as control. For the movement of control and hydrogels at the affected sits, Tegaderm (adhesive tape) was fixed to sericin hydrogels and PELNAC. It was found that 98% of defective area healed using sericin hydrogels, 83% by PELNAC, and 48% by Tegaderm within 21 days treatment of mice. The defective skin area recovered using sericin hydrogels is scarless as well as have large number of replenish hair follicles than PELNAC and Tegaderm. Injectable self-healing chitosan-based POSS−PEG hybrid hydrogel is used in wound dressing to promote diabetic wound healing (Fig. 5.3).

4.4 Disease treatment

The disturbance in blood flow of the brain causes ischemic stroke, which is the fifth most eminent cause of death worldwide. In this regard, Zhao et al. (Zhao & He, 2022) reported the synthesis of genipin-conjugated sericin-based hydrogels along

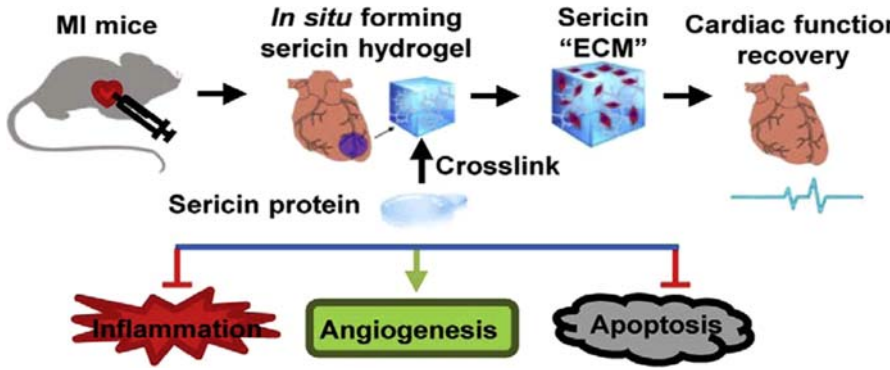


Figure 5.4 Assessment of sericin-based hydrogels in a mouse myocardial infarction model. Reprinted with the permission of Elsevier (License Number−5603560314024). Song, Y., Zhang, C., Zhang, J., Sun, N., Huang, K., Li, H., Wang, Z., Huang, K. and Wang, L., 2016. An injectable silk sericin hydrogels promotes cardiac functional recovery after ischemic myocardial infarction. Acta Biomaterialia, 41, pp. 210−223. https://doi.org/10.1016/j.actbio.2016.05.039.

with a porous morphology as well modest swelling rate using a silk protein (natural) sericin. These hydrogels have high % age for cell survival and promotion of cell proliferation. So, these kinds of hydrogels act as a usable carrier for therapy as well as recovering of ischemic strokes via transporting of neuronal cells and protecting them from oxidative destruction. In another study, Song et al. (2016) developed an injectable sericin hydrogels for curing myocardial infarction (MI). MI is a significant form of ischemic heart diseases. The medical consequences of this hydrogels were assessed in a mouse myocardial infarction model (Fig. 5.4). When sericin hydrogels are injected into myocardial infarction area, they minimize the scar formation as well as size of infarct, enhance the thickness of wall and neovascularization, and prohibit the inflammatory reactions.

4.5 Pharmaceutical applications

Silk sericin is an applicable protein obtained from silk cocoon that are consisted of polar amino acid chains along with various functional groups (hydroxyl, amino, and carboxy). It possesses the features such as biocompatibility, nontoxicity, strong affinity toward drug molecules, hydrophilicity, biodegradability, etc., and hence employed in various pharmaceutical applications. In addition to this, sericin has the potential to form gels. Gou et al. (2023) developed an injectable SS/silk fibroin supramolecule (SS-SF-SMC) reintegration hydrogel and utilized for the delivery of anti-CD47 antibody. The prepared hydrogel shows self-boosting in high hydrogen peroxide concentration of microenvironment of tumor. The SS-SMC changes hydrogen peroxide to reactive oxygen species in the interior of the hydrogel, further activating additional interlinking among the sericin fibroin polymers.

4.6 Biosensors

The hydrogels with characteristics such as selectivity, flexibility, stability, sensitivity, and biocompatibility are optimal for different kinds of biosensors. Hence, these biosensors are utilized in environmental monitoring, soil quality monitoring, food quality monitoring, water quality management, disease detection, drug discovery, etc. Environmentally sensitive hydrogels have the ability to sense changes of pH, temperature, and concentration of pollutants. Jaramillo-Quiceno et al. (2023) developed SS/CMC/PVA hydrogels and utilized them to evaluate the moisture content in the soil. The sericin silk, a natural polymer, increases the biodegradability as well as water absorption capacity of adsorbent material (hydrogels). Also, blending of SS with polyvinyl alcohol or glycerol/cross-linking with glutaraldehyde, polyphenols, and enzymes strengthens its mechanical properties. They assessed two soil samples: sand loamy type without hydrogels and sandy loamy soil with hydrogels (1%). SEM images of SS/CMC/PVA show the appropriate morphology was water retention in agricultural soils (Fig. 5.5). The water retention curves of these soil samples the increased content of moisture for soil sample with hydrogels (Fig. 5.6). Hence, developed material can be used to detect soil water retention. In another study, Zhang et al. (2020) synthesized optically transparent hydrogels fabricated by sericin and polyacrylamide. The resulting hydrogels have pH-dependent degradation, along with high porosity, as well as porous structure. The sericin polyacrylamide hydrogels may act as a visualized dressing constituent for monitoring of wounds.

4.7 Bioprinting

The bioprinting process depicts as computer-aided material relocation process of biological structures likewise cells as well as biomaterials to construct material fabrication

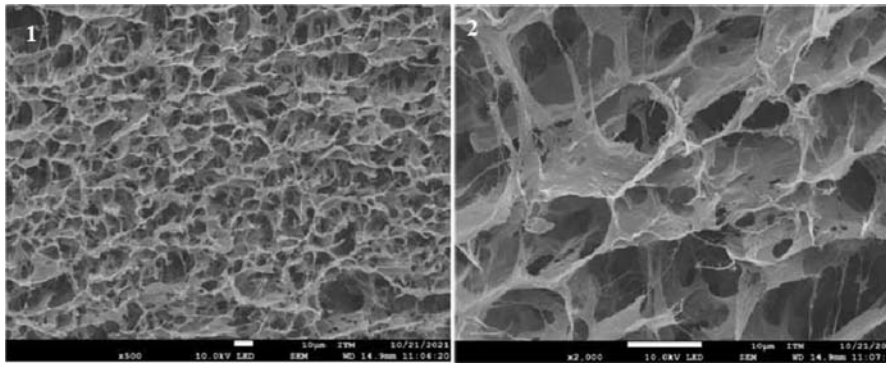


Figure 5.5 SEM images of 500× (**1**) and 2000× (**2**) of the hydrogels obtained from the SS/CMC/PVA mixture.
Reprinted from Jaramillo-Quiceno, N., Álvarez-López, C., Hincapié-Llanos, G.A., Hincapié, C.A. and Osorio, M., 2023. Characterization of a new silk sericin-based hydrogels for water retention in soil. *Polymers*, *15*(13), p. 2763. https://doi.org/10.3390/polym15132763.

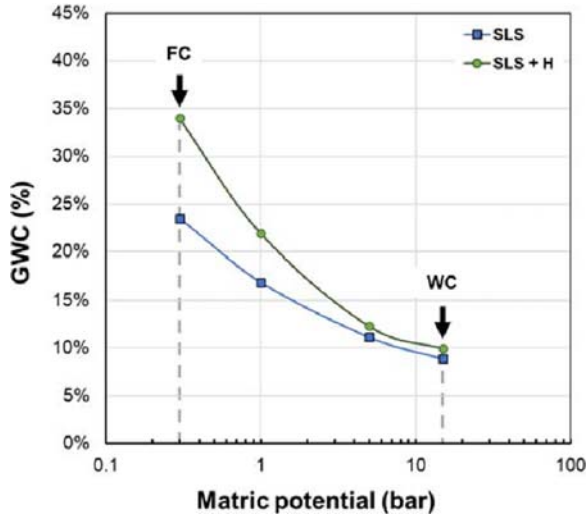


Figure 5.6 Semilogarithmic water retention curves for sandy loam soil (SLS) and sandy loam soil + hydrogels (SLS + H). Here *GWC*, gravimetric water content; *FC*, field capacity; *WC*, wilting coefficient.
Reprinted Jaramillo-Quiceno, N., Álvarez-López, C., Hincapié-Llanos, G.A., Hincapié, C.A. and Osorio, M., 2023. Characterization of a new silk sericin-based hydrogels for water retention in soil. *Polymers*, *15*(13), p. 2763. https://doi.org/10.3390/polym15132763.

for different applications (tissue engineering, bioengineering, material science, drug validation, and pharmaceutical development). Mostly, three dimensional (3D) bioprinting technologies are utilized to print living organs (liver, kidney, lungs, etc.). Biocompatible nature of hydrogels increased its utility in the field of 3D bioprinting. Also, the hydrogels provoked body's soft tissues, high level swelling in water, and possess similar mechanical features as the body soft tissues have. In bioprinting field, the biocompatible inks substituting plastic or metal raw substances employed in convex 3D printers. The hydrogels materials (both synthetic and natural) are frequently used in bioprinting. The naturally derived hydrogels are mostly appealing due to their biocompatibility, biodegradability, safety, and eco-friendly nature. These hydrogels are obtained from different natural sources such as animals, plants, microorganisms, etc. Jang et al. (2019) developed SS, a 3D printable self-gelling hydrogels. The sericin-based hydrogels possess mechanical stability, antiinflammatory, and angiogenic properties. The biocompatibility of sericin gel was investigated in vitro employing mouse myoblast (C2C12) and fibroblasts (3T3). During this assessment, matrigel was used as control. Easy isolation from silk, low cost, and simple processing are some of the advantages of the SS over silk fibroin hydrogels. Thus, sericin-based hydrogels have good printability as well as maintains in gel form after printing. In another study, Chen et al. (2018) synthesized SS-based hydrogels scaffold and utilized for the wound visualization. The scaffold was formulated from a complete interpenetrating network hydrogels consisted of SS and methacrylic anhydride altered gelatin by

three-dimensional printing. This study reveals that SS-based hydrogels scaffold possess superior biocompatibility through 3D printing, and hence, this hydrogels act as a suitable material for visualization of wound care as well as drug delivery.

5. Conclusions

In summary, the SS hydrogels with one or multiple functions can be designed by controlling the SS molecular structure, hydrogels microscopic size, development and accumulation of the properties of various materials, etc. In this way, the SS hydrogels have been altered from conventional hydrogels to smart as well as intelligent hydrogels. Addition of new functions, features, capabilities, or properties to sericin-based hydrogels imparts an outstanding set of characteristics to the hydrogels. This fictionalization firmly compensates for the scarcity of the mechanical features of the conventional SS hydrogels. So, the fictionalization makes SS hydrogels biometric, effectual during use as well as more intelligent. For example, hydrogels used in injectable form possess targeted drug delivery system along with both treatment effects as well reduction in severe side effects. The biodegradability and biocompatibility of sericin-based hydrogels remarkably improve the life as well as safety of these hydrogels during their use in environmental applications. High healing and regenerative properties of these hydrogels are utilized for the treatment of diabetic wounds. Cross-linked injectable sericin-based hydrogels are perfectly adjusted to the wound area along with no inflammatory reaction throughout the healing process. Based upon the properties of sericin hydrogels such as thermosensitivity, molecular structure, and rheological behavior, they are mostly utilized in the field of tissue engineering. When employed for sensing, these hydrogels materials show sensitive and authentic responses. In brief, the fictionalization of SS hydrogels depicts a significant strategy for their future development.

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Electrospun nanofibers based on silk sericin

6

Jidnyasa Pantwalawalkar[1], *Sopan Nangare*[2], *Niraj Kale*[1], *Namdeo Jadhav*[2], *Petra Nnamani*[3] *and Vilas Jagtap*[4]

[1]Department of Pharmaceutics, Bharati Vidyapeeth College of Pharmacy, Kolhapur, Maharashtra, India; [2]Department of Pharmaceutics, Krishna Vishwa Vidyapeeth, Krishna Institute of Pharmacy, Karad, Maharashtra, India; [3]Department of Pharmaceutics, University of Nigeria, Nsukka, Enugu State, Nigeria; [4]Department of Pharmacognosy, R.C. Patel Institute of Pharmacy, Shirpur, Maharashtra, India

1. Introduction

1.1 Electrospinning

In recent times, the advancement in nanotechnology has offered numerous novel approaches for constructing nanomaterials demonstrating finely tunable physicochemical characteristics. Among the several nanocomposites reported, nanofibers have secured much attention in the scientific fraternity owing to their outstanding properties and wide applicability. The key merits that make them distinct from other nanomaterials include a high surface area-to-volume ratio, flexibility, mechanical strength, and high porosity. These outstanding features make this nanomaterial an ideal candidate for tissue engineering, drug delivery, sensors, etc., (Muthukrishnan, 2022). Particularly, electrospinning is widely utilized for the production of nanofibers. It is an easy, efficient, and versatile method for the fabrication of advanced nanomaterials. Using electrospinning, ultrafine nanofibers can be generated (Nangare et al., 2020). According to data from PubMed (website: https://pubmed.ncbi.nlm.nih.gov), there are nearly 17,730 scientific articles available on electrospinning (Fig. 6.1a).

The electrospinning setup is assembled from four main parts: a glass syringe containing polymer solution, a metallic needle, a collector, and a power supply. Initially, the electric charges get transferred through a metallic needle into the polymer solution, causing instability in polymer droplets due to the introduction of charges (Haider et al., 2018). Concurrently, this reciprocal repulsive force opposes surface tension. Thus, the interaction between internal and external forces causes the whipping of the solution and eventually promotes its flow in the direction of the electric field. Specifically, the rise in the electric field causes the deformation of spherical droplets into conical forms, producing ultrafine nanofibers that can be collected on metallic collectors (Shitole, Dugam, Desai, et al., 2020).

Because of this process, three key factors can substantially affect the electrospinning of fibers. It includes the characteristics of the polymer solution, process parameters, and environmental conditions. The properties of a polymer solution include the

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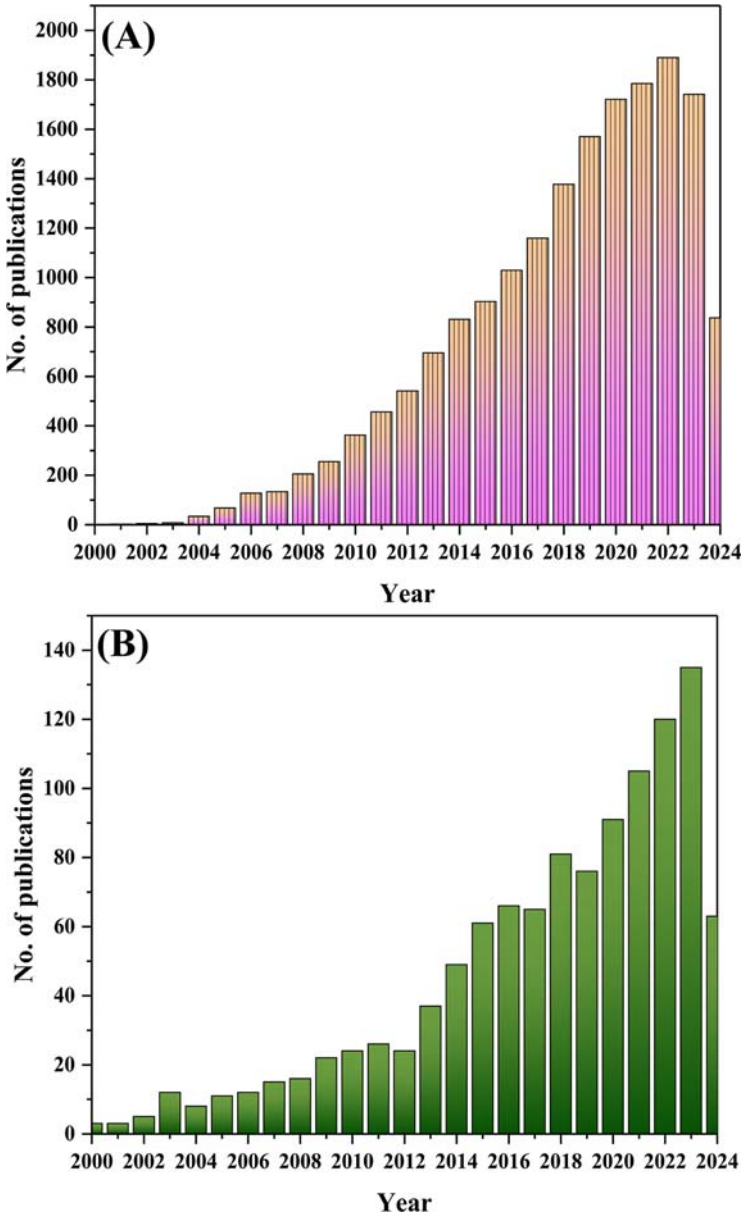


Figure 6.1 Number of scientific publications published as per Pubmed database from 2000 to June 2024 on (a) electrospinning and (b) sericin.
Database: Pubmed, Data collection: June 2024.

consideration of the relative molecular mass of the polymer, viscosity, surface tension, temperature, and solvent properties of the electrospinning fluid (Kailasa et al., 2021; Nangare et al., 2020). The relative molecular mass of the polymer is one of the important factors that influence the rheological as well as electrical properties of electrospinning fluid. Notably, polymers with a low molecular mass incline toward bead formation, while those with an increase in molecular mass tend to produce fibers with uniform diameter (Xue et al., 2019). Another variable, viscosity, reflects the polymer concentration in electrospinning liquids. Too low viscosity leads to inconsistent fiber production. However, if it exceeds a certain range, it may become difficult to pass through the nozzle, resulting in fiber sticking. Thus, optimum viscosity is necessary to form uniform spindle-shaped fibers. Considering surface tension, the electrostatic repellent force must be greater than surface tension. The surface tension can be modulated by altering the solvent composition or by adding solvent (Islam et al., 2019).

Solvent properties like conductivity, solubility, and volatility significantly affect the morphology of electrospun fibers. Specifically, an increase in conductivity decreases the diameter of fibers. Additionally, highly volatile solvents might block the spinning nozzle, while slowly volatile solvents endorse the adhesion of nanofibers (Sun et al., 2019). The key environmental factors that affect electrospinning include temperature and humidity. Particularly, extremely high temperatures promote the evaporation of electrospinning fluid, thus reducing its viscosity and subsequently causing the jet to solidify in advance, destroying the uniformity of fibers. Likewise, low humidity promotes solvent volatilization, whereas high humidity makes it difficult. Thus, the required morphology of nanofibers can be attained by altering humidity (Liu, Gough, et al., 2020). Process parameters include voltage, needle size, receiving distance, and spinning solution flow rate. Among them, voltage is a pivotal variable. Precisely as the applied voltage surpasses the critical voltage, a steady jet can be expelled. But, if it exceeds the confined range, the motion time is reduced, thereby leading to incomplete evaporation of the solvent (Zafar et al., 2016).

The distance between the nozzle and the collecting device can influence the strength of the electric field. Especially, a short distance can develop a strong electric field, and too short stretching distance can lead to fiber nonuniformity. An appropriate distance, stretching time, and length permit sufficient solvent volatilization, generating uniform fibers. Reportedly, the flow rate can be directly correlated with the diameter of the fibers. Similarly, reducing needle size leads to decreasing fiber diameter (Liu, Gough, et al., 2020). The voltage, flow rate, and distance between the needle and collector are critical parameters in electrospinning. These conditions affect the characteristics of the resulting electrospun nanofibers. Specifically, the voltage used in the electrospinning process impacts the formation of the Taylor cone and jet stability. High voltage can produce fine nanofibers but may also lead to bead formation. Regarding flow rate, a high flow rate can result in thick fibers or beads, while too low a flow rate can cause needle clogging. Finally, the distance between the needle and the collector drum affects fiber solidification and morphology. Therefore, optimizing this distance is necessary to prevent nanofiber fusion and ensure uniform deposition (Ji et al., 2024; Keirouz et al., 2023; Nangare et al., 2020; Shitole, Dugam, Desai, et al., 2020).

The presence of moisture in the electrospinning unit can significantly affect fiber production and its unique properties. High levels of moisture in the processing unit can lead to nanofibers with pores due to rapid solvent evaporation and moisture condensation. Moisture also affects the tensile strength and elasticity of the fibers. Additionally, moisture in the processing unit affects the conductivity of both the polymer solution and the air, influencing the electrostatic forces during the electrospinning process. Consequently, this influences the fiber diameter and the uniform distribution of the nanofibers. In addition to the aforementioned processing conditions, the solution properties play an imperative role in electrospinning. It is essential to focus on the conductivity, viscosity, and surface tension of the selected polymeric solution. A highly viscous solution may cause the formation of thicker fibers, whereas a low viscous solution may result in bead formation in the fibers. In applications such as energy, health, and the environment, fiber morphology plays a key role. The diameter of electrospun nanofibers can be influenced by voltage, solution properties, and flow rate. Fine electrospun nanofibers offer a high surface area-to-volume ratio, which is beneficial in filtration and catalysis. The impact of humidity in the electrospinning process can produce porous nanofibers, which are helpful for drug delivery and tissue engineering applications. The solvent evaporation rate and solution properties affect the surface texture of fibers, which plays a key role in cell attachment in tissue engineering and offers significant benefits for pollutant interaction in filtration processes (Ji et al., 2024; Keirouz et al., 2023; Nangare et al., 2020; Nezarati et al., 2013; Shitole, Dugam, Desai, et al., 2020).

The material properties, such as thermal stability, functional properties, and mechanical properties of electrospun nanofibers, are crucial for their use in various applications. The diameter and alignment of electrospun nanofibers can affect their elasticity, toughness, and tensile strength. Similarly, functional properties such as conductivity, antimicrobial activity, and drug release profiles can be modified through different electrospinning processes and surface tuning of the electrospun nanofibers. The choice of polymer and other excipients influences the thermal properties of electrospun nanofibers, which play a key role in applications such as environmental remediation and protection (Hiwrale et al., 2023; Langwald et al., 2023; Lasenko et al., 2023).

In terms of its types, generally, uniaxial electrospinning and coaxial electrospinning have been widely used for drug loading into nanofibers. The former approach involves simple blending. Here, the drug is dissolved in the polymer solution. Further, by utilizing this solution, the nanofibers are formed using a single nozzle. Interestingly, this simple process can encapsulate both hydrophilic and hydrophobic drugs as well. However, during this process, sensitive drugs can be denatured in the presence of organic solvents, leading to insufficient encapsulation efficiency and an uneven distribution of the drug in nanofibers (Sun et al., 2019). Coaxial electrospinning involves the development of core-shell nanofibers. Herein, core layer solution (solution of compound) and shell layer solution (polymer solution) are simultaneously electrospun using a co-axial nozzle to develop the core−shell structure. The controlled drug release can be obtained through shielding effects. This process has been widely employed in tissue engineering and medical dressings (Buzgo et al., 2018).

The advanced version of the coaxial process is the multineedle spinner's core−shell electrospinning. It enhances the process in terms of production efficiency and allows the simultaneous production of a maximum number of nanofibers. The key merits of multineedle spinners in electrospinning include increased output within a short time, scalability, the ability to combine multiple materials, and diverse functionalities such as controlled release characteristics, improved properties, and tailored surface characteristics (Beaudoin et al., 2022; Liu et al., 2024). Other techniques used for electrospinning include emulsion electrospinning, melt-blow electrospinning, gas-assisted electrospinning, roller electrospinning, self-bundling electrospinning, etc. Specifically, emulsion electrospinning is beneficial for producing a single fiber from two immiscible solutions. In a melt-blow setup, the diameter of the melted polymer is drastically reduced in the presence of a hot air stream. As the name suggests, in roller electrospinning, the roller electrode is dipped in a polymer solution. Another electrode fixed at the spine produces a nanofiber layer (Nadaf et al., 2022). In the case of magnetic field-assisted electrospinning, in addition to the basic components of the electrospinning apparatus, parallel permanent magnets or Helmholtz coils are used to produce nanofibers. These fibers show better uniformity and less splitting (Yuan et al., 2017, pp. 125−147). Another technique called centrifugal electrospinning involves the application of centrifugal force, which surpasses the surface tension and stretches the jet, and ultimately, the nanofibers are deposited on the collector (Peng et al., 2017). In the charge injection method, an emission electrode with a sharpened tip is placed over a blunt electrode. A strong electric field is developed in the solution placed between the electrodes. As this polymer solution travels between electrodes, it is continuously pushed out of the orifice under high pressure to produce fine fibers. In near-infrared electrospinning, the distance between the needle and collector is reduced to 500−3 mm to minimize curving unsteadiness. For solvent-free electrospinning, novel techniques like supercritical CO_2-assisted electrospinning and UV-curing electrospinning are widely employed. In the previous approach, the conventional solvent was replaced by supercritical CO_2 (Nadaf et al., 2022).

1.2 Applications of electrospinning

Electrospinning has been widely explored for biomedical and environmental applications. The extensive literature reveals the importance of electrospinning in both fields. In short, electrospinning has been extensively investigated in the development of drug delivery systems, either to improve the physicochemical properties of drug molecules or to achieve site-specific drug release. Fundamentally, the electrospun fibers have a high surface area, and typically, they encapsulate an amorphous form of active. Thus, this imbibes the suitability of nanomaterials for the development of fast-dissolving tablets by employing hydrophilic polymers. On the contrary, by utilizing hydrophobic polymers, extended drug release can be secured (Dziemidowicz et al., 2021). Interestingly, the electrospun fibers, which can potentially respond to external stimuli like pH and temperature, can be used to target drug release. In this line, core−shell fibers are used for targeting drug release in the small intestine using pH-sensitive polymers (Li et al., 2018). Recently, protein-loaded biomaterials have been in the

limelight owing to their promising application in immunotherapy. However, the delicate structure of proteins necessitates advanced materials for their delivery. Considering their simplicity and feasibility, electrospun scaffolds have been used to deliver proteins (Yıldız et al., 2020). Additionally, electrospun materials demonstrate great promise in diagnosis and imaging. This can be achieved by replacing the active with an imaging agent. Moreover, electrospinning has attracted the attention of researchers for theranostic applications due to its ability to incorporate multiple functional components into a single fiber (Nirwan et al., 2022). Overall, the literature indicates the potential of electrospinning in biomedical applications.

As well, in multidisciplinary fields like tissue engineering, electrospun fibers play an important role. It emphasizes damaged tissue regeneration by encapsulating cells into porous biomaterial-based scaffolds that can temporarily replace extracellular matrix to favor the growth of new tissues, organs, etc. This technique has been widely employed in the regeneration of bone, cartilage, tendon, ligament, skin, cardiac tissues, etc., (Liu, Ramakrishna, & Liu, 2020). In addition, electrospun nanomaterials have displayed remarkable potential in wound healing by encapsulating biomolecules that promote healing. In addition to biocompatibility and biodegradability, the morphological resemblance of electrospun scaffolds to extracellular matrix accelerates closure by improving tissue regeneration (Fahimirad & Ajalloueian, 2019).

Given environmental applications, electrospun scaffolds have been widely adopted for the construction of sensors. By adjusting the membrane material, pore size, and surface area of the nanofiber, specificity, as well as diversity, in sensing can be imparted. A high surface area offers numerous active sites for the adsorption of analytes. Thus, the strong molecular recognition potential of electrospun sensors provides high sensitivity and rapid response at a low cost (Song et al., 2023). In recent years, air pollution has drastically increased due to accelerated industrialization, which can lead to physiological dysfunction. Electrospun scaffolds have been used for sensing environmental pollutants like CO, SO_2, NO_2, and H_2S, and volatile compounds. Additionally, nanofibers fabricated by electrospinning offer an excellent ability to remove air pollutants compared to conventional filters due to their high permeability (Lu et al., 2021). Another widespread environmental issue is water pollution, which endorses a detrimental role in aquatic life as well as human health. Next, heavy metals present in water can be detected by electrospun nanomaterials (Chen et al., 2020). Additionally, antibiotics and pesticides can also be sensed by these nanocomposites. Thin-film biomembranes have been developed for water treatment. Besides these, biological contaminants like bacteria and viruses can also be detected by these electrospun scaffolds (Song et al., 2023). Separation of the gas mixture is of utmost importance for purification. In this line, metal-organic framework (MOF)-embedded nanofibers have been widely investigated for gas storage and separation owing to their extremely high surface area and tunable pore size. Investigation of advanced electrochemical devices is important for energy storage. For sustainable energy, the fabrication of high-performance electrodes is very important. Owing to their high surface area and flexibility, MOF nanofibers have become a promising candidate for energy storage and conversion (Dou et al., 2020). Overall, electrospun nanofibers can be used in the energy field, such as membranes in fuel cells, electrodes in batteries, and electrode

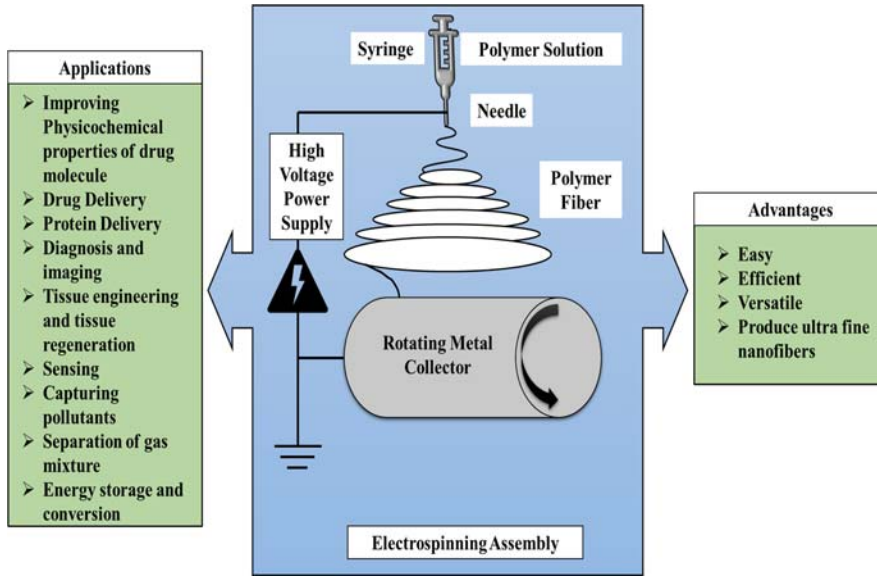


Figure 6.2 Representation of electrospinning assembly, advantages, and applications.

materials in supercapacitors. In the health field, electrospun nanofibers are utilized in drug delivery systems, tissue engineering, and wound dressings. The environmental applications of electrospun nanofibers include air filtration, water purification, and environmental remediation. In short, the literature indicates the promising potential of electrospinning in biomedical and environmental fields (Fig. 6.2).

2. Sericin: Suitable candidate for electrospun nanofibers

Silk is a natural fiber produced by *Bombyx mori* to develop cocoons and provide an ideal environment for the metamorphosis of larvae (Shitole, Dugam, Tade, & Nangare, 2020). The two key components of silk are fibroin (75%) and sericin (SS, 25%). Basically, in raw silk, SS encapsulates fibroin. Other minor components (1%−2%) in silk include carbohydrates, ash, waxes, etc. Fundamentally, SS is a glycoprotein composed of 18 amino acids, essentially serine (32%), aspartic acid (18%), and glycine (16%). Majorly, it is found in highly soluble amorphous coil form, while minor, it exists as an insoluble β-sheet. The favorable characteristics of this polymer, viz., biodegradability, biocompatibility, immunocompatibility, antiinflammatory, antibacterial, antioxidant, photoprotective activities, etc., make it suitable for biomedical and environmental applications. In the following section, we have discussed the extraction of SS from silk, its characteristics beneficial in the biomedical field, and its application in pharmaceuticals (Shitole, Dugam, Tade, & Nangare, 2020).

2.1 Sericin from silk

Insects like spiders, scorpions, bees, etc., synthesize silk. However, the commercial use of these biological sources for extraction is limited due to their unsuitability for extraction conditions. Thus, silk cocoons produced by the silkworm *Bombyx mori* are a favorable source for extracting pure SS, as it is a nonadulterated product due to the absence of thermal or chemical processing except drying for preservation (Ahsan et al., 2018). The SS gum is unglued from the fibroin by a process called degumming (Mowafi & El-Sayed, 2023). The classification of sericin includes sericin A, sericin B, and sericin C. Table 6.1 shows the classification of SS based on the position layer, amino acids, nitrogen content, water solubility, etc., (Shitole, Dugam, Tade, & Nangare, 2020).

Several methods have been reported for the extraction of SS from cocoons, which can be classified into three types: physical, enzymatic, and chemical methods (Ahsan et al., 2018). Among conventional physical processes, simple hot water extraction is the most commonly used. Herein, silk is heated in water excluding the addition of any chemicals. Notably, the time and temperature of heating play a key role in the quantity of SS extracted. Even though, it is a simple method, the purity of the SS obtained by this method is of substandard quality compared to that obtained by the other techniques and gives very little information related to its composition (Rangi & Jajpura, 2015). In some reports, the addition of sodium bicarbonate and soap in the aqueous solution of silk fibroin and its subsequent heating is reported. Nevertheless, in this procedure, the quantity of SS is very low due to its low recovery rate, subsequently losing its functional characteristics. Frequently, the silk structure is damaged by the extraction done by the boiling process. Furthermore, the prolonged boiling

Table 6.1 Classification of SS based on different parameters.

Sr. No.	Parameter	Sericin A	Sericin B	Sericin C
1.	Layer position in sericin	Outermost	Middle	Innermost
2.	Nitrogen in percent	17.2%	16.8%	16.6%
3.	Amino acids	Aspartic acid, glycine, threonine, serine	Aspartic acid, tryptophan, threonine, serine, glycine	Proline, threonine, serine, glycine, aspartic acid
4.	Solubility in water	Insoluble in hot water	Not reported	Insoluble in hot water
5.	Acid hydrolysis method	Not reported	It provides amino acids of sericin A in addition to tryptophan.	It provides proline in addition to the amino acids of sericin B.

process affects the molecular weight. The fragmentation of SS results in the lowering of the molecular weight. It brings about the amorphous region's degradation, counting their hydrophilic properties. Taking into account the insufficiency of conventional extraction processes, other enzymatic and chemical processes are being established for SS extraction (Arango et al., 2021). On the other hand, SS obtained by enzymatic extraction procedures has superiority in amino acids, total amino acid value, and DPPH radical scavenging activity as its quantity is three-fold higher compared to those obtained by conventional water extraction methods. Relative to other methods, the enzymatic extraction process yields shorter peptides and free amino acids as the protease enzyme utilized in the extraction process of SS brings about the breakage of peptide bonds. The only limitation to using this process is its high price when used on a large scale. On the contrary, the chemical extraction process involves the utilization of chemicals such as sodium chloride, sodium carbonate, urea, and urea–mercaptoethanol. Thus, the removal of the chemicals adds one more step to the purification of SS, which makes it hard to extract SS of higher quality (Seo et al., 2023).

Interestingly, SS demonstrates several beneficial properties, which make it relevant for pharmaceutical applications. One of the major requirements of the biomedical field is biocompatibility. Fortunately, biocompatibility has been confirmed for SS in many literature reports. It is also biodegradable, eliminating the need to remove it from the system. As well, it displays antioxidant, antiinflammatory, antibacterial, and photoprotective activity. In addition, owing to the amphiphilic characteristics of SS, it can be used for both hydrophilic and hydrophobic drug delivery. Considering this, scientists have attempted various delivery systems based on SS (Silva et al., 2022).

2.1.1 Life cycle assessment

To provide the technical and economic feasibility of the process developed to recover products from waste is essential in the resource recovery concept (Capar et al., 2022). Life cycle assessment (LCA) helps study and evaluate the product's impact on the environment throughout its entire life cycle, from the extraction of the required raw materials to the final waste product (such as the cradle-to-grave approach). The applications of LCA have provided major successes in product development and decision-making processes (Malara et al., 2021). According to the literature, LCA is a suitable tool for evaluating the impact of a product on the environment throughout its life cycle (Wani & Mishra, 2024). As mentioned in the literature, the silk protein (silk fibroin) separation process results in silk degumming water that contains a high amount of SS. This waste product can cause major environmental issues, including toxicity, acidification, climate change, nonrenewable energy consumption, and ozone layer depletion. Importantly, the recovery of SS from the waste has a significant impact on the environment. According to LCA, sericin recovery from this wastewater can be conducted using two different scenarios. The base scenario considers no recovery, while the second scenario involves SS recovery using membrane hybrid processes. These processes include nanofiltration, precipitation, lyophilization, sedimentation, silk degumming, and spray drying. In contrast, the base scenario involves the silk degumming process and the treatment of degumming wastewater. Despite the major benefits

of LCA, its use in silk production is very limited, and there is not much information on the LCA of silk production. Only a few studies have mentioned the direct and indirect impacts on the environment. It has been reported that sericin has a higher environmental impact than other natural fibers (Capar et al., 2022). According to the data from PubMed (website: https://pubmed.ncbi.nlm.nih.gov), there are nearly 1130 scientific articles available on sericin (Fig. 6.1b). In this section of the book chapter, we shed light on the different properties of SS along with its dosage forms and biomedical and environmental applications.

Hydrogel formulations are hydrophilic, cross-linked polymeric networks that can absorb and retain water without solubilizing. Among the different natural biopolymers, SS is a potential polymer for hydrogel formulation as it is composed of amino acids comprising hydroxyl side chains. In another study, Tao et al., synthesized SS-based antibacterial hydrogel for wound dressing. Initially, the sodium alginate has been functionalized with SS using calcium ions to form a moldable and injectable network of hydrogel. Moreover, to enhance the antibacterial activity, silver nanoparticles have been developed via the in situ process. The hydrogel showed an optimum swelling ratio and a retention ratio. The antibacterial activity was achieved due to the disruption of the bacterial membrane. Further, the cytocompatibility study proved the cytocompatibility of hydrogel. In addition, an animal study confirmed that hydrogel promoted wound healing (Tao et al., 2021). On the other hand, Guo et al. developed a micellar formulation based on SS for targeted delivery in gastric cancer. Researchers used vitamin B, synthetic poly(benzyl-L-glutamate) (PBLG), and SS for fabricating micelles loaded with paclitaxel (PTX). Initially, the SS-PBLG conjugate has been formed by a ring-opening polymerization reaction. Further, vitamin B12 (VB12) has been dissolved and added to the SS-PBLG reaction mixture. Lastly, VB12-SS-PBLG micelles have been developed by dialysis. Here, VB12-SS-PBLG-PTX micelles showed optimum particle size and biosafety. Micelles excluding drugs showed biocompatibility with BGC-823/PR cells, while drug-loaded micelles displayed significant cytotoxicity. In addition, in vivo studies revealed that VB12-SS-PBLG-PTX micelles could target CD320-positive tumors. The evaluation related to the physicochemical properties of micelles, their antitumor activity mechanism, and cellular uptake was based on studies that showed that VB12-SS-PBLG-PTX micelles showed less particle size distribution and great stability. On the other hand, the in vitro, in vivo, and cell line studies proved biocompatibility and better cellular uptake. Further studies demonstrated the antitumor mechanism involved to be altering mitochondrial transmembrane potential/apoptosis by endocytosis mediated by the transcobalamin II (CD320) receptor, which helps tackle drug resistance. Overall, the study concludes that the caliber of SS-PBLGPTX micelles for targeted delivery (Guo et al., 2019). In a similar line, Deng and co-researchers developed IR780-loaded SS nanomicelles. Generally, IR780, a near-infrared dye, is widely used in photodynamic therapy (PDT) and photothermal therapy (PTT). But, its inherent hydrophobicity and photosensitivity limit its application. Considering this, the researchers modified hydrophilic SS with hydrophobic cholesterol to develop an amphiphilic conjugate. Further, folic acid was linked to this conjugate for tumor targeting. Finally, IR780 was encapsulated into this macromolecule to develop micelles by self-assembly. Notably, the solubility and

photostability of IR780 were significantly improved. In addition, the conjugate was absorbed by gastric cancer cells owing to the presence of folic acid. Remarkably, the conjugate depicted improved PDT and PTT cytotoxicity for BGC-823 cells in the presence of laser irradiation, thus confirming its potential as a carrier for PDT and PTT therapy (Deng et al., 2019). Because of its noninvasiveness, low toxicity, and flexibility, PDT has been widely employed to treat cancer. However, hydrophobicity and poorly targeted accumulation of photosensitizer limit its potential. To surpass these limitations, Gao and co-researchers developed chlorin e6 (Ce6)-loaded SS-based nanoparticles. Briefly, amine-functionalized SS has been synthesized by the carbodiimide coupling method. Further, chlorin E6 has been loaded onto it by the amidation reaction. Further, Ce6-loaded SS-based nanoparticles have been fabricated by the dialysis method. Relative to free Ce6, the prepared nanoparticles demonstrated enhanced intracellular uptake potential and penetrability into tumor cells. Also, this nanoagent showed negligible cytotoxicity toward 4T1 cells in darkness, while significant cytotoxicity was observed in the presence of irradiation. In vivo studies showed superior accumulation of Ce6 at the tumor site and improved tumor growth suppression relative to neat Ce6. Overall, SS-based nanoagents displayed promising potential for phototherapy of cancer (Gao et al., 2021). In 2016, Ersel and colleagues assessed the wound-healing activity of the SS gel. For this, SS gel was prepared by adding Na-CMC to distilled water. Further, a 1% aqueous solution of SS was added to the Na-CMC dispersion to produce a gel. To evaluate wound healing activity, 28 Wistar-Albino rats were selected and divided into four equal groups, from which the control group was excluded from intervention. The histopathological study and biochemical analysis showed that in comparison to the sham group and placebo group. There seemed to be an increased thickness of the epidermal layer and increased vascularization. As well as the necrosis, hair root degeneration, edema, collagen discoloration, and cellular infiltration, they were reduced to a much greater extent in the SS-treated group. There was also a decrease in malonyl dialdehyde levels and an increase in glutathione peroxidase, superoxide dismutase, and catalase activities. In conclusion, SS showed a potential wound healing and antioxidant effect, and SS-based formulations can boost the wound healing process (Ersel et al., 2016). In recent times, modified delivery systems have replaced conventional dosage forms to improve the therapeutic efficacy of drugs. In this line, Bezerra and his team developed modified-release furosemide-loaded SS/alginate beads. Reportedly, furosemide exhibits a short half-life and thus necessitates multiple administrations. To extend the half-life of active, researchers synthesized SS/alginate beads by adding alginate to the SS solution. Consecutively, proanthocyanidin has been added to the blend to achieve a high incorporation rate. Further, the drug has been incorporated into the blend, and then the resultant solution has been added to the cross-linking solution. It has been observed that SS/alginate beads showed sustained release of furosemide. Thus, this modified release system could improve patient compliance (Bezerra et al., 2021). In another study, Vidart and co-researchers fabricated diclofenac-loaded SS and alginate particles. Briefly, for the preparation of the SS/alginate blend, sodium alginate has been dispersed into the SS solution, followed by the addition of diclofenac. Further, the particles have been developed by the ionic gelation technique, in which the blend has been added to a calcium chloride solution

for cross-linking. The spectrophotometric analysis supported the drug incorporation. The optimized batch showed 81.06% drug release. In vitro dissolution showed that SS delayed diclofenac release and alginate-aided formulations' gastro-resistance. Overall, SS/alginate particles demonstrated promising potential for gastro-retentive drug delivery (Vidart et al., 2018).

In terms of environmental applications, SS can efficiently remove heavy metals that contaminate the environment. In this line, Silva and co-researchers prepared an SS-alginate blend by gelation technique followed by thermal cross-linking. Notably, the blend demonstrated excellent adsorption potential for copper and zinc ions (da Silva et al., 2016). In another similar study, Silva and team fabricated an SS-alginate blend employing the diffusion method, and its affinity toward toxic metals has been assessed. Particularly, copper (Cu), cadmium (Cd), lead (Pb), and chromium (Cr) have been effectively removed by the blend (da Silva et al., 2017, pp. 57–86). In 2017, Verma and co-researchers investigated SS as an adsorbent to remove ibuprofen from the aqueous solution in an integrated adsorbent-membrane process. The researchers performed a study at different adsorbent concentrations, physiological conditions, temperatures, and pH. Notably, complete ibuprofen removal was observed at 10 mg/L ibuprofen concentration using 10 g SS at pH 4 and 40°C (Verma & Subbiah, 2017). In another study, Verma and co-researchers fabricated an SS-coated polyester-based filter to remove particulate matter. Herein, dip-coating and thermal fixation were used to coat SS on the polyester. The filter was evaluated for its potential to remove particulate matter and volatile compounds. Notably, the SS-coated air filter also proved very effective for the removal of particulate matter and volatile compounds like benzene, toluene, etc., (Verma et al., 2019). Hence, it confirmed that the preference for SS opens a new era for biomedical and environmental remediation applications.

2.2 Preparation of SS electrospun nanofibers

The SS is a versatile protein that offers a multitude of benefits in diverse fields. Relative to other excipients, SS is nontoxic, biocompatible, economical, and readily available. In addition, SS exhibits excellent antioxidant potential, antibacterial activity, and good thermal stability. Moreover, due to the presence of polar functional groups, SS can be co-polymerized with numerous additives (Shitole, Dugam, Tade, & Nangare, 2020). Because of these benefits, several researchers have employed electrospinning techniques to develop SS nanofibers. In addition, the researchers have investigated the impact of several constraints on the morphology of SS nanofibers. Particularly, solvent selection plays a key role in electrospinning as it influences the spinnability of the solution. The selected solvent should have an optimum boiling point, vapor pressure, and volatility. In the case of SS, various solvents, viz., dimethyl sulfoxide, N, N-dimethyl-formamide, 1,1,1,3,3,3-hexafluoro-2-propanol, trifluoroacetic acid, and lithium chloride, have been screened for electrospinning as it is slightly soluble in water below 75°C. Among these solvents, SS showed high solubility in trifluoroacetic acid due to the protonation of amino groups in SS and its ionic interaction with trifluoroacetate anions, which improved the spinnability of the polymer solution (Khan & Tsukada, 2014).

Zhang and co-researchers investigated the effect of SS concentration on nanofiber morphology. Herein, a sample solution has been prepared by dissolving 40 wt%, 50 wt%, and 60 wt% of SS in deionized water, and the resultant solution was subjected to electrospinning. Isolated spindle-like beads were found at 40 wt%. While smooth morphologies of beads were observed at 50 and 60 wt%. Nevertheless, the diameter of the fibers was increased to 60 wt%. In this, an increase in the concentration of SS leads to higher viscosity, which favors the fabrication of smooth fibers without beads. In the same study, researchers also investigated the effects of varying voltage from 13 to 25 kV on the nanofibers. At low voltage (13 kV), bead formation has been noticed, whereas smooth nanofibers have been formed as the voltage was increased to 25 kV (Zhang et al., 2011). In a similar line, Goudarzir and the team studied the effects of varying voltage and distance on the morphology of chitosan(CS)/SS/poly(vinyl alcohol) [PVA] fibers. It has been noted that the mean diameter of fibers was reduced with increasing voltage, from 17 to 21 kV. It may be due to the stretching of the polymer solution. Because of the spinning distance, at a shorter distance (10 cm), the diameter distribution has been narrower, whereas as the distance increased (15 cm), bead formation has been observed along with a larger diameter distribution. Overall, the optimization of parameters is of utmost importance in electrospinning to obtain nanofibers displaying smooth surface morphology (Hadipour-Goudarzi et al., 2014).

3. Pharmaceutical applications of SS-mediated electrospun nanofibers

A literature survey revealed that the SS has huge potential in the research area. Therefore, the biomedical applications of SS-based electrospun nanofibers for drug administration and wound dressing are discussed in this book chapter. In 2022, Chachlioutaki and colleagues published SS-polylactide-co-glycolic acid (PLGA) as a ketoprofen-eluting scaffold for the therapy of periodontal health issues. In summary, the concentration of SS (0.5% W/W of PLGA) has been regarded as an optimum concentration for ketoprofen loading. In this case, the adhesive behavior and hydrophilicity of SS aid in the modification of PLGA characteristics, including mechanical qualities. Furthermore, it increased the total degradation rate, resulting in the development of outstanding candidates for cell attachment and proliferation in human gingival fibroblasts (HGFs). In this study, scaffolds containing 0.5% w/w SS-PLGA exhibit a high rate of cell metabolic activity as well as high cell survival after 24 h when compared to control cells. As a result, it ensured high biocompatibility. Furthermore, the proposed composite demonstrates continuous release of ketoprofen (85% in 15 days) at the illness site, which aids in the management of inflammation at the disease site. The in vivo murine macrophage model demonstrates that the proposed scaffold has strong antiinflammatory capability. As a result, the usage of a ketoprofen-loaded SS-PLGA-based electrospun scaffold can be an effective choice for periodontal disease management (Chachlioutaki et al., 2022). Bakhsheshi-Rad and colleagues demonstrated the use of PVA (10%w/v)-CS (2%w/v) with SS

(concentration range of 1%−5% w/v) based electrospun nanofibers for tetracycline administration followed by wound dressing applications (Fig. 6.3). In summary, a PVA: SS (1:1) solution has been combined with CS (1:1%w/v) to create electrospun nanofibers. Here, the hydrophilicity of this fiber has grown as the SS content has increased. Importantly, it may aid in increasing cell adherence on the surface of designed fibers. The SS concentration also has a proportionate association with the swelling ratio. The biocompatibility research of developed nanofibers with low-concentration SS on L929 cells shows that they have stronger proliferation than fibers with only CS and PVA. In this case, cell viability has a linear connection with the nanofiber incubation period. Interestingly, it demonstrates the quick followed by a gradual release of tetracycline, which is related to the quantity of tetracycline and polymeric composition. Furthermore, due to the synergistic benefits of SS and tetracycline,

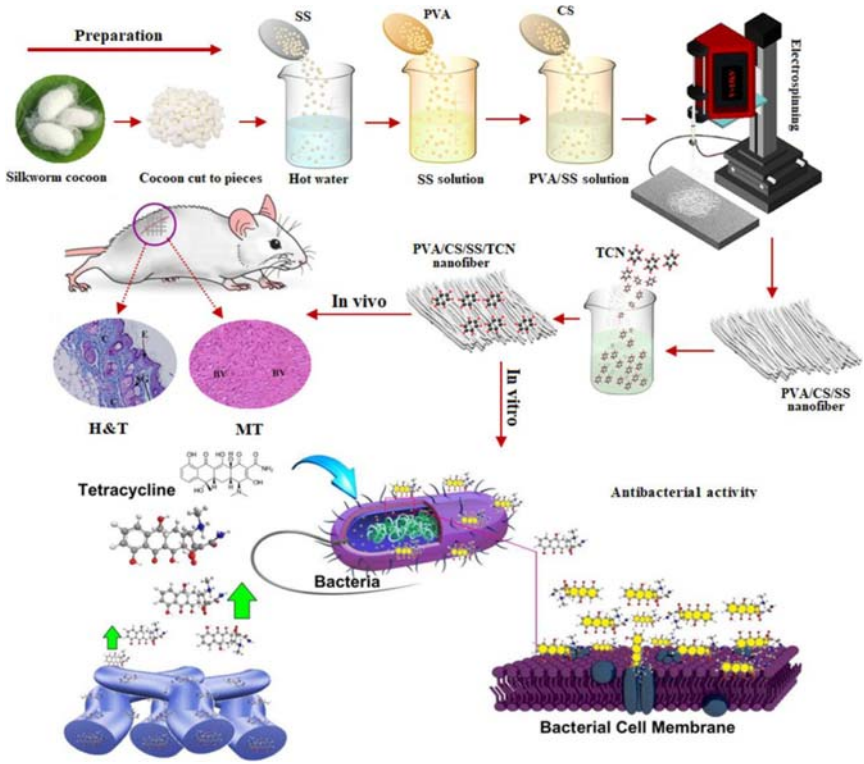


Figure 6.3 Design of PVA (10%w/v)-CS (2%w/v) with SS (concentration range of 1%−5% w/v) based electrospun nanofibers for tetracycline administration followed by wound dressing applications.
Reprinted (adapted) with permission from reference Bakhsheshi-Rad, H. R., Ismail, A. F., Aziz, M., Akbari, M., Hadisi, Z. Omidi, M., Chen, X. (2020). Development of the PVA/CS nanofibers containing silk protein sericin as a wound dressing: In vitro and in vivo assessment, *International Journal of Biological Macromolecules, 149*, 513−521. Copyright 2020 Elsevier B.V.

it displays high antibacterial activity for *Staphylococcus aureus* (*S. aureus)* and *Escherichia coli* (*E. Coli)*. Furthermore, in vivo, testing showed that the nanofibers containing SS improves wound healing efficacy. In addition, it promotes collagen deposition and re-epithelialization more than nanofibers containing only CS and PVA (Bakhsheshi-Rad et al., 2020).

Green-synthesized silver nanoclusters with SS-based electrospun nanofibers have been described by Mehdi and colleagues for better antibacterial uses. In summary, silver nanoclusters including SS have been generated using a single-step in situ technique in which silver nitrate (50 mg/mL) had been added to SS. In this case, SS is used as a precursor for the production of silver nanoclusters, acting as a stabilizing agent, reducing agent, and capping agent. Following this synthesis, the resulting solution (1.7 mg/mL) has been combined with cellulose acetate (CA, 17%), and electrospun nanofibers have been created. Finally, the antibacterial activity of produced nanofibers is outstanding against *E. coli* and *S. aureus,* which might be attributed to a combination of SS and silver nanoclusters (Mehdi et al., 2021). In 2021, Marvi and colleagues used electrospinning to create SS and *Equisetum arvense* (EA) adorned titanium implants to boost stem cells with osteogenic differentiation. In short, the electrospinning approach was used to create EA-containing PVA- and SS-(20:80) based bioactive nanofibrous coating. The release of an EA profile has been shown exactly related to the concentration of EA in this study. The cell line investigation with hADSCs revealed 90% cell viability, indicating high biocompatibility. As well, cell proliferation has been shown proportional to culture duration in this study. Overall, the PVA and SS covering of EA promote cell adhesion, proliferation, and differentiation. As a result, it is a viable option for bone regeneration applications (Marvi et al., 2022). Basaran and colleagues described electrospun nanofiber-mediated scaffolds based on SS and gelatin (1:2) for wound healing applications. In summary, heparin has been integrated into PLGA nanoparticles before designing SS and gelatin nanofiber for topical distribution. The developed SS and gelatin (1:2) nanofibers release 40% of the drug from the scaffold in 1 week, but the heparin-loaded PLGA nanoparticles including gelatin nanofibers release 85% of the drug in 1 week. According to the degradation research, including SS in the scaffold reduces the rate of deterioration. It also has a great fiber shape and high water retention, making it a perfect option for wound healing applications. The biocompatibility investigation of the developed scaffold reveals that it has good cell viability (80%) after 24 h, which is comparable to the control group. This cell viability was determined to be high in this case in terms of time. On the fifth day, an Alamar blue cell viability assay verified the increase in cell proliferation. As a result, the planned scaffold may pave the way for novel skin tissue engineering applications such as wound healing or skin regeneration (Başaran et al., 2021). Lin and Zuo created the novel dressing material utilizing an electrospinning process using SS and silk fibroin (SF). In summary, the optimal concentration of SS and SF (3:7) has been discovered for the construction of electrospun nanofiber−mediated dressing materials with good surface hydrophilicity, consistent fiber structure, and high water vapor transfer rate (MVTR). Specifically, the concentration of SS provides excellent membrane porosity and hence good MVTR. Furthermore, the developed dressing materials provided a high degree of swelling due to the hydrophilic functional groups of SS, as well

as superior tensile qualities due to the high viscosity of SS. The biocompatibility research utilizing a cell line from mouse embryonic fibroblasts validated the improved cell adherence and proliferation. Overall, the developed SS-SF-based dressing materials can be an ideal alternative to standard dressing materials in terms of hydrophilicity and moisture vapor transfer rate (Lin & Zuo, 2021). In 2021, Vineis and colleagues reported the combined performance of nanofibers consisting of SS and keratin in different in vivo applications. In summary, the presence of SS (10 %w/v) in keratin (10 %w/v)-based electrospun nanofibers resulted in a reduction in amine group hydrogen bonds while providing a wide diameter distribution for generated electrospun nanofibers. This has been verified in a biocompatibility investigation of human mesenchymal stem cells (hMSCs) at various periods. After 7 days, the synergistic impact of SS and keratin on hMSC showed a considerable increase in cell proliferation. As a result, this natural protein-based combination has the potential to be employed for tissue engineering as well as other biomedical applications in the future (Vineis et al., 2021). In 2021, Li and colleagues developed SS/poly(N-isopropylacrylamide)/poly(ethylene oxide)-based electrospun nanofibers as (SS/PNIPAM/PEO) modified cotton fabric for tissue engineering and other biomedical applications. In summary, three distinct strategies for designing the required fabric have been reported: crosslinking, interpenetrating polymer networks, and electrospinning. The concentrations of SS and PEO have been chosen to be 6% and 15%, respectively, with 6.5 wt% monomers NIPAM utilized to form the SS/PNIPAM/PEO composite. Consequently, the pH- and temperature-sensitive function of the developed nanofiber-based fabric has been proven. At pH 4, the hydrophobic and noncharged version of the SS side chain gives a low swelling ratio. In this case, the protonated $-NH_3^+$ of SS at pH less than or more than four causes a considerable swelling ratio. The antibacterial activity of the developed SS-based nanofabric was confirmed in the presence of *S. aureus* and *E. coli*. In this case, the preference for SS in nanofibers can govern the normal movement of bacterial species while also inhibiting respiration, which leads to death. Furthermore, SS provides electrostatic attraction, which can limit bacteria conductivity and lower cell membrane permeability. As a result, it may be employed in multifunctional stimuli-responsive smart materials for biomedical and other applications (Li et al., 2021). In 2022, Anand and colleagues created electrospun ferulic acid (FA)-loaded SS-polycaprolactone (PCL)-cellulose acetate (CA)-based nanofibrous biomimetic multifunctional mats for wound healing applications. In summary, the nanofibrous mat has been produced by isolating SS from silk cocoons via degumming. Using 8% w/v of SS, hybrid nanofibers have been developed. Other ingredients in the polymer solution include CA (12% w/v), PCL (12% w/v), and FA (2% w/v) that play the key part in mat. Because of the high hydrophobicity of CA, the swelling index demonstrates a greater water retention capacity and swelling in a blend of SS- and PCL-based nanofibers than in SS and CA. In this case, FA−SS−PCL mat provides continuous FA release for an extended period (71.23% in 12 h), whereas FA−SS−CA-based mat provides 59.24% drug release in 12 h. The biodegradability analysis reveals that the PF-loaded SS-PCL-based composition degrades about 95.63% faster than the CA-mediated mat (72.42%). Because of the integration of SS and FA, the antibacterial action against *Pseudomonas aeruginosa (P. aeruginosa,*

gram-negative) and *S. aureus* (gram-positive) was obtained to be strong. The cell cytotoxicity investigation in human keratinocytes (HaCaT) cells confirmed the developed nanofiber-based mat's low cytotoxicity. Diabetic rats had good wound healing capacity, and histopathological analysis demonstrated the recovery of normal skin structure. Overall, these FA−SS−PCL and CA-based mats are promising options for treating diabetic foot ulcers (Anand et al., 2022). In 2023, Karthick and colleagues created green-synthesized silver nanoparticles loaded electrospun nanofiber-mediated dressing material for wound healing utilizing SS, CS, and PVA. In brief, SS has been extracted from a silk cocoon (*Bombyx mori*) using a previously described alkali degumming procedure in this research. In this case, the PVA: SS: CS (8:1:1) blend performs admirably as a dressing material. Because of the presence of SS and CS, MVTR revealed that the specified matrix provides a suitable vapor transmission rate. As a result, it aids in the regulation of water dehydration at the affected wound site. The antibacterial efficacy against *S. aureus* and *E. coli* ensured a 32 and 17 mm zone of inhibition, respectively (Fig. 6.4). Importantly, the broadest zone of inhibition has been provided by the high concentration of CS and SS because of their inherent characteristics. Furthermore, the cell viability analysis on L929 cells displays no obvious cytotoxicity because of the

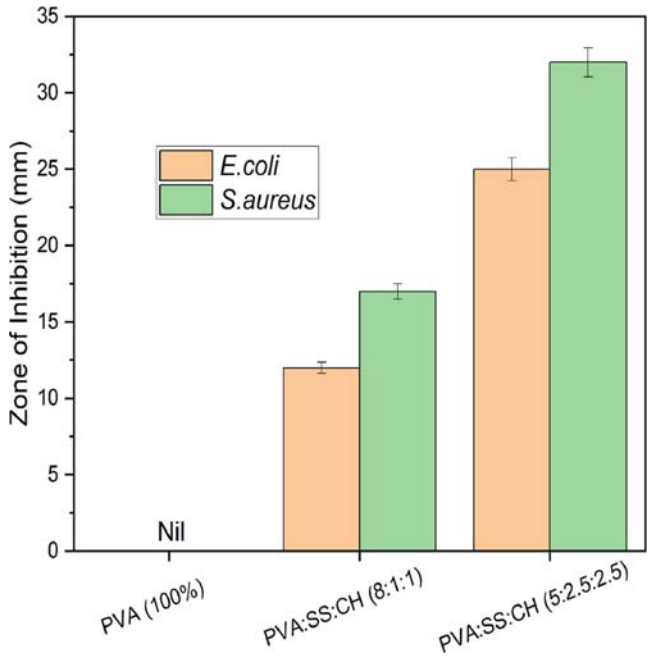


Figure 6.4 Antibacterial assay of silver nanoparticle−loaded electrospun nanofiber−mediated dressing material.
Reprinted (adapted) with permission from reference Karthick, S.A., Manjari, K., Devi, M. G. (2023). Biocompatible and bioactive PVA/Sericin/Chitosan nanofibrous wound dressing matrix. *Applied Surface Science Advances, 13*, 100362. Copyright 2022, Elsevier.

nontoxic behavior of SS and CS. As a result, it may be recommended as an appropriate wound dressing matrix for future considerations (Karthick et al., 2023).

In 2018, Gilotra et al. published a novel wound dressing material made from PVA and SS (8:1 w/w) by an electrospinning technique. In summary, due to the use of SS as an ideal component, this created mat has high swelling capacity, biocompatibility, antibacterial activity, and antioxidant activity. Furthermore, this developed mat has a higher proliferation rate than its single parts when tested with murine fibroblasts (L-929) and human keratinocytes (HaCat). The wound healing activity ensured that there would be no inflammatory reaction, followed by a high wound healing recovery rate. Overall, the utilization of stainless steel in the design of wound dressing materials is critical. As a result, in the future, SS-based electrospun nanofibers-based materials may be employed to treat diabetic chronic wounds (Gilotra et al., 2018). In a similar line of research, SS and PVA-based electrospun nanofibrous scaffolds have been developed. In summary, the SS was extracted from silk cocoons using a simple hot water degumming procedure, whereas the electrospun nanofiber was fashioned utilizing a variety of SS and PVA proportions. Consequently, the optimized SS/PVA ratio (7.5:1.5 and 10:1.5%w/w) gives excellent mechanical characteristics and stability. It also provides fiber sizes ranging from 60 to 500 nm, with the high concentration of SS and PVA having a proportionate connection with the diameter of the nanofibers. The biocompatibility investigation employing Primary Normal Human Dermal Fibroblasts (NHDF) cells confirmed the suggested nanofibrous scaffold's nontoxic behavior. Overall, the SS/PVA nanofiber is a good choice for use in biological applications (Kumkun et al., 2019). In 2018, Massoumi and colleagues published a study detailing the electrospinning procedure used to create wound dressing materials made of SS and gelatin. In short, the developed SS-gelatin nanofibers have been individually loaded with zinc and copper ions integrated halloysite nanotubes. Due to the combined actions of copper ion and SS, nanofibers containing copper ions provide fine fibers as well as strong antibacterial potential. Cell viability declines in the instance of a cell line investigation on L929 cells. On the other hand, zinc ion−integrated nanofibers demonstrate improved cell survival and other metrics such as collage secretion, cell adhesion, and so on. Furthermore, it has a high antibacterial activity against both Gram-positive and Gram-negative microorganisms. As a result, the zinc-loaded halloysite nanotubes with SS/gelatin nanofibers as a dressing material open up new possibilities for antibacterial wound dressing applications (Massoumi et al., 2019). Sapru and colleagues have created the SS-based CS nanofibrous loaded with cephalexin hydrate for wound healing applications. In short, the optimized concentration SS (2/4 %w/v) was mixed with 2% w/v CS (1:1) before adding 10 %w/v PVA (1:1 %w/v). The inclusion of SS in electrospun nanofibers increases mechanical strength and stability, which is useful for tissue engineering applications. In this case, the cephalexin hydrate-loaded SS nanofibers enable wound healing with minimal inflammation and no evidence of infection. Overall, the in vivo wound healing verified the use of design nanofibers in real time. The MTT test confirmed cell adherence and proliferation in the HaCaT cell line. Its antibiotic-loaded SS nanofibers have a high antibacterial capability against both Gram-positive and Gram-negative bacteria. Overall, the incorporation of

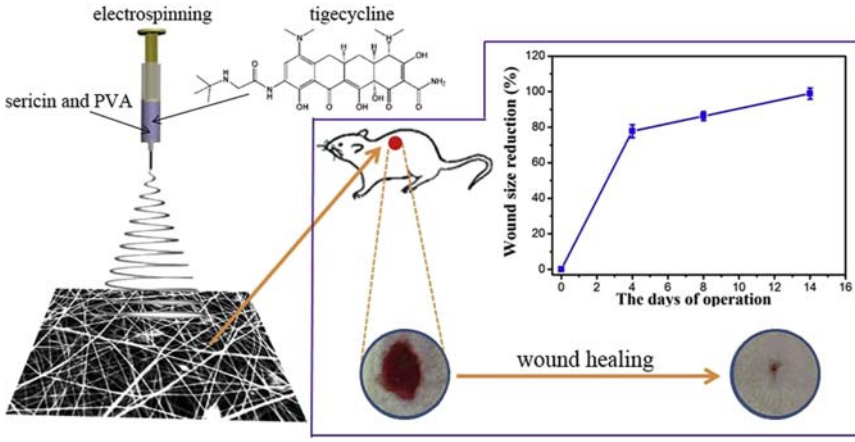


Figure 6.5 Tigecycline-loaded SS/PVA electrospun nanofiber−based composite for wound healing application.
Reprinted (adapted) with permission from reference Chao, S., Li, Y., Zhao, R., Zhang, L., Li, Y., Wang, C., Li, X. (2018). Synthesis and characterization of tigecycline-loaded sericin/poly (vinyl alcohol) composite fibers via electrospinning as antibacterial wound dressings. *Journal of Drug Delivery Science and Technology, 44*, 440−447. Copyright 2018, Elsevier.

SS in the creation of wound dressing materials provides an effective therapeutic option for chronic wounds (Sapru et al., 2018) (Fig. 6.5).

In 2018, Chao and colleagues created a tigecycline-loaded SS/PVA electrospun nanofiber−based composite with increased antibacterial potential in wound dressing applications. In summary, for the electrospinning procedure, PVA (0.6 g) and SS (0.2 g) were blended with tigecycline. As a result, it has outstanding porosity, mechanical properties, and morphology with a nanoscale diameter that is consistent and smooth. Furthermore, this SS-based nanofiber composite provides appropriate WVTR, which aids in wound healing. The release profile guarantees 75% release of drugs within 100 min. Finally, the combination of tigecycline with SS results in high antibacterial efficacy against *Bacillus subtilis* and *E. coli*. The high rate of wound healing was validated by the in vivo wound healing investigation. As a result, the usage of SS-based composites in the future will open the way for antibacterial wound dressings (Chao et al., 2018). In 2023, Joshi and his team designed chlorhexidine acetate-loaded polyurethane/halloysite nanotubes and SS-based electrospun antibacterial nanocomposites. This design offers a controlled release of antimicrobial agents, playing a key role in sustained antibacterial activity against both Gram-negative and Gram-positive bacteria. The 1:1 ratio of halloysite nanotubes to chlorhexidine acetate allows for high drug loading in electrospun nanofibers. Cell line studies of the designed nanofibrous composite confirmed good biocompatibility. Therefore, the fabricated nanocomposite can be used in various biomedical applications, including wound healing and antimicrobial treatments (Joshi et al., 2023). Fig. 6.6 depicts the applications of SS-based electrospun nanofibers. In conclusion, the utilization of

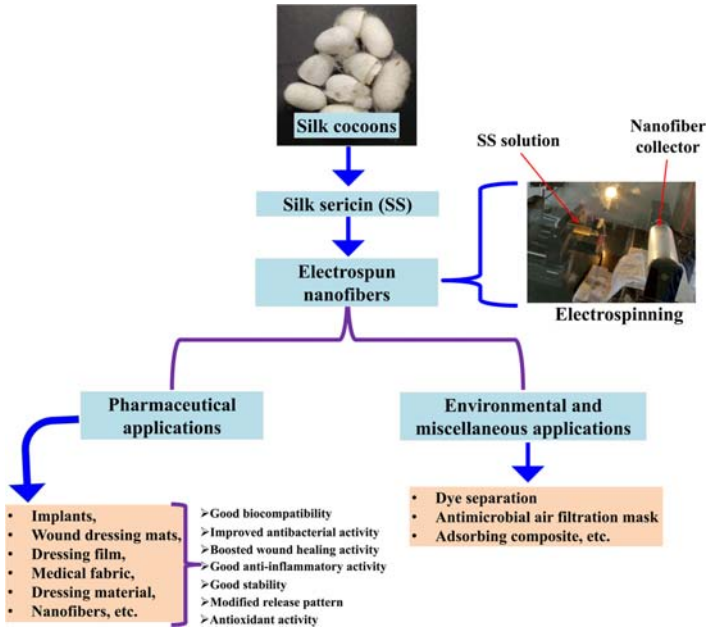


Figure 6.6 Applications of SS-based electrospun nanofibers in pharmaceutical, environmental, and other field.

SS-based electrospun nanofibers offers a new option for biomedical applications. Table 6.2 summarizes the pharmaceutical applications of SS-mediated electrospun nanofibers.

4. Environmental and miscellaneous applications of SS electrospun nanofibers

To address environmental contamination, a superior composite must be designed. In recent years, the use of nanotechnology for environmental restoration has attracted significant attention from the scientific community. Electrospun nanofibers have excellent properties that are necessary for the adsorption, degradation, and separation of contaminants from environments. In this shade, in 2017, Zhao and colleagues created SS/PVA-based methylene blue molecularly imprinted electrospun fibers for the particular separation of dye, namely, methylene blue, from wastewater. In summary, an electrospinning combination of PVA:SS (2:1) and methylene blue has been utilized, and the produced nanofibers have been crosslinked using glutaraldehyde. Following this procedure, the methylene blue molecules have been separated by washing, resulting in methylene blue imprinted crosslinker electrospun nanofibers. Finally, methylene blue (cationic dye) adsorption has been achieved utilizing methylene blue imprinted SS/PVA electrospun nanofibers. Because of the competing adsorption of hydrogen

Table 6.2 Summary of pharmaceutical applications of SS-mediated electrospun nanofibers.

Sr. No.	Concentration	Other components	Type of dosage form	Activity performed	Cell viability	Inference	References
1.	SS-PLGA (0.5 %W/W of PLGA)	Ketoprofen	Scaffolds	Anti-inflammatory	HGFs cells	It shows the sustained release of ketoprofen, good biocompatibility, and anti-inflammatory activity.	Chachlioutaki et al. (2022)
2.	PVA, CS, and SS	Tetracycline	Nanofiber for wound dressing	Antibacterial activity	L-929 cells	It shows enhanced wound healing and antibacterial activity	Bakhsheshi-Rad et al. (2020)
3.	CA, SS (1.7 mg/mL)	Silver nanoclusters	Nanofiber	Antibacterial	–	It shows good antibacterial potential against Gram-positive and negative bacteria	Mehdi et al. (2021)
4.	PVA:SS (20: 80)	EA	Implants	–	hADSCs	It shows good biocompatibility	Marvi et al. (2022)
5	SS: Gelatin (1: 2), and PLGA	Heparin	Scaffolds	–	L-929 cells	The use of SS resulted in a decline in the degradation of a designed scaffold.	Başaran et al. (2021)
6.	SS, silk fibroin	–	Dressing film	–	Mouse embryonic fibroblasts	It offers good biocompatibility and high WVTR	Lin and Zuo (2021)
7.	SS, Keratin (10 %w/v)	–	Nanofibers	–	hMSC	It shows good biocompatibility and stability	Vineis et al. (2021)

Continued

Table 6.2 Summary of pharmaceutical applications of SS-mediated electrospun nanofibers.—cont'd

Sr. No.	Concentration	Other components	Type of dosage form	Activity performed	Cell viability	Inference	References
8.	SS- PEO -NIPAM (6 wt% - 15 wt%- 6.5 wt%)	–	Fabric	Antibacterial	–	It shows the pH response characteristic and good antimicrobial activity	Li et al. (2021)
9.	SS, CA, and PCL (8% w/v of SS)	FA	Mat	Antibacterial, wound healing study	HaCaT cells	It shows the sustained release of FA, good biocompatibility, and excellent antibacterial activity as well as wound healing potential	Anand et al. (2022)
10.	8:1:1 (PVA: SS: CS)	AgNPs	Dressing materials	Antibacterial	83.05% (L929)	The use of SS and CS shows good antimicrobial potential as well as biocompatibility	Karthick et al. (2023)
11.	PVA: SS (8:1 w/w)	–	Nanofibrous mats	Wound healing assay	L-929 and HaCaT cells	It shows the antioxidant and wound-healing potential	Gilotra et al. (2018)
12.	SS: PVA (10: 1.5 %w/w) or (7.5:1.5 %w/w)	–	Nanofiber based scaffold	In vitro cytotoxicity	NHDF cell line	It demonstrates good biocompatibility	Kumkun et al. (2019)

13.	SS, gelatin (1:1)	Copper ions, zinc ions, halloysite nanotube	Nanofibers	Antibacterial	L-929 cell line	It shows good antimicrobial activity as well as good biocompatibility	Massoumi et al. (2019)
14.	SS (2/4% w/v), CS, PVA	Cephalexin hydrate	Nanofibers	Antimicrobial and wound healing	HaCaT cell line	It offers excellent antimicrobial potential, biocompatibility, and wound-healing activity	Sapru et al. (2018)
15.	PVA (0.6 g), SS (0.2 g)	Tigecycline	Antibacterial composite	Antibacterial and wound healing	–	It offers good antimicrobial and wound-healing potential	Chao et al. (2018)
16.	Halloysite nanotubes	Chlorhexidine acetate	Antibacterial composite	Antibacterial activity	–	It shows the sustained antibacterial action.	Joshi et al. (2023)

ions and cationic dye with SS-containing functionality, the low pH of the sample influences the adsorption potential of composites. It also has greater adsorption at higher pH (it is stable at pH 7). Finally, the design of SS-/PVA-based methylene blue–imprinted electrospun nanofibers provides better and more selective methylene blue adsorption for samples. As a result, the suggested imprinted electrospun nanofibers can be employed as an adsorbing material for the effective removal of methylene blue in the future (Zhao et al., 2017). Purwar and colleagues described antimicrobial air filtration masks made from SS/PVA and clay: cloisite 30B) electrospun nanofibers. In summary, SS: PVA (1:1 %w/w) with clay subjected to the design of the nanofibrous mat. Following that, the mats were tested for antibacterial capability and other characteristics. Consequently, it demonstrates antibacterial activity against *E. coli* (clay: 0.75%) and *S. aureus* in plates, where no growth was seen below the mat. It also does not depict the zone of inhibition around the matting in plates. As a result, the barrier mechanism in the planned clay-based SS/PVA electrospun nanofiber–based mat has been ensured. Furthermore, the respirable suspended particulate matter (RSPM) test demonstrated good particulate matter adsorption capacity. As a result, the clay-based SS/PVA mat may usher in a fresh era of particulate material filtration (Purwar et al., 2016). Zhao and colleagues created an adsorbing nanomaterial for methylene blue separation utilizing SS/PVA and β-cyclodextrin. In short, the composite has been created by electrospinning SS (0.2 g), PVA (0.7 g), β-cyclodextrin (0.1 g), and citric acid (0.2 g, crosslinker). The dye adsorption investigation demonstrates that the developed composite has a strong adsorption potential, with the inclusion of SS and β-cyclodextrin offering an enhancement in adsorption potential. It also demonstrates strong dye desorption potential from electrospun composite, confirming the reusability of nanofiber-based composite. As a result, the created water-insoluble mat may open up new avenues for the treatment of dye-containing wastewater in the future (Zhao, Wang, et al., 2015). Overall, the combination of SS with appropriate polymers in the form of electrospun nanofibers can open up new avenues for environmental applications.

5. Biocompatibility of SS-based electrospun nanofibers

The preference for biocompatible polymers is a basic need in biomedical applications. Importantly, biocompatibility is the capacity of polymers to be compatible with the body and its fluids. In this case, the usage of biocompatible polymers helps to improve the body's functioning without interfering with regular bodily processes or causing other adverse effects (Arif et al., 2019). Recently published literature reported the design of an SS-loaded electrospun nanofiber-based composite scaffold using cationic gelatin/hyaluronan/chondroitin sulfate. In this study, the biocompatibility of the scaffold has been assured using a cell line study on human foreskin fibroblast, human keratinocyte, and human mesenchymal stem cells (hMSCs) via lactate dehydrogenase (LDH) and deoxyribonucleic acid (DNA) assay. Here, both assays of preferred cell lines confirmed the good biocompatibility of the SS-based scaffolds (Bhowmick

et al., 2016). As well, PCL and CA have also been employed to create SS and fibroin-containing electrospun nanofiber mats. Herein, the L-929 cell line investigation demonstrates increased cell adhesion and proliferation. As a result, it proved the nontoxic behavior, and, therefore, the high biocompatibility of the SS-based developed nanofiber (Barnthip et al., 2022). The design of an SS/CS-based electrospun nanofiber scaffold as an antibacterial dressing material has been evaluated for biocompatibility using L-929 cells, and cell viability has been confirmed using the MTT assay. As a result, at 24 h, it has more than 90% cell viability. It has higher cell viability than the control group after 72 h of incubation. Overall, it ensured that nanofibers were nontoxic. As a result, it established the biocompatibility of SS/CS electrospun nanofibers (Zhao et al., 2014). The nitrofurazone-loaded PLLA/SS-based electrospun nanofiber mat was invented in 2015 for wound healing applications utilizing an electrospinning technique. The MTT experiment has been performed on L-929 cell lines, and cell viability has been observed to decrease as the quantity of SS and PLGA increased. Similarly, adding medicines to electrospun nanofibers results in a smaller drop in cell viability than plain nanofibers. Cell viability was reported to be 100% at 3 days for plain SS/PLGA (1:2) nanofibers, but it has been decreased to 95% for drug-loaded fibers. As a result, it has been determined that SS is an excellent biocompatible material for biomedical applications (Zhao, Li, et al., 2015). Taken as a whole, the reported documents demonstrated that SS is a biocompatible material suitable for biomedical applications.

6. Current challenges, prospects, and scale-up of the process

Current challenges and prospects: Currently, the SS is extensively reported in research for biomedical as well as other applications because of its plentiful versatile properties such as biocompatibility, availability, hydrophilicity, tuneability, and so on. In recent decades, SS has been reported for the formation of electrospun nanofiber–based carriers for biomedical and environmental applications. In biological applications, it demonstrates great potential in antibacterial activity, medication delivery, wound healing, and so forth. Similarly, environmental applications validated the dye removal and air filtering capabilities. Regardless of these uses, there is a need to focus on the correct commercial design of SS-based electrospun nanofibers. To achieve repeatability, the biological source, isolation procedure, and molecular weight of SS must be addressed. Furthermore, the construction of SS nanofibers with novel polymers at optimized concentrations might give a new application in the biological and other fields. The usage of SS-based electrospun nanofibers in wound healing applications demonstrates high antibacterial potential. Despite these advantages, there has been little study published on the use of SS nanofiber as dressing materials or as a dosage form for the management of health ailments. Hence, there is a need to investigate this SS in biological applications with other antibiotics, antiinflammatory drugs, antibacterial agents, and natural phytoconstituents. There is a significant need

to concentrate on many aspects of SS-based electrospun nanofibers, which primarily comprise the surface area, porosity, composition, fiber diameter, and specific volume. Overall, the use of SS in electrospinning requires extensive research for a wide range of applications. Here, SS may be used to create advanced dosage forms such as floating drug delivery, targeted medication delivery, and mucoadhesive drug delivery. Few studies looked at release kinetics, antibacterial action, and wound healing. As a result, in the future, the size, as well as sufficient preclinical and clinical research, will be required to launch biological applications. In this shade, several microorganisms cause diseases that must be considered for antibacterial action in recent times. Presently, silk industry waste is a major problem that affects human life as well as the environmental cycle. Hence, there is a necessity to form electrospun nanofibers from waste SS as west to best for biomedical and other field applications that can ease the pollution problem while also providing economic advantages. Furthermore, the usage of SS electrospun nanofibers for various applications can help both agriculture and industry. Because of the present increase in pollutants and illnesses, improved SS-based nanofibers are required to handle these circumstances.

Scale-up of the process for commercial application: The literature reports that electrospinning technology is the simplest process for the production of electrospun nanofibers. The use of electrospinning provides 0.01−1 g of yield within 1 h, which remains a challenge to meet the needs of clinical and commercial or industrial applications. Hence, there is a major technological challenge in electrospinning that needs to be overcome. Since its inception, laboratory-scale electrospinning has been widely used for drug delivery, wound dressing, and other various applications. Recently, different scale-up productions of electrospun dosage forms such as nanofiber mats, melt electrospun fibers, and drug-loaded fibers have been documented. As a result, production rates have risen to 350 g/h (Vass et al., 2020). Therefore, the use of SS-based electrospun nanofibers for biomedical and environmental applications at an industrial scale is possible. Unfortunately, no reports are available on the scale-up of SS electrospun nanofibers. Hence, in the future, there is a need to work on scaling up SS electrospun nanofibers from laboratory to commercial or industrial scale.

7. Conclusion

Silk protein is a good choice of material for biomedical and environmental applications due to its unique and diverse features such as biocompatibility, hydrophilicity, mechanical qualities, antibacterial potential, and so on. The construction of appropriate types of composites employing SS provides great performance in both biological and environmental remediation applications. Mainly, the use of electrospinning techniques to create acceptable carriers based on electrospun nanofibers adds benefit to polymeric materials that are ideal for medication administration, wound dressing, and environmental cleanup. As a result, the creation of SS-based electrospun nanofibers for biological and environmental applications has been a significant focus of the scientific community in recent years. This book chapter concludes that the SS

concentration affects the shape and dimensions of electrospun nanofibers. The designed SS-based electrospun nanofibers also have remarkable antibacterial activity against several Gram-positive and Gram-negative bacteria species due to the presence of SS, other polymers, and antimicrobial agents. The biocompatibility experiment, which included several cell lines, confirmed that the SS-based composite was nontoxic and biocompatible. Furthermore, the in vivo wound healing experiments using designed SS-based electrospun nanofibers validated the increase in cell adhesion, proliferation, re-epithelization, and so on. The drug's release can be tailored by combining a sufficient concentration of SS with other polymers. Furthermore, according to a recent publication, antibacterial wound dressings employ SS-based electrospun nanofibers. Overall, the usage of SS in biomedical applications revealed that it is a superior alternative to currently employed solutions for wound healing and medication administration. Furthermore, the usage of electrospun SS-based adsorbing composite for environmental applications ensured the removal of various colors and other impurities from water. In addition, the SS-based electrospun composite has been reported as an antimicrobial filter. Unfortunately, despite its many advantages, the usage of SS in environmental remediation applications is underutilized. Overall, the use of SS with an adequate concentration of other polymers makes them an excellent composite/blend for the design of electrospun nanofibers for several biomedical and other applications. In the future, SS-based electrospun nanofibers might be used in a variety of environmental applications, including pesticide removal and filtration as well as biomedical applications including drug delivery and wound healing. Finally, the preference for SS-based different forms of electrospun nanofiber composites will pave the way for novel biomedical, energy, environmental, and other applications.

Conflict of interest

The authors state that they have no conflicts of interest.

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Blended polymer composites of sericin

7

Ana Beatriz Vitorino de Farias, Thiago Lopes da Silva, Wedja Timóteo Vieira, Caroline Santinon, Meuris Gurgel Carlos da Silva and Melissa Gurgel Adeodato Vieira
State University of Campinas, School of Chemical Engineering, Campinas, Brazil

1. Introduction

Sericin and fibroin are the two main groups of protein polymers that constitute the silkworm cocoon. These proteins are produced by the silkworm that extrudes a continuous thread composed of a pair of parallel fibroin fibers, linked by disulfide bridges, surrounded by layers of sericin, which acts by gluing the fibers and maintaining the structure of the cocoon ram (Aramwit et al., 2012). Worldwide, the most cultivated cocoons are those produced by *Bombyx mori* silkworms (Reizabal et al., 2022).

The industrial production of silk yarn is achieved through the solubilization of sericin through treatments with heated aqueous solutions (e.g., hot water with alkaline compounds). This process allows the release of the thread from the cocoon and the production of commercial silk yarns (Vidart et al., 2018). Once removed from the cocoon by the degumming process, sericin is often considered an industrial residue and is discarded in the silk processing effluent, increasing the organic matter load in the wastewater (Zhao & Zhang, 2020).

Fibroin is a fibrous protein characterized by a highly repetitive primary sequence that implies a homogeneous secondary structure with β-sheets. For this reason, this type of protein has important mechanical properties, being highly resistant and insoluble in water (Altman et al., 2003). In contrast, sericin is a globular, amorphous, and water-soluble protein with its secondary structure affected by how it is extracted and handled to produce other materials (Aramwit et al., 2012). As a globular protein, sericin has catalytic and molecular recognition functions (Altman et al., 2003), showing antioxidant, anticoagulant, antibacterial action (Oh et al., 2021), moisturizing ability, mitogenic effect, which is useful in cell growth culture (Lamboni et al., 2015), immunocompatibility, anti-inflammatory, biodegradability, and photoprotective (Silva et al., 2022), among others. Despite the weak mechanical structure of sericin, its polar nature allows blending with other polymers, copolymerization, crosslinking processes, and composite formation (Silva et al., 2021). These and other actions enable the use of sericin in various types of materials such as bone tissue engineering, drug delivery, and stable materials such as films, sponges, particles, hydrogels, etc.

In this chapter, subjects related to the individual characteristics of sericin and sericin-based materials are addressed. The physicochemical properties of the protein,

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composition, forms of presentation and applications in pharmaceutical, cosmetic, biomedical, food, and environmental fields are presented throughout the text.

2. Sericin properties and composition

Silk sericin is a globular glycoprotein that constitutes 25−30% of the cocoon mass. Its molecular weight ranges from 10 to 400 kDa (Da Silva et al., 2014; Zhang, 2002), and the secondary structure of the protein is predominantly random coils (63%) with a lower proportion of β-sheet (35%) without content of α-helix (Aramwit et al., 2012). Due to its high content of random coils, sericin appears as an amorphous and brittle material in the dry state (Lamboni et al., 2015). The solubility of sericin is due to the composition and high proportion of random coil in its structure and decreases as the random coil structures transform into β-sheet. The gelling and sol-gel properties of sericin are temperature-dependent and are related to the change of a certain amount of random coil to β-sheet structures when the temperature drops, which leads to gel formation. Gelling is fast at a temperature of 10°C and pH between 6 and 7 (Aramwit et al., 2012), but it is also achieved at room temperature. From the gel state, sericin can dissolve into sol (sol state, 50−60°C) and return to gel state upon cooling (Padamwar & Pawar, 2004). These properties are interesting for applications in the cosmetic and biomedical areas (Jo et al., 2015).

The molecular weight of the protein depends on the solvent used in the degumming process (acid, soap-alkaline and Na_2CO_3 solutions, or degraded by protease) and on factors such as pH, temperature, and processing time (Zhang, 2002). The use of degumming compounds (acids, bases, salts, and soaps) increases the yield of sericin extraction from the cocoons but can degrade the extracted protein and requires a difficult and laborious purification step to obtain sericin without contaminants. These residues in extracted sericin can promote toxicity in the materials made with this protein. Processes using hot water and pressurized hot water have the advantage of obtaining sericin without adding impurities (Lamboni et al., 2015). Low-molecular-weight sericin peptides (<20 kDa) are commonly used in cosmetics and personal care products, and high-molecular-protein peptides (>20 kDa) are used in degradable biomaterials, blends, membranes, films, fibers, and hydrogels (Zhang, 2002).

Sericin consists of 18 amino acids (Fig. 7.1), most of which present highly polar-side groups such as hydroxyl, carboxyl, and amino groups. (Zhang, 2002) presents the sericin amino acid composition and some characteristics. Its high hydrophilicity comes from the high content of serine (∼33.4%), aspartic acid (∼19%), and glycine (8.8%) (Aramwit et al., 2012; Balcão et al., 2020; Wu et al., 2007). Due to the more content of acids than the basic amino acid residues, the sericin isoelectric point is about 3.5−4.0 (Ashe et al., 2020). Regarding amino acids, about 70% are hydrophilic groups, 30% hydrophobic groups, and 6.6% aromatic groups (Wu et al., 2007). The organic composition of sericin is approximately 46.5% carbon, 31% oxygen, 16.5% nitrogen, and 6% hydrogen (Kunz et al., 2016). As with the molecular weight, the

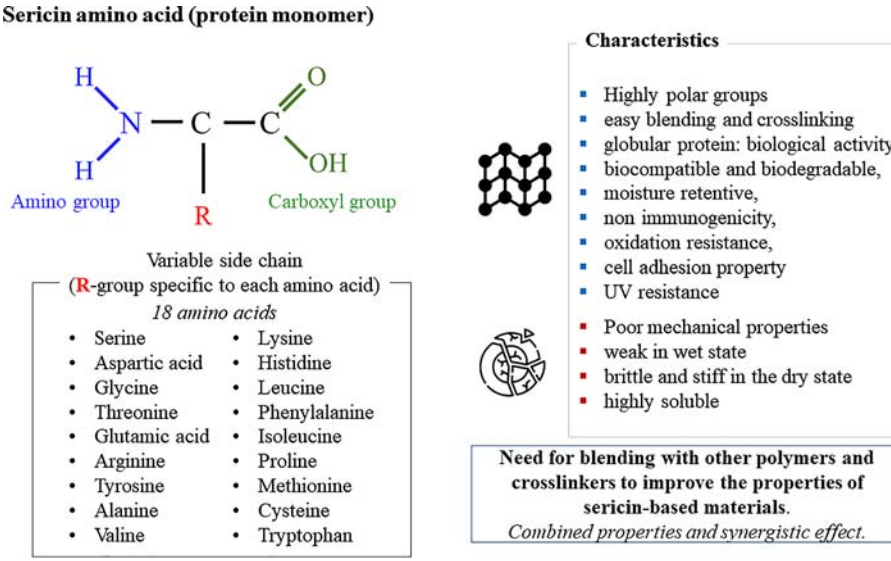


Figure 7.1 Structural features of the sericin protein.

amino acid composition of sericin can vary depending on the degumming method applied, as each method can lead to protein denaturation and degradation (Lamboni et al., 2015), which in turn affects its physicochemical properties and biological activity (Zhao & Zhang, 2020).

The high content of polar groups is responsible for outstanding characteristics including biological properties useful for biomedical and pharmaceutical applications. In addition, the mostly polar composition also gives sericin the ability to blend, copolymerize, and crosslink with other polymers and crosslinking agents (Silva et al., 2021; 2022). These abilities are of fundamental importance, as sericin alone forms soluble materials with low mechanical strength, which limits and hinders its use and development of stable structures.

The rheological properties of sericin are dependent on the extraction method, and its fragility makes the use of polymeric adjuvants mandatory to improve the mechanical strength of sericin-based materials. In general, natural biomaterials themselves are normally unable to meet all the requirements of their applications (Aramwit, Kanokpanont, et al., 2010), but due to sericin's ability to bind to other polymers and compounds, it can be used as an additive to improve the final characteristics of biomaterials. The development of sericin-based materials should always involve processes such as blending with other polymers or polymer grafting (Oh et al., 2021; Silva et al., 2022). When sericin is crosslinked or combined with other polymers, it can be incorporated into hydrogels, films, sponges, particles, and fibers with particular properties relevant to several applications (Silva et al., 2022).

3. Blends and composites materials with sericin

Due to the poor mechanical and structural properties of sericin, blending is necessary for the production of 2D and 3D biomaterials. Sericin-based biomaterials can incorporate the protein's characteristics of being antioxidant, anti-inflammatory, antibacterial, biocompatible, and immunologically inert, which allows the production of safe materials with applications aimed at biomedicine, tissue engineering, wound healing, and drug delivery systems. Also, its high ability to establish bonds with polymers and crosslinkers opens up a wide possibility of application in the production of films, sponges, hydrogels, and particulate systems aimed at the environmental field, among others.

Sericin can be blended with another natural or synthetic polymer. The new polymer combination material is expected to have enhanced mechanical and/or biological properties compared to the individual components. Natural polymers such as sericin are often biocompatible, while synthetic polymers can contain residues and impurities (including initiators) that preclude their use in biomedical systems. In contrast, synthetic polymers have better mechanical properties and thermal stability. While synthetic polymers can be manipulated to produce a wide range of materials in different shapes, natural polymers pose difficulties in preparation and structural formation. It is noteworthy that protein polymers can be temperature sensitive, as high temperature can denature or destroy their polymer structure. The blending of natural and synthetic polymers produces materials called bioartificial or biosynthetic polymeric materials. The blend formed is expected to overcome the limitations of the individual components (Girdhar et al., 2016; Sionkowska, 2011).

Among the natural polymers used in sericin-based blends, the following polymers stand out: chitin, chitosan, collagen, keratin, silk fibroin, elastin, gelatin, among others of animal origin, and algae and plant polymers, such as alginate, carrageenan, starch, cellulose, etc.

Along with polymer blends and composites, the addition of crosslinking agents improves the physicochemical characteristics of the biomaterials produced. Some examples of crosslinkers applied in sericin-based biomaterials include: dimethylolurea in sericin films (Santana et al., 2019), poly(ethylene glycol) diglycidyl ether sericin-alginate adsorbent particles for palladium uptake (Silva et al., 2021), proanthocyanidins (natural polyphenolic compounds) in particles targeting gold recovery from aqueous media (Santos et al., 2020), glutaraldehyde in the production of sericin and cellulose films (Wang et al., 2017), fibroin and sericin sponges (scaffold) (Siavashani et al., 2020), sericin-PVA composite films (Manesa et al., 2022), genipin (compound extracted from gardenia fruit) in the production of sericin nanoparticles (Kanoujia et al., 2016), sericin−PVA scaffold (Aramwit, Siritientong, et al., 2010) and films (wound dressing) (Siritientong et al., 2013), and N,N′-methylenebisacrylamide (MBA) in silk sericin-g-poly(acrylic acid-co-acrylamide) superabsorbent hydrogel (Hu, 2011), among others.

Also, physical thermal processes can be applied to modify the characteristics of the materials produced. da Silva et al. (2016) evaluated drying processes of adsorbent

particles produced from sericin and alginate, developed for metal uptake, and observed a decrease in solubility when the particles were dried at 100°C, compared to other temperatures. In adsorptive systems, it is expected that the adsorbent remains integral in aqueous environments, that is, that the solids are nonsoluble or sparingly soluble. Tao, Wang, et al. (2019) produced wound dressing from sericin and poly(vinyl alcohol) with silver nanoparticles and subjected the hydrogel to four freeze−thaw cycles in order to improve the mechanical characteristics of the films. Jo et al. (2015) evaluated the effect of temperature on the properties of sericin gels and films. The authors reported an increase in sericin gel strength and gelation with decreasing storage temperatures. Regarding the films, dried at different temperatures (4−100°C), an increase in crystallinity and decomposition temperature was observed at the lowest drying temperatures.

Table 7.1 provides an overview of some of the main polymers used in blends and composites with sericin, detailing their origin, the type of material produced, the inorganic compounds added to the composites, the crosslinking agents used, and the applications of the resulting materials.

4. Structural forms of sericin-based materials

Depending on the application, the way in which blend polymer composites are developed greatly influences the efficiency and characteristics of the materials. By employing diverse techniques, sericin can be manipulated to assume a wide array of forms, including films, nanofibers, sponges (scaffolds), hydrogels, micro, and nanoparticles (Qi et al., 2017). Fig. 7.2 illustrates the different structures that can be synthesized from sericin-based composites.

In the upcoming topics of this section, information about different structures derived from sericin is present. In the following sections, applications in environmental, cosmetic, food, and biomedical fields are discussed.

4.1 Hydrogels

Hydrogels are defined as three-dimensional cross-linked polymeric structures that retain a large amount of water in its porous network. The hydrogels' ability to retain water arises from the presence of hydrophilic groups in the polymer chain, such as amido, amino, carboxyl, and hydroxyl groups (Samchenko et al., 2011). Hydrogel structures from natural polymers, such as sericin, naturally possess higher biocompatibility and biological activity, compared to synthetic polymers. These characteristics allow these 3D structures to be applied in biomedicine, aiming to develop drug delivery systems, cell culture, and bio-responsive scaffolds (Zhang, Jiang, et al., 2019).

Sericin has a remarkable ability to form hydrogels, which is attractive for a variety of applications. The gelling behavior of sericin depends on factors such as temperature, polymer concentration, pH, and addition of crosslinking agents (Jang & Um, 2017). In addition to the chemical composition, the formation of three-dimensional networks is

Table 7.1 Overview of different polymers used in sericin-based blends and composites.

Polymer	Origin	Type of material produced	Inorganic compound	Crosslinking agent	Application	References
Alginate	Algae	Particles	–	Poly(ethylene glycol) diglycidyl ether	Palladium adsorption	Silva et al. (2021)
		Particles	–	Proanthocyanidins	Gold adsorption	Santos et al. (2020)
		Particles	–	Dibasic sodium phosphate, poly(vinyl) alcohol and poly(ethylene glycol)	Naproxen delivery	Freitas, Freitas, et al. (2021)
		Particles	–	Proanthocyanidins	Valsartan delivery	Santinon, Borges, et al. (2021)
Fibroin	Animal	Spongy scaffold	–	–	Bone tissue engineering	Siavashani et al. (2020)
		Particles	–	–	Drug delivery	Srisuwan et al. (2017)
		Hydrogel	–	–	Exosomes encapsulation	Han et al. (2021)
		Film	–	–	Wound dressing	Tsubouchi (2001)
Cellulose	Plant	Film	–	Glutaraldehyde	Not specified	Wang et al. (2017)

Poly(vinyl alcohol)	Synthetic	Film	–	Glutaraldehyde	Biomedical devices	Manesa et al. (2022)
		Film	–	Genipin	Wound dressing	Siritientong et al. (2013)
		Film	Silver nanoparticles	–	Wound dressing	Tao, Cai, et al. (2019)
		Film	Silver nanoparticles	–	Tissue engineering and wound dressing	He, Cai, et al. (2017)
		Membrane	–	Dimethylurea	Water/ethanol separation	Gimenes et al. (2007)
		Nanofiber	–	–	Methylene blue adsorption	Zhao, Wang, et al. (2015)
k-carrageenan	Algae	Particles	–	–	Mefenamic acid delivery	Nicolini et al. (2023)
				Poly(vinyl alcohol), carboxymethylcellulose, hydroxypropylmethylcellulose	Indomethacin delivery	Vieira et al. (2023a, 2023b)
Chitosan	Animal	Particles	–	Genipin	Hepatocytes encapsulation	Nayak et al. (2014)
		Particles	–	–	Sericin antioxidant delivery	Theeraphol and Baimark (2017)
		Film	–	–	Food packaging	Mei et al. (2022)
		Membrane	–	–	Carbon dioxide separation	Prasad et al. (2019)
		Nanofiber	–	–	Wound dressing	Zhao et al. (2014)
		Film	Silver nanoparticles	–	Moxifloxacin delivery	Shah et al. (2019)

Continued

Table 7.1 Overview of different polymers used in sericin-based blends and composites.—cont'd

Polymer	Origin	Type of material produced	Inorganic compound	Crosslinking agent	Application	References
Poly(ethylene glycol)	Synthetic	Nanoparticles	–	–	Not specified	Cho et al. (2003)
Pectin	Plant	Film	–	–	Food packaging	Meerasri et al. (2023)
Glucomannan	Plant	Film			Food packaging	Sothornvit and Chollakup (2009)
Collagen	Animal	Membrane	Zinc oxide nanoparticles	Glutaraldehyde	Wound dressing	Akturk et al. (2011)
Polypropylene	Synthetic	Membrane	–	Glutaraldehyde	Saltwater and greywater microfiltration	Verma and Subbiah (2019a, 2019b)

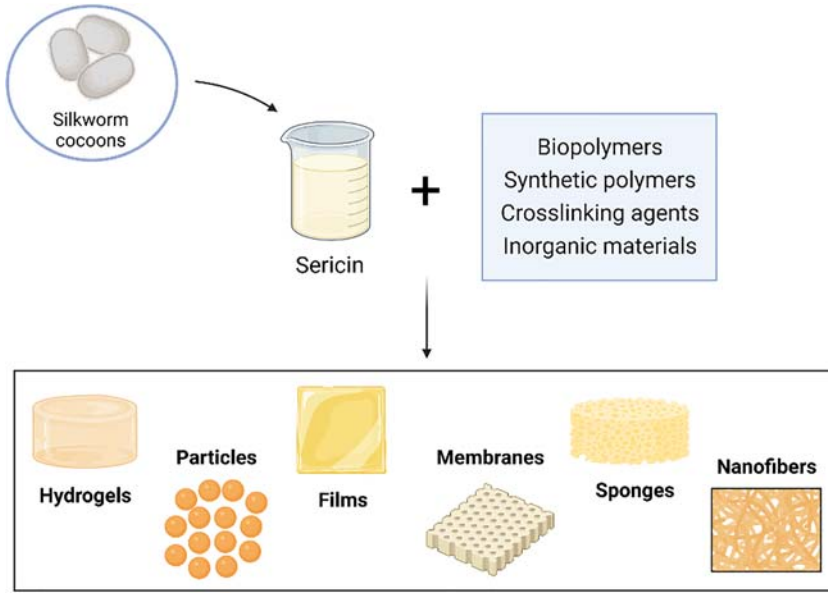


Figure 7.2 Production of different forms of sericin-based composites. Created in BioRender.com.

attributed to changes in sericin conformation from a random coil to a β-sheet structure (Zhu et al., 1995).

Unlike fibroin, the fibrous protein of the silkworm cocoon, which has a greater proportion β-sheet structures, sericin has mostly random coil structures which gives it, among other characteristics, high solubility in water. However, these structures may vary according to the temperature of the medium, and it is related to the transition of sol−gel state. The sol−gel transition is temperature-dependent, and gel formation is related to conformation and changes in sericin structures (Jo et al., 2015). When solubilized in heated aqueous medium, sericin is in a soluble state (sol). The random coil structures are solubilized in heated aqueous medium, and as the temperature drops, they are converted to β-sheet structure, which leads the solution gel state. The gel turns into sol state in the temperature range of 50−60°C and returns to gel with cooling (Padamwar & Pawar, 2004). The speed of gel formation occurs faster at low temperatures (10°C) and low pH (6−7). (Aramwit et al., 2012; Jo et al., 2015) reported an increase in gel strength with decreasing storage temperature (4°C) because of the decrease in free movement of molecules due to the formation of hydrogen bonds, which leads to the formation of a sericin gel. Zhang, Jiang, et al. (2019) prepared sericin hydrogel without chemical crosslinkers using the physical method by ultrasound. The authors observed that increasing concentration of sericin in solution implied in an increase in the speed of gel formation, 2 min at a sericin concentration of 2.5%, and 1440 min at a concentration of 0.5%. Also, greater time and amplitude of ultrasonication increased the gelation speed. In the treatment for 10 s in ultrasound,

the gelation time was 121 min, while in 30 s, the gelation time decreased to 3.8 min. When the amplitude applied was 6%, the gelation time was 60 min, and in 14%, the time was only 20 s.

The mechanisms that occur in the formation of hydrogels depend on the blend composition and the gelling method used and may involve a combination of physical and chemical interactions. Free hydroxyl groups are abundant in the sericin structure due to the presence of hydrophilic amino acids and are responsible for most of the electrostatic interactions with functional groups of other macromolecules (Sapru et al., 2017). Crosslinking agents can be used to establish covalent bonds between the components of the polymeric matrix (Wang et al., 2014), thereby modulating the final characteristics of the sericin-based hydrogel.

Sericin hydrogels are strongly hydrophilic, which provides them poor mechanical properties (Barcelos da Costa et al., 2021), and the formation of blends and composites with other compounds is a strategy to design materials with greater stability. The strongly polar groups present in sericin amino acid chains allow crosslinking, copolymerization, or combination with other polymers (da Costa et al., 2020). Some examples of polymers and crosslinking agents used in the production of sericin hydrogels are: sericin with short-chain poly(ethylene glycol) diacrylate for wound healing treatment (Punyamoonwongsa et al., 2019); human platelet−derived growth factor functionalized sericin hydrogels for cell proliferation and osteogenic differentiation (Wang et al., 2020); hydrogel crosslinking by horseradish peroxidase for wound healing (Baptista-Silva et al., 2021); and sericin, gelatin, and carrageenan blended hydrogel composite for cell therapies (Ashe et al., 2020), among others.

Despite the easy interaction of sericin with other polymers and crosslinkers, depending on the desired application for the hydrogel, the toxicity of the compounds used may limit its use due to side effects. The dosage of these agents also deserves attention. For example, residual glutaraldehyde present in sericin scaffolds may be associated with skin irritation, allergy, and possible neurotoxicity, and genipin, despite its low toxicity, may affect the kinetic profiles of carried drugs (Zhang, Jiang, et al., 2019).

In agriculture, hydrogels can be used for soil moisture retention. Jaramillo-Quiceno et al. (2024) prepared hydrogels by casting a mixture of sericin, carboxymethylcellulose, and PVA. The formed hydrogel was thermally crosslinked at 90°C for 4 h. The crosslinked films exhibited microcrystals in the sericin and PVA fractions with a dense network of hydrogen bonds. The developed biodegradable material was capable of retaining soil moisture and supporting plant growth.

4.2 Particles

There are different methods used to prepare particles based on sericin blends; some of the most common include ionotropic gelation (Costa et al., 2022; da Silva et al., 2016; Vieira et al., 2023a, 2023b) and emulsification (Srisuwan et al., 2017; Theeraphol & Baimark, 2017). The ionotropic gelation and emulsification−diffusion methods are illustrated in Fig. 7.3.

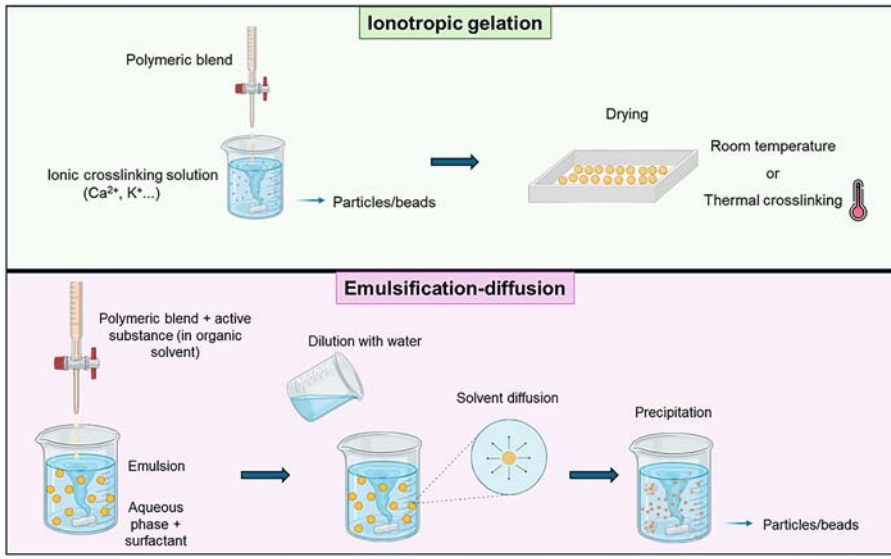


Figure 7.3 Ionotropic gelation and emulsification-diffusion methods for particles production. Created in BioRender.com.

Ionotropic gelation is a method that stands out for its simplicity, nontoxicity, and low cost. This technique consists of the formation of an insoluble gel by electrostatic interactions between the ionic groups present in the polymers and oppositely charged ions (Hoang et al., 2022). The polymers are dissolved and then added dropwise into an ionic solution so that crosslinking occurs and the particles are formed (Vidart et al., 2018).

Blending sericin with other natural polymers namely chitosan (Nayak et al., 2014), k-carrageenan (Nicolini et al., 2023; Vieira et al., 2023a, 2023b), and alginate (Barcelos da Costa et al., 2021; Freitas et al., 2018; Santos et al., 2019) enables the production of microparticles via ionotropic gelation. In this case, the ionotropic gelation occurs by the crosslinking of the auxiliary polymer of the sericin blend, such as alginate, which crosslinks in the presence of divalent ions (mainly Ca^{2+}) and k-carrageenan in the presence of potassium ions (K^{+}). These blends when in contact with the salt solutions with ions present leads to crosslinking reaction and particle formation. Usually, the blend solution is dripped onto the crosslinking saline solution, and the rapid reaction leads to the formation of particles (beads). Alginate turns into stable hydrogels with reduced solubility after ionic crosslinking, forming hydrogel beads with crosslinked chains in the so-called "egg-box" model (da Silva et al., 2017). K-carrageenan forms the hydrogels by binding sulfate groups with the ions in the solution. The blends may also have other polymers, crosslinking compounds, plasticizing agents, and other additives.

Sericin-/alginate-based blends have been explored by several researchers for the production of particles via ionotropic gelation. Often the hydrogel beads are subjected

to the drying process to obtain the final particle. Application areas for these materials primarily include environmental remediation and recovery of high-value products by adsorption and multiparticulate drug delivery systems. Some examples include sericin and alginate adsorbent particles for removal of toxic metals from aqueous media (da Silva et al., 2016), particles crosslinked with poly (ethylene glycol) diglycidyl ether for recovery of noble metal palladium (Silva et al., 2021), proanthocyanidins for gold recovery (Santos et al., 2020), blend with poly (vinyl alcohol) (PVA) for rare earth metal recovery (Barcelos da Costa et al., 2021), etc.

Particles produced from sericin/alginate mixtures demonstrated excellent regeneration capacity in multiple adsorption cycles for recovery of high-value metals. Because acidic eluents generally produce the best results in metal recovery, it is essential that the adsorbent material remains as intact as possible to withstand the harsh conditions of the reuse process. Reuse is particularly important because it not only increases the viability of applications but also reduces raw material consumption and improves the overall cost-benefit ratio of the process.

Particles composed of sericin and alginate, cross-linked with poly(vinyl alcohol) or poly(ethylene glycol) diglycidyl ether showed good stability when applied in the recovery of metals such as ytterbium (Costa et al., 2022), europium (Da Costa et al., 2023), and dysprosium (da Costa et al., 2021). High adsorption efficiencies were maintained for up to four or five adsorption−desorption cycles using nitric acid and hydrochloric acid as eluents. After contact with acidic eluents, some changes in the surface structure of the adsorbent materials were identified through analyzes such as scanning electron microscopy (SEM), including increased roughness. However, the internal structure of the particles did not show significant changes. In fact, exposure to acidic solutions led to an increase in the solubility of the materials, resulting in a mass loss of almost 15% during regeneration with nitric acid to recover dysprosium. Despite this, the particles composed of sericin and alginate maintained good adsorption efficiencies, achieving metal recovery efficiencies greater than 95%.

In drug delivery systems, the presence of sericin influences the dissolution profile, prolonging the drug release time, and also favors the sphericity of the particles (Vidart et al., 2018). Sericin-based particles have been shown to be suitable for drug incorporation for drug release in gastric and enteric systems. Sericin particles with alginate were evaluated for incorporation of naproxen (Freitas, Freitas, et al., 2021) and valsartan (Santinon, Borges, et al., 2021); sericin with k-carrageenan was investigated for entrapment of indomethacin (Nicolini et al., 2023; Vieira et al., 2023a, 2023b), etc. Drug-loaded particles have been shown to be effective in extending and modifying drug delivery in simulated human physiological systems.

Sericin particles can be employed in agriculture for the controlled release of fertilizers. Priya et al. (2024) developed beads of sericin, alginate, and acrylic acid-co-acrylamide with encapsulated NPK fertilizer. The beads were produced using a microwave-based grafting technique, with a size range of 0.83−1.46 mm, and the 7:3 ratio between alginate and sericin was found to be optimal for the release of fertilizers.

Emulsification methods are also extensively used for particle production, particularly in blends of sericin with other biopolymers such as chitosan (Theeraphol &

Baimark, 2017), and silk fibroin (Srisuwan et al., 2017). The emulsification−diffusion technique starts with the formation of an emulsion by mixing a partially water-miscible solvent containing the polymers (saturated with water) with an aqueous phase (saturated with the solvent) containing a surfactant (Pineda-Reyes et al., 2021). In the next step, the emulsion is diluted with water, which induces the diffusion of the solvent through the droplets, leading to the creation of polymer aggregates and particle formation (Domínguez-Delgado et al., 2022).

4.3 Nanoparticles

Nanoparticles, which are colloidal units with sizes below 1 μm, have been widely researched in different scientific areas. These include histological studies, separation technologies, cosmetics, and drug delivery systems. Their applications offer several advantages, including simple purification and sterilization, high potential for targeted drug delivery, and the ability to provide sustained release (Cho et al., 2003).

There has been a growing interest in sericin-based nanomaterials because they offer the potential to create biologically compatible and degradable substances for various biomedical uses such as antimicrobials and antioxidants (Hu et al., 2013). Furthermore, their low propensity to cause immune reactions, strong physicochemical stability, and prolonged shelf life makes them suitable for large-scale production (Das et al., 2021).

There has been considerable focus on sericin/hydroxyapatite nanocomposites in injectable bone tissue engineering (Chen et al., 2015). This attention is primarily due to characteristics such as improved flowability, adsorptivity, biocompatibility, and osteo-conductivity (Liu et al., 2013). Sericin's remarkable hydrophilicity and its capability to act as nucleation sites for hydroxyapatite are advantageous in inducing nanoparticles formation. Researchers have found that increasing the concentration of sericin leads to larger and more crystalline structures (Bhattacharjee et al., 2017).

Conventional methods for synthesizing sericin/hydroxyapatite nanoparticles include chemical precipitation (Cai et al., 2010). Usually, this method is carried out in stirred tank reactors, and although it is a simple and low-cost process, it is time-consuming and presents challenges to scale-up (Veiga et al., 2020). Thus, meso-oscillatory flow reactors have been employed as an alternative for the nucleation of hydroxyapatite using sericin as an organic matrix, providing lower synthesis times (Veiga et al., 2021).

Self-assembly is another method used in the synthesis of sericin-based nanoparticles. This technique refers to the spontaneous and reversible association of certain molecules through noncovalent interactions to form ordered structures (Quiñones et al., 2018). This process occurs by interactions acting on a local level, resulting in the nanostructure building itself without external interference. Self-assembly technique has been extensively studied recently, particularly in drug delivery applications (Kundu & Kundu, 2012).

Self-assembled nanoparticles can be obtained by reacting sericin with synthetic polymers such as poly(ethylene glycol). Introducing poly(ethylene glycol) chains into sericin changes its conformation from random coil to β-sheet, and sericin's

presence affects the crystallization of poly(ethylene glycol) (Cho et al., 2003). The combination of sericin with copolymers namely Pluronic F-87 and F-127 (Mandal & Kundu, 2009; Orlandi et al., 2020) has also been explored to develop self-assembled nanoparticles for drug delivery applications.

4.4 Films

Films are defined as thin and continuous two-dimensional structures, typically with a thickness up to 200 μm (Drobny, 2020, pp. 3−38). Films composed of pure sericin are brittle and have weak tensile properties. This, along with their vulnerability to swell in aqueous solutions, has imposed limitations on their practical applications (Aramwit et al., 2012; Nam et al., 2021). Thus, in order to obtain films with improved mechanical properties, it is desirable to combine sericin with other materials.

Through the incorporation of plasticizers or mechanical fillers, the mechanical properties of sericin films, such as ductility and brittleness, can be effectively controlled. For instance, the addition of cellulose-derived nanocrystals as fillers to sericin films resulted in improvements in physicochemical, mechanical, and optical properties. Glycerol was used to address the brittleness of sericin, and a more resistant film with antioxidant activity was obtained (Nam et al., 2021).

To overcome the limitations of single-component films, a common approach is to combine different polymers through physical or chemical crosslinking, enhancing film performance. Notably, crosslinking, mixing, or copolymerizing sericin with other polymers is a straightforward process, making it easy to implement (Mei et al., 2022). In this sense, it is interesting to explore the ease that sericin has to form blends with water-soluble polymers, mainly poly (vinyl alcohol) (PVA), capable of producing films with high mechanical resistance (Aramwit et al., 2012).

Due to its unique characteristics, the mixture of sericin and PVA is well established in film production. Ishikawa et al. (1987) studied the physical and structural properties of sericin and PVA-based films produced by solvent casting. Characterization analyzes such as X-ray diffraction (XRD) and differential scanning calorimetry (DSC) revealed that the films presented independent crystalline phases of sericin and PVA, indicating the presence of a structure separated by microphases. Tensile tests showed that the films had high flexibility and thermal stability.

Other studies have found that phase separation in films is more pronounced when sericin is used in high concentrations in blends with PVA. To address this issue, chemical crosslinking can be applied to blends, where a crosslinking agent such as glutaraldehyde, dimethylolurea, or genipin acts as a bridge between sericin and PVA, increasing miscibility and reducing phase separation (Gimenes et al., 2007; Purwar et al., 2015; Siritientong et al., 2013).

Purwar et al. (2015) produced films for food packaging based on sericin and PVA in a 1:1 (w/w) ratio and effectively reduced phase separation by employing glutaraldehyde as a crosslinking agent. In addition to increasing the miscibility of the blend, crosslinking with up to 5% glutaraldehyde also improved the thermal and mechanical properties of the films and reduced their solubility in hot water. However, as crosslinking promotes a reduction in the mobility of polymer chains, the structure becomes

more rigid, which significantly reduced flexibility. To address this issue, glycerol was added to the blend as a plasticizer, resulting in more flexible films. In addition, nanoclays were incorporated into the polymeric blend, leading to enhanced mechanical properties, including increased tensile strength and elastic modulus.

The improvement in mechanical properties was evident in the production of a sericin/PVA blended film through consecutive freeze-thawing cycles. The blended film presented good mechanical performance, capacity of water retention, low mass loss, and hygroscopicity. The good mechanical performance of the film was attributed to the formation of a hydrogen bond network between PVA and sericin. To further augment the antibacterial activity of the film for skin tissue engineering and wound dressing applications, in-situ synthesis of silver nanoparticles was carried out via UV-assisted method (He, Cai, et al., 2017).

Jiang et al. (2024) developed flexible thermally conductive films using boron nitride nanosheets, polydopamine, PVA, and sericin. The hybrid films exhibited a highly oriented structure between the nanosheets and sericin, high conductivity, and satisfactory mechanical properties. Ramesan et al. (2024) investigated nanocomposites developed from sericin, PVA, and boehmite (a material composed of reactive aluminum oxyhydroxide). The dispersion of boehmite nanoparticles in a sericin and PVA blend forms flexible films. The blend with nanocomposites exhibited improved optical, mechanical, thermal, and electrical characteristics, with a focus on being used in flexible electronic devices.

Sericin-based films also have high potential for applications in food science. Features such as biodegradability, antiultraviolet, antimicrobial, and antioxidant properties, in addition to the ability to inhibit food browning, make sericin-based films great alternatives for food packaging, replacing plastic films (Mei et al., 2022; Shree G et al., 2023). For this type of application, it is essential to combine sericin with other nontoxic and biocompatible materials, for example, polysaccharides, proteins, and gums (Seo et al., 2023).

The properties of pectin such as tensile strength and its ability to act as a barrier against aroma and oil were explored in the production of composite films with sericin for food packaging by (Meerasri et al., 2023). Other biomaterials that have been combined with sericin to produce films for food applications include chitosan (Mei et al., 2022), glucomannan (Sothornvit & Chollakup, 2009), aloe vera (Tarangini et al., 2022), and glucose (Oh et al., 2021).

4.5 Membranes

A membrane is defined as a structure with lateral dimensions significantly larger than its thickness, which facilitates the transfer of substances under various driving forces. Specifically, polymeric membranes refer to thin layers of polymeric materials that serve as a barrier, allowing selective mass transport of certain species (Koros et al., 1996).

Transforming pure sericin into membranes poses challenges, given its inherent properties. It is difficult to produce robust and elastic membranes solely from sericin (Wang et al., 2019). Due to the substantial presence of amino acids with neutral polar

functional groups, the membranes usually exhibit pronounced hydrophilicity, with a high propensity to swell when exposed to aqueous solutions (Zhang, 2002). Under elevated temperatures, these membranes can even undergo dissolution. Thus, an effective approach to addressing this issue is through the development of composites with other materials that offer enhanced mechanical properties (Dash et al., 2009).

Chemical crosslinking has proven to be a useful method for reducing excessive swelling in membranes. In addition, crosslinking contributes to enhancing the chemical, thermal, and mechanical stabilities of the materials. However, this can sometimes lead to a decrease in the permeation flux during separation processes (Ahmad et al., 2012; Gimenes et al., 2007). Glutaraldehyde was used as a crosslinker by (Akturk et al., 2011) in the production of sericin/collagen membranes for wound dressing. The membranes were prepared through the dissolution of collagen and sericin in acetic acid, followed by mixing the solutions, casting onto petri plates, and drying at room temperature. Subsequently, they were crosslinked with glutaraldehyde. Oxygen permeability is desirable to effective wound healing materials, and the addition of sericin was found to increase this property in the composite membranes.

The hydrophilicity of sericin-based membranes can be advantageous in some applications, including solvent dehydration by pervaporation. The separation of water/ethanol mixtures was studied using sericin/polyvinyl alcohol (PVA)-blended membranes chemically crosslinked with dimethylurea. Blending the two polymers resulted in membranes preferentially water-permeable with higher sorption selectivity (Gimenes et al., 2007).

In water purification using filtration processes, fouling formation is a common issue due to the hydrophobicity of most polymeric membranes, which leads to the accumulation of hydrophobic foulants in the pores. The hydrophilic property of sericin also becomes advantageous in such applications. In a study by (Verma & Subbiah, 2019a, 2019b), membranes composed of polypropylene modified by sericin coating were developed for the treatment of produced water (saltwater) and greywater through microfiltration. The sericin coating significantly increased the hydrophilicity of the membrane, resulting in reduced fouling formation. In comparison with the uncoated membrane, sericin-coated membranes presented 15% and 10.5% less fouling for greywater and produced water, respectively.

Another sericin-based composite membrane used for a separation process was developed by (Prasad et al., 2019). The membrane was produced by blending sericin with chitosan and incorporating sodium carbonate as a mobile carrier for carbon dioxide separation. Sericin played a crucial role in increasing membrane swelling and improving the efficiency of carbon dioxide separation.

4.6 Sponges

Sponges are highly porous water-absorbing materials with good air permeability that have drawn attention in the biomedical and cosmetic fields (Jang & Um, 2017; Zheng et al., 2023). In wound dressing applications, these characteristics of spongy materials offer advantages, due to the possibility of absorbing blood and other body fluids, while facilitating drug release to promote wound healing with minimal contact area

(Boonpavanitchakul et al., 2020). However, the humid environment within sponges makes them susceptible to the growth of microorganisms. Therefore, it is fundamental that they be developed based on materials with antimicrobial properties, such as sericin (Ai, He, et al., 2019).

An important aspect is that sericin composite sponges can be easily synthesized by consolidated methods, among which freeze-drying can be highlighted (Jang & Um, 2017). Freeze-drying is a method where the sample is fully frozen and subjected to low pressure conditions, making the water undergo sublimation. This causes the water to directly transition from solid to the gas phase, completely bypassing the liquid phase (Katrilaka et al., 2023). The prior freezing of water within the material hinders chemical, biochemical, and microbiological reactions, preserving the properties of the material. The removal of water by sublimation results in the creation of structures with high porosities in the freeze-dried materials (Nowak & Jakubczyk, 2020).

Pure sericin presents challenges in sponge formation due to its amorphous structure, requiring improvements in its toughness. To address this, blending sericin with polymers such as poly (vinyl alcohol) has been considered as an approach to improving the mechanical properties of sericin-based sponges. Additionally, the incorporation of nanoparticles, for example, composed of zinc (Ai, He, et al., 2019) or silver (Boonpavanitchakul et al., 2020; Tao, Cai, et al., 2019), into the polymeric matrix has been shown to enhance the antibacterial properties of the composite.

The use of support materials is another effective strategy to overcome the structural limitations of sericin in sponge development. Nanofibrillar structures such as chitin whiskers and cellulose nanofiber can act as a support framework for sericin. As a natural adhesive, sericin easily adheres to the surface and binds the fibers together to form a cohesive sponge structure (Ang-atikarnkul et al., 2014).

4.7 Nanofibers

Nanofibers are highly esteemed nanomaterials known for their vast potential in various applications. They have remarkable attributes, particularly their high surface area, surface area to volume ratio, and substantial porosity (Ramakrishna et al., 2006). Their ability to create interconnected networks of highly porous meshes further adds to their appeal as a preferred option for a wide range of advanced applications, particularly in the biomedical area (Kenry & Lim, 2017).

One of the most important and most used methods in the production of nanofibers is electrospinning (Fig. 7.4). Electrospinning is recognized for being an adaptable and simple method for producing polymer or composite nanofibers (Zhao et al., 2014). This technique enables the production of nanofibers using various materials and in diverse fibrous assemblies. The relatively high production rate and simple setup make electrospinning extremely appealing to both academic and industrial interests (Barhoum et al., 2018, pp. 1–42).

Electrospinning involves stretching and splitting a polymer solution under an electric field with high voltage, resulting in a three-dimensional porous network composed of nanofibers with high aspect ratios and substantial specific surface areas (Zhang et al., 2012).

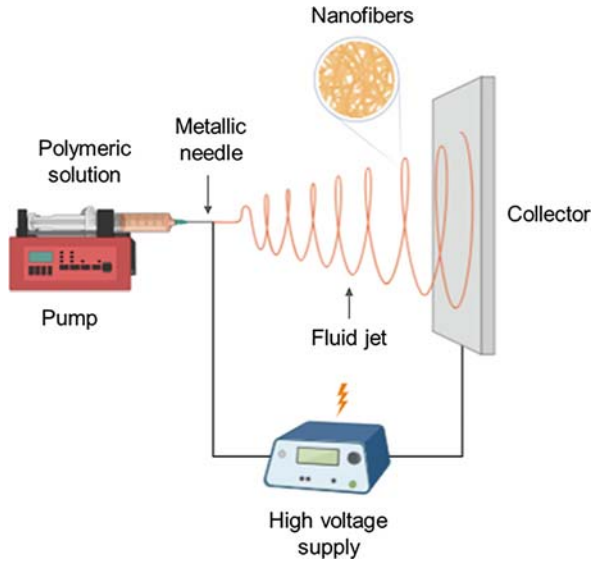


Figure 7.4 Schematic representation of electrospinning technique. Created in BioRender.com.

In recent times, there has been a growing interest in the development of electrospun sericin-based nanofibers for biomedical applications. In a protein-based nanofiber material composed of sericin, gelatin, and keratin, sericin influenced the morphology of the fibers, increasing their average size. Sericin also contributed to an increase in the biochemical signal of the nanofibers, improving their in-vitro stability for human cell proliferation in tissue engineering (Vineis et al., 2021).

Electrospun polymeric nanofibers are highly effective for membrane production due to their large surface area, light weight, and interconnected porous structure, resulting in materials with high porosity and controlled pore size (Wang & Hsiao, 2016). Recent patent applications have focused on nanofiber membranes based on sericin blends and composites, with two distinct materials developed to produce nanofibers via electrospinning.

Fengcai and Shiyu (2024a) prepared a mixture of sericin, acrylonitrile, acrylamide, and acrylic acid, to which an initiator was added to start a polymerization reaction (CN Patent No. 118087265A). Following polymerization, hydroxyethyl cellulose and a crosslinking agent were incorporated to obtain the spinning solution. The resulting material was then immersed in chitosan solution to produce the sericin-based composite. The crosslinking of sericin with the polyacrylonitrile matrix and subsequent modification with chitosan combines the good weather resistance of polyacrylonitrile fiber, the moisture permeability of sericin, and antibacterial properties of chitosan. Thus, the nanofiber membrane holds potential for a wide range of applications, particularly in biomedicine.

Fengcai and Shiyu (2024b) used a different approach to produce a modified chitosan/sericin nanofiber membrane (CN Patent No. 118007319A). In this method, chitosan was first mixed with acetic acid and freeze-dried to create a scaffold, which was crosslinked with sodium alginate. The modified chitosan was then mixed with sericin, and electrospinning was carried out to produce the nanofiber membrane. This method is notable for using natural polymers as the main components of the material, without the need for chemical crosslinking agents, resulting in nanofiber membranes with enhanced biocompatibility, antibacterial properties, and mechanical resistance.

Electrospun nanofibers also show significant potential in environmental applications, particularly in adsorption, owing to their high surface-to-volume ratio and porosity. Furthermore, they offer distinct advantages over traditional membranes, as they can be readily tailored to incorporate functional surface adsorption sites or specific structures, resulting in improved adsorption capacity (Huang et al., 2014; Zhao, Wang, et al., 2015).

In adsorption applications, solubility is a crucial factor that must be carefully considered during the development of fibrous materials. To address this concern, techniques like thermal crosslinking can be applied to reduce the solubility in aqueous media. For instance, in the development of electrospun nanofibers comprising a sericin/poly(vinyl alcohol)/β-cyclodextrin blend, in-situ thermal crosslinking was employed to make the composite insoluble in water. The addition of sericin in the blend contributed to increase the adsorption capacity of the composite nanofibers toward methylene blue (Zhao, Wang, et al., 2015).

5. Applications

Sericin-based composites have found application in the medical, pharmaceutical, food, cosmetics and textile industries, and environmental remediation. The antibacterial property conferred on the protein enables its use in the manufacture of medical devices such as sutures, gloves, aprons, and surgical drapes, as well as materials such as compresses (Zhao et al., 2014) and wound dressings (Chao et al., 2018; Xu et al., 2022). The antioxidant and anticoagulant effects and potential of sericin have motivated the development of various types of drug delivery devices (Santinon, de Freitas, et al., 2021; Nicolini et al., 2023). Furthermore, the ability of the protein to proliferate cells makes it suitable for use in scaffolds (Chachlioutaki et al., 2022), corneal dressings (Nagai et al., 2018), and prostheses (Veiga et al., 2020). In addition to its biocompatibility and biodegradability, the moisturizing effect of sericin and protection against UV radiation also justify the use of the protein in cosmetic products to hydrate skin, nails, and hair (Kumar & Mandal, 2019a, 2019b). The hydrophilicity of the protein gives lotions, creams, and ointments increased skin elasticity and is reported to be effective against wrinkles and skin aging (Das et al., 2021; Silei Li et al., 2023). Moreover, the composition and properties of sericin make sericin-based materials capable of facing challenges in the environmental area, given their affinity for organic and inorganic pollutants.

5.1 Pharmaceutical

Sericin, considered a low-cost glycoprotein, has attracted attention in the pharmaceutical industry due to its potential applications in various fields. The nontoxicity, biocompatibility, bioactivity, gelling ability, and biodegradability of sericin are unique properties that contribute to its potential as a pharmaceutical material approach for drug delivery, dissolution, solubility enhancement, crystal stabilization, wound healing, and dressing application (Ode Boni et al., 2022). Several research studies have explored the pharmaceutical potential of sericin blend polymer composites, paving the way for the development of innovative drug delivery systems (Bezerra et al., 2021; Freitas, Freitas, et al., 2021; Freitas, Vidart, et al., 2021; Nicolini et al., 2023). In addition, the immunomodulatory effect of sericin may have implications for the treatment of immunological diseases (Das et al., 2021). Sericin also exhibits antioxidant and anti-inflammatory properties, making it a potential candidate for the treatment of cardiovascular disease (Kunz et al., 2016), neurodegenerative disorders (Perteghella et al., 2021), and skin inflammation (Han et al., 2021) (Fig. 7.5).

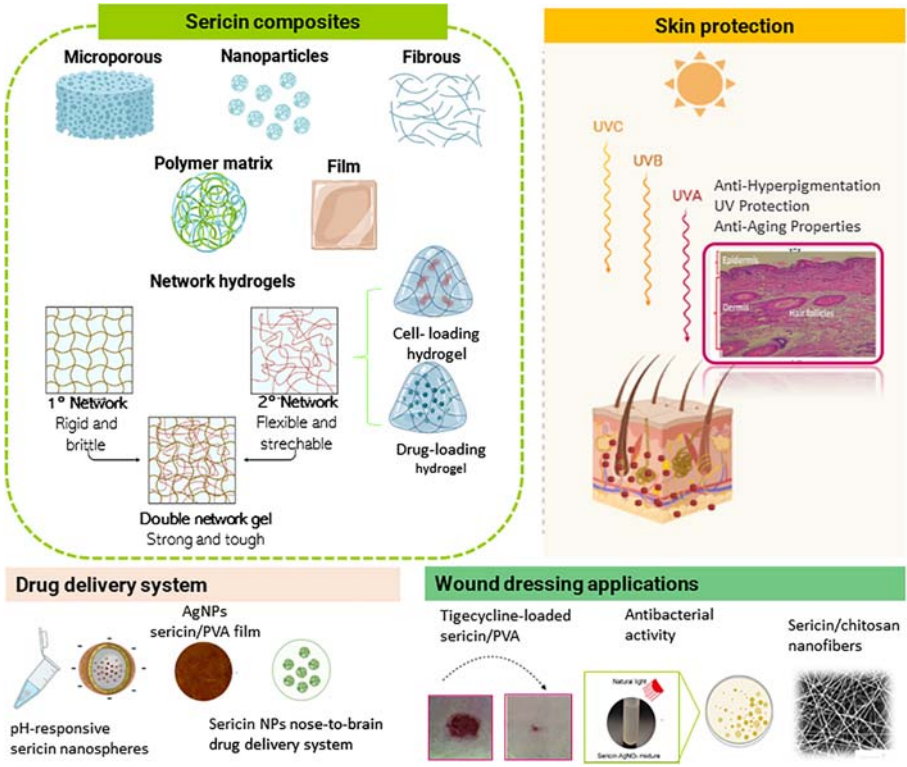


Figure 7.5 Schematic representation of sericin silk-based composites and several applications to the pharmaceutical field.
Created in BioRender.com.

Advanced drug delivery systems based on sericin composites have been reported, which are characterized by their amphiphilic nature, reasonable in vivo half-life, high moisture absorption, desorption properties, and swelling and deswelling ability. Several sericin-based mixed polymer composites have been investigated for the preparation of hydrogels, nanoparticles, films, and micelles for drug delivery or disease treatment (Li et al., 2023; Silva et al., 2022) (Table 7.2).

These drug delivery systems have been developed to incorporate hydrophilic (Joshi et al., 2023), hydrophobic molecules (Bhuyan et al., 2019), or natural active ingredients at a targeted location according to the therapeutic need to increase the bioavailability, stability, and solubility of these active ingredients (Salunkhe et al., 2018; Salunkhe & Jadhav, 2018). The amphiphilic property of sericin enables crosslinking with other structures for the transport of hydrophilic (Chao et al., 2018) and hydrophobic drug molecules (Al-Tabakha et al., 2021; Jahanshahi et al., 2019). Furthermore, sericin can be associated with different materials to increase solubility. Jahanshahi et al. (2019) modified the hydrophobic nature of fluorinated graphene oxide with polyethylenimine anchored to sericin polypeptide (SPF), which gave FGO the property of charge reversal. The composite was loaded with curcumin (entrapment efficiency 61%−64%, drug loading 22%−24%) as a core target for cancer cell lines HeLa, SkBr3, and PC-3. Composites with a surface crosslinked with sericin increased the charge of curcumin due to the electrostatic interactions of the amine groups ($-NH_3$) of the protein with the negative charges of curcumin. The nanocarrier was able to transport cells specifically into the nucleus and release curcumin slowly (>25%). It had no regular cell-killing activity, indicating excellent cytocompatibility. In addition, the composites promote apoptosis of SkBr3 (human breast cancer cells), HeLa (cervical cancer cells), and PC-3 (prostate cancer cells) cell cultures.

Some composites have intelligent release of the active ingredient depending on the conditions, such as the change in pH (Al-Tabakha et al., 2021; Arjama et al., 2018; Kurland et al., 2014). In particular, (Arjama et al., 2018) studied a green pH-responsive nanocomposite based on bran albumin and gellan gum functionalized with sericin (SC-GG-RBA). SC-GG-RBA nanocomposite was able to encapsulate a large amount of doxorubicin (DOX) and release 85% of DOX in an acidic tumor environment (pH 4.0), and 66% of the cells died after treatment with the green nanocomposites. This is due to the effective absorption of the nanoparticles by the cancer cells, with DOX being released in the cytoplasmic region. Kurland et al. (2014) developed a composite poly(amino acid) hydrogel of poly(aspartic acid) with the silk protein sericin, which is porous and responsive to stimuli. Furthermore, the presence of sericin resulted in a material with an internal microarchitecture with greater porosity, which enhanced the swelling capacity.

The addition of sericin improves the mechanical performance of the materials but also strategies such as chemical modification of the protein can be used. Several chemical agents such as genipin, glutaraldehyde, and 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide/N-hydroxysuccinimide have been used as crosslinking agents to improve sericin properties, but the inconvenience of chemical residues in the hydrogel, low cytocompatibility, and drastic treatment conditions are discouraging aspects. More ecological methods such as enzymatic catalysis of copolymerization have been

Table 7.2 Several sericin blend composites obtained by different methods for various applications.

Composite/blend	Active pharmaceutical ingredient	Method of synthesis	Type	Application	References
Sericin/acrylic acid (AA)/N′-N'-methylene bis-acrylamide (MBA)	Acyclovir	Polymerization	Hydrogel	Drug delivery system	Al-Tabakha et al. (2021)
Sericin-polypeptide (FPS)/ fluorinated graphene oxide/ polyethyleneimine	Curcumin	Oxidation process/ chemical activation/ anchoring	Nanocarrier	Nuclear delivery of antitumor drug	Jahanshahi et al. (2019)
Sericin/Chitosan/silver	Moxifloxacin	Solvent casting technique	Film	Wound healing and antibacterial potential	Shah et al. (2019)
Sericin−silver nanoparticle composite	–	In situ in solution through a one-pot procedure.	Nanoparticle	Antibacterial agent and wound care	He, Tao, et al. (2017)
ZnO nanoparticles on sericin/ polyvinyl alcohol composite		Conventional mixture	Film	Antibacterial biomaterials (*Escherichia coli* and *Staphylococcus aureus*), wound dressing	Ai, Wang, et al. (2019)
Sericin/silver nanoparticles (AgNPs)	–	Green synthesis by ultrasonication	Sponge	Antibacterial material *Escherichia coli* and *Staphylococcus aureus*, infection-resistant materials, wound dressing and blood absorbent pads	Boonpavanitchakul et al. (2020)
Gellan gum-sericin-rice bran albumin (SC-GG-RBA)	Doxorubicin (DOX)	Dissolution	Nanocomposite	Drug delivery system	Arjama et al. (2018)
Chitosan/sericin composite nanofibers	–	Electrospinning	Nanofibers	Wound dressing	Zhao et al. (2014)
Silk sericin/chitosan composite	–	Blended by stirring	Film	Wound dressing	Pankaew et al. (2015a)

investigated due to the milder temperature conditions and neutral environment of these catalytic processes. Hu et al. (2020) proposed the modification of sericin with poly(-ethylene glycol) dimethacrylate (PEGDMA) prepared by graft polymerization of poly-PEGDMA onto the oxidized phenolic hydroxyl groups of the tyrosine residues of the protein. The modified sericin composite had a significant effect on the average porosity, which increased by up to 60%, and on the swelling rate, which reached 1250%. Increasing the amount of sericin also improved the elasticity of the composite and the drug release behavior from the hydrogel was influenced by the water content and porosity of the composite. In addition, all hydrogels showed cell viability >84%, demonstrating the potential of the material for application in drug delivery systems. Al-Tabakha et al. (2021) used a chemical modification approaches such as radical pathway polymerization using acrylic acid as a monomer, ammonium persulfate as an initiator, and N′, N′-methylenebisacrylamide (MBA) as a crosslinker to obtain a sericin-co-acrylic acid composite. The composite showed reasonable oral tolerance, good acyclovir entrapment (∼74.0 acyclovir (mg)/hydrogel disc), and good swelling dynamics. The swelling behavior of the material and the release of acyclovir were controlled by the pH of the medium and show a sericin concentration pendant relationship with the highest swelling rate observed at pH 6.8 and 7.4.

The hydrophilic character and antimicrobial activity of sericin, together with its capacity for proliferation and cell adhesion, allow the protein to be used in various healing materials. As it has much lower mechanical properties than most substances, it is recommended to combine it with other structures. For example, the association of sericin with fibroin fibers can adjust the compressive modulus of sericin. The Young's modulus of fibroin hydrogels (6.41−63.98 kPa at concentrations of 1.5%−4% (w/v)) is consistent with the biologically relevant compressive modulus and comparable stiffness of human tissues (Floren et al., 2016; Han et al., 2021). Therefore, they proposed the formation of the sericin/fibroin hydrogel for the encapsulation of exosomes. Tests on mice showed that the composite was able to absorb wound exudates while maintaining the moist area and promoting vessel growth due to the elasticity of the matrix (Han et al., 2021; Shah et al., 2019) also utilized the properties of sericin to develop a hydrophilic, elastic, flexible, and antimicrobial film that can be used in burn wounds. The unloaded and the moxifloxacin (MOX)-loaded chitosan-sericin-silver nanocomposite (CSSN) were prepared by an in situ chemical reduction method to obtain the nanoparticles, followed by conventional polymer blending to form films. The MOX-loaded films showed slow release of the antibiotic fitted by the Higuchi and Korsmeyer-Peppas model, suggesting coupled diffusion and chain relaxation as the drug release mechanism, in addition to good in vivo permeation. In vitro antibacterial efficacy was demonstrated for Gram-positive (*S. aureus*, *S. epidermidis*) and Gram-negative (*P. aeruginosa* and *A. baumannii*) pathogenic bacteria, which mainly occur in skin infections in hospitals. In addition, in vivo tests conducted on a burn-induced wound model in male Sprague−Dawley rats showed that the developed nanocomposite films have fast healing properties.

He, Tao, et al. (2017) developed a simple and environmentally friendly method to obtain a green sericin−AgNP composite with effective antibacterial activity against

S. aureus and cytocompatibility for embryonic fibroblast cells (3T3) > 90% to sericin-AgNP > 25 mg/L. Ai, Wang, et al. (2019) produced a sericin-based wound dressing consisting of polyvinyl alcohol (PVA) and polydopamine (PDA) and modified zinc oxide nanoparticles (ZnO NPs) forming the ZnO NPs PDA-SS/PVA composite film. The films showed good improved mechanical performance due to the SS/PVA blend and greater stability at pH 4.0 due to the presence of proteins in the composite. This result is suitable for the application of the biomaterial in support systems and curative materials. In the synthesis of nanocomposites, sericin can not only act as a reducing agent but also impart a biodegradable property to the composite.

Boonpavanitchakul et al. (2020) have prepared sponge nanocomposite material (BS-NCMs) by a simple, eco-friendly and rapid method (30 min) using ultrasonic technique. The composite sponge showed more pronounced antibacterial activity for Gram-negative (*E. coli*) and Gram-positive (*S. aureus*) bacteria and rapid water absorption by adding AgNPs, which is suitable for wound dressings and blood-absorbent pads. Patent documents on sericin-based composites have been reported, such as a Chinese patent CN103194856A, which claims a process for the production of chitosan/sericin nanocomposites fibers with antibiotic and wound-healing activity, a US patent US6175053B1 (Tsubouchi, 2001), which describes a novel sericin-/fibroin-based wound dressing for healing burn skin, another Chinese patent CN114601974A provides a sericin composite hydrogel consisting of sericin modified with methacrylic anhydride, glucan modified with methacrylic anhydride and a photo-initiator for wound healing and tissue engineering.

A sericin-based compound can be used not only as a healing material but also as a delivery system for active molecules to be released at the wound site, thus avoiding complications in treatment due to infection. Joshi et al. (2023) proposed the development of an electrospun nanofiber composite consisting of a solution of thermoplastic polyurethanes (PU) and silk sericin mixture with chlorhexidine acetate (CA) encapsulated in halloysite nanotubes (HNTs). The polyurethane/sericin/HNT nanofiber composites loaded with CA showed effective antibacterial activity against *S. aureus* and *E. coli* bacteria, and the addition of sericin to PU promotes cell growth and proliferation and makes the composite fibers highly compatible with 3T3 cells. Additionally, the entrapment of CA in the HNTs reduced the initial burst release compared to a conventional electrospun polymer-based drug delivery system. Therefore, these nanofiber composites have a high potential for use as a topical wound dressing and drug delivery system through hydrophilic molecules.

There are several methods applied to obtain sericin composites based on unfolding the protein and reducing the hydrophobic interaction points between the polymer chains. In general, the techniques are simplified by milder processing conditions. These methods include crosslinking, in situ synthesis of nanocomposites followed by solvent casting to obtain films (Kumar Dan et al., 2022; Shah et al., 2019), one-step in situ biosynthesis (He, Cai, et al., 2017), mixing of polymers under suitable temperature conditions have been identified (Ai, Wang, et al., 2019), dispersion with stirring and drying (Han et al., 2021; Yuan et al., 2020), and ultrasonic technique to reduce silver in sericin composites with this metal and the electrospinning. Electrospinning has gained great suitable attention due to its versatility and effective

production method as well as its similarity. The electrospun fibers are similar to the extracellular matrix and have a high specific surface area and cell proliferation rate (Joshi et al., 2023).

5.2 Cosmetics

Structurally, 80% of the amino acid content of sericin has hydrophilic side groups with high water absorption capacity, such as serine (30%−33%) and aspartic acid (17%). The soft and smooth film formed by serine prevents transepidermal water loss, thus reducing skin dryness. In addition, sericin-based moisturizers reduce impedance, increase the content of hydroxyproline, an amino acid found in collagen, and increase the hydration of epidermal cells. These properties have led to sericin being increasingly used in cosmetic products such as creams, personal care products, and moisturizers as it improves skin elasticity and also has an antiaging effect (Crivelli et al., 2018; Tao, Cai, et al., 2019).

The Expert Panel for Cosmetic Ingredient Safety (Panel) reviewed the safety of silk protein ingredients in cosmetic products. It found that hydrolyzed silk (MW = 300 Da), an amino peptide concentrate consisting mainly of sericin and fibroin, is the most commonly marketed form. Hydrolyzed silk is marketed as a solution with 20%−30% water in concentrations up to 0.024% v/v and may contain heavy metals and arsenic in its composition. More than 675 formulations of hydrolyzed silk for rinsing and 177 powdered (leave-on formulations) for application to the skin have been reported. Sericin is present in four formulations at estimated concentrations up to 0.00,047% for facial powders (Johnson et al., 2020).

In cosmetic mixtures, low-molecular-weight sericin is used to facilitate the penetration of the molecule into skin membranes. Therefore, sericin with molecular weight between 12,000 and 17,000 Da is suitable for use in hair care and health products, and MW 5000−7000 Da is more recommended for skin care products (Sheng et al., 2013). Other properties such as the ability to inhibit hyaluronidase and protection from UV radiation extend the use of sericin in products for topical application. Studies show that treatment with sericin extracted from different sources (Philosamia ricini sericin [PRS] and Antheraea assamensis) increased the viability of human keratinocytes and prevented arrest and apoptotic/necrotic cell death when exposed to UVA radiation (12 J/cm2) and UVB (120 mJ/cm2). It also reduced the expression of skin inflammation and lipid peroxidation in the skin of female SKH-1 hairless mice (Kanpipit et al., 2023; Kumar et al., 2018) developed a hydrogel of sericin (5% w/v)/PVA (10% w/v)/alginate (5% w/v) to incorporate purple waxy corn cob extract (PWCC). The blend between the polymers improved the physical properties and the presence of sericin increased the hydration capacity of the hydrogel as well as the permeation of anthocyanins. The thickness of the stratum corneum of the hydrogel-treated skin increased compared to the control group, showing that the sericin-based hydrogel can restore the skin barrier due to its moisturizing effect. In addition, the sericin hydrogel loaded with PWCC showed a significant response in inhibiting collagenase and elastase, suggesting its use as an antiwrinkle and antiaging product, as well as a lightening effect due to the inhibition of tyrosinase and reduction of melanin pigment in

B16F10 cells (Kanpipit et al., 2023). Additionally, (Pankaew et al., 2015b) investigated the properties of silk sericin/gelatin composite films. The composite showed elastic behavior, suitable UVB protection, homogeneous surface, and no porosity suitable for use in cosmetic films.

Antioxidant, antityrosinase, and antielastase activity are biological properties that depend on the amino acid composition of sericin, and this is directly related to the degumming process used. Tengattini et al. (2020) proved that autoclave extraction dissolves the outermost layer of sericin, which is rich in amino acids with polar side groups that preserve these biological properties. While hydrophobic interactions are necessary for the inhibition of elastase, apolar amino acid residues can originate from the inner layers of the protein, for example, from extraction with sodium carbonate.

5.3 Biomedical

The use of sericin as a biomaterial is a relatively new perspective. Until a few decades ago, this material was mistakenly associated with skin inflammation after contact with living tissue and in the respiratory tract, leading to cases of asthma in silk workers (Chirila et al., 2013; Uragoda & Wijekoon, 1991). However, after several studies, it was found that the combination of sericin and fibroin proteins was responsible for inducing the chronic immune response, promoting allergenicity and immunogenicity. The mechanism that triggers this adverse effect is still unclear, but it is believed that the presence of structural conformation of the intrinsically hydrophobic β-sheet may favor chronic inflammation (Ode Boni et al., 2022). Finally, the safety of isolated sericin was proven and can currently be applied in several biomedical areas, such as skin and bone tissue engineering, wound dressings, micro- and nanoformulations for drug delivery, antitumor treatment, and sensors for medical electronic devices (Kunz et al., 2016; Liu et al., 2022; Silva et al., 2022).

It is noteworthy that the structural composition of sericin is highly dependent on the extraction processes used, that is, proteins extracted by sonication have more β-sheets than those extracted by aggressive processes, in which the recurrent conformation is coil shaped (Kim et al., 2021; Liu et al., 2022). Thus, for each specific purpose within biomedicine, it is necessary to evaluate the extraction method to be used in the protein and the molecular weight obtained, in addition to other factors that may be toxic to humans.

5.3.1 Tissue engineering and wound dressings

In the past years, sericin has been highlighted in the tissue engineering area for its ability to promote the production of type I collagen, which was attributed to the presence of the substance methionine in its structure (Aramwit, Kanokpanont, et al., 2010). Sericin treatments are also able to boost fibroblast migration and keratinocyte growth, rebuilding epithelial tissue and significantly contributing to the healing process (Kunz et al., 2016; Aramwit et al., 2013). Fig. 7.6 illustrates a schematic representation of the use of sericin in tissue engineering applications.

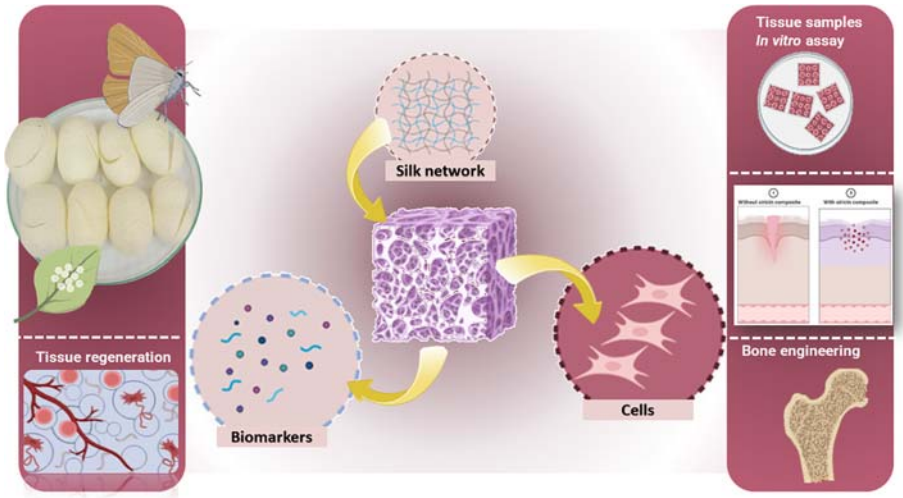


Figure 7.6 Use of sericin in tissue engineering area.
Created in BioRender.com.

One of the most striking advantages of using sericin in the treatment of wounds is its biodegradability. The body can gradually eliminate the dressing through proteolytic enzymes after its effect has ended, without the need for manual removal, which could reopen the lesion. The complete absorption process, until the product is fully absorbed by the body, can take up to 6 weeks (Cao & Wang, 2009; Holland et al., 2019; Silva et al., 2022).

Generally, other polymers are added to sericin via blending, crosslinking, or copolymerization reactions in order to improve the stability or structure, overcoming the fragility barrier of the dressing (Bakhsheshi-Rad et al., 2020; He, Tao, et al., 2017; Peng Wang et al., 2019). For example, sericin and collagen membranes were prepared by (Akturk et al., 2011). While collagen is capable of stimulating cell reorganization and favoring cell adhesion, sericin increases the water-swelling property of membranes but also their brittleness. The authors made it clear that collagen must be in higher proportion to ensure the dressing flexibility. With the same aim of improving elasticity properties, (Tyeb et al., 2018) produced hydrogels based on agar, sericin, and glycerol for treatment of chronic wounds. Unlike usual, sericin improved the malleability of the composite due to increased moisture retention, which considerably reduced the hydrogen bonding between the agar chains. Another alternative, gelatin has also been successfully incorporated with sericin by (Kumar et al., 2016; Mandal et al., 2009) for assembling 2D and 3D structures with enhanced mechanical strength compared to sericin alone, in addition to also improving cell proliferation and healing.

Beyond the several options of natural polymers, synthetic polymers may also be used in tissue engineering as long as they present compatibility with the organism. PVA, for example, is a neutral polymer at physiological pH and with low toxicity, allowing its application in different biomaterials (Teodorescu et al., 2018). Although

PVA improves the mechanical characteristics of films and scaffolds produced with sericin, it is necessary to add a plasticizer and/or a crosslinking agent, such as such as glycerin, genipin, or glutaraldehyde, to reduce the phase separation between both polymers, in addition to improving the permeability of the dressing (Manesa et al., 2022; Aramwit et al., 2015). Silver nanoparticles can also be incorporated to amplify antimicrobial activity and prevent other types of infections due to its inhibitory broad spectrum (He, Tao, et al., 2017; Cai et al., 2017).

Veiga et al. (2024) produced bilayer structures of fibroin and sericin. While fibroin provides mechanical stability, enabling its use in protective outer layers, sericin produces gels that promote cellular interactions, making it suitable for direct contact with wounds. In this study, the cryopreservation of sericin preserved the secondary structures of the protein, which was rehydrated to form a hydrogel layer over a salt-leached fibroin scaffold, creating the multiphase structure. Mariello et al. (2024) investigated the production of hydrogel dressings based on PVA/carboxymethyl cellulose and sericin, which were crosslinked through the freeze-thawing process. The produced dressings exhibited a honeycomb-like macroporous structure, an important characteristic for biomedical applications. Additionally, they were nontoxic, with compression and stretch properties similar to human skin.

The growing interest in the application of sericin-based composites in the development of wound dressings is evident in recent patent literature. Yuan et al. (2024) developed a photothermal antibacterial hydrogel wound dressing comprising methacrylic acid−modified sericin and copper sulfide nanoparticles (CN Patent No. 118304464A). Although methacrylic acid−modified sericin hydrogels exhibited excellent biocompatibility, they lacked antibacterial properties. To address this, copper sulfide nanoparticles, known for their antibacterial activity, were incorporated. The method proposed by the inventors resulted in a dressing with better porosity, good cell affinity, and biocompatibility. In vivo tests demonstrated that the hydrogel could promote wound healing, enhance collagen deposition, and reduce bacterial growth at the wound site. These findings show that sericin-based composite hydrogels have great potential for use in skin wound healing dressings.

Tissue engineering area may also interface with pharmaceutical applications, as the dressings can suit as carriers for in situ delivery of specific drugs, especially antibiotics, preventing further infections and promoting faster healing. Tao, Wang, et al. (2019) produced antimicrobial hydrogels based on sericin and PVA loaded with gentamicin sulfate, aspirin, and silver nanoparticles for gradual release and managed to effectively inhibit the growth of *S. aureus*, *E. coli,* and *P. aeruginosa* bacteria. Other pharmaceutical actives such as tetracycline (Bakhsheshi-Rad et al., 2020), nitrofurazone (Zhao, Li, et al., 2015), tigecycline (Chao et al., 2018), and amoxicillin (Diab et al., 2022) were also found in the literature as released drugs with appropriate antimicrobial effect from polymeric matrices composed of sericin.

Wu et al. (2024) produced composite hydrogels constructed by an interpenetrating network from sericin, alginate, and cellulose nanocrystalline for tissue engineering purposes. The composites created by the physical blending of alginate and sericin exhibit a consistent three-dimensional porous structure. Although sodium alginate alone forms biocompatible structures, it lacks cell recognition sites and has low

mechanical strength, limiting its use in real systems. In this study, the swelling stability and mechanical properties were improved when the composite structure was formed. Cell compatibility tests indicated better attachment and cell proliferation in the hydrogel. Deb et al. (2024) utilized a blend of sericin and polycaprolactone to produce hydrogels with encapsulated diclofenac. It was observed that 67% of the drug was released in the first 130 min with an encapsulation efficiency of 60%. Both hydrogels, with and without the drug, exhibited antimicrobial activity against Gram-positive and Gram-negative bacteria.

Another great advance in tissue engineering was the production of a sericin-based product for the treatment of second-degree burns. Aramwit and Sangcakul (2007) developed a cream composed of 8% sericin for treating wounds in rats. The study proved the greater effectiveness in reducing the size of the wound, in addition to the lower occurrence of inflammation, in comparison with the commercial ointment tested as a control (Betadine). In 2013, this same research group tested the cream with 8% sericin and the antibiotic silver sulfadiazine, commonly indicated prophylactically to avoid complications in wounds (Aramwit et al., 2013). The research showed that the presence of sericin accelerated the healing process, significantly reducing the treatment time, when compared to results without the sericin. The cream is especially suitable for burns, as other actives in the formulation manage to promote skin hydration, which ensures greater comfort to the patient and helps in cell proliferation.

Sericin is a very versatile protein in tissue engineering, not only applied to wound treatments, but also with evidence of bone, cartilage, and nerve regeneration (Lamboni et al., 2015). According to the publication by (Noosak et al., 2022), sericin increased the proliferation of osteoblast cells by up to 135%, in addition to having shown antibacterial activity against *S. aureus*, enabling its application in osteomyelitis treatment. After a study published by (Jo et al., 2021), it was found that high-molecular-weight sericin (>30 kDa) can increase the expression of bone morphogenetic protein (BMP-2/4) in macrophages, which is primarily responsible for bone regeneration. The use of sericin is a cheaper and more viable alternative than the administration of recombinant human BMP-2, which is synthesized from cells and is expensive due to the need for high doses to form a new bone (Lee et al., 2023). However, the acceleration of osteogenesis is not the only target to be considered in tissue engineering but also the immunomodulatory activity preventing fibrous encapsulation and failures in bone integration. Thus, recent studies indicate that sericin can inhibit the immune response through the transition of M1 macrophages (proinflammatory cytokines) to the M2 phenotype (anti-inflammatory cytokines), which creates a favorable environment for direct osteoinduction of bone marrow stem cells (BMSCs) into osteoblasts, responsible for producing the organic part of the bone matrix (Fu et al., 2023; Jiang et al., 2021; Qi et al., 2020).

Regarding the regeneration of nerve injuries, sericin can contribute to the recovery of nerve morphology and functions through the production of conduits (Liu et al., 2022). Additives such as silicone and carbon nanotubes can be incorporated to improve structural properties and electrical conductivity, respectively. (Zhang, Wen, et al., 2019; Li et al., 2020; Xie et al., 2015) reported the insertion of the drug clobetasol in a sericin-based conduit in order to increase the number of mature

oligodendrocytes and help in the regenerative process. According to the results, silk protein has neurotrophic and neuroprotective effects, contributing to Schwann cells adhesion and proliferation, facilitating nerve impulse conduction and regeneration of lesions between 5 and 10 mm in rats. (Millesi et al., 2020, pp. 1−29; Yao et al., 2024) prepared sponge materials made of fibroin and sericin crosslinked with glutaraldehyde as neural brackets for nerve regeneration. The studies indicated that the different sponges are noncytotoxic, aid in cell differentiation and proliferation, and suggest that they are suitable for use in nerve regeneration.

In summary, sericin is an excellent candidate for applications in the biomedical area, mainly targeting tissue engineering and wound dressings. As recent studies have proven no immunogenic properties, the use of this protein in biomaterials has been growing in recent years and tends to spread even further. In fact, the use of sericin brings great advances for the treatment of chronic wounds, mainly those resulting from burns or even diseases such as diabetes mellitus. These patients have a longer healing process than usual and may result in ulcerations, severe tissue infections, and even amputation (Baptista-Silva et al., 2022). In addition, applications in repair of bones (Fu et al., 2023; Jiang et al., 2021; Jo et al., 2021; Lee et al., 2023; Qi et al., 2020), nerves (Rao et al., 2017; Xie et al., 2015), and even hair follicles and sebaceous glands (Qi et al., 2018) have been reported in the literature. Thus, due to the characteristics of biocompatibility, biodegradability, and the easily binding to other polymers, sericin has the potential to replace more expensive components and with similar or greater effectiveness in different types of wounds.

5.3.2 Antitumor treatment

Another relevant property of sericin is the anticancer action. Studies show that the consumption of this protein was able to reduce the incidence of colonic adenoma in rats and mice by up to 62%, in addition to presenting a greater antioxidant activity in the colon, resulting from the undigested content of sericin (Sasaki, 2000; Zhaorigetu et al., 2001; Zhaorigetu et al., 2007). Furthermore, according to the publication of (Kaewkorn et al., 2012), the silk protein acts as a chemopreventive agent through induction apoptosis in human colon carcinoma cells. Evidence of antitumor action was also found in breast, lung, and cervical cancer cells (Jolly Devi et al., 2023; Mumtaz et al., 2023; Niu et al., 2021).

The mechanism of sericin antitumor action is related to its polypeptide chain, along with the secondary metabolites (polyphenols and flavonoids), which play a prooxidative role, increasing the intracellular production of reactive oxygen species (ROS), resulting in oxidative stress−mediated apoptotic death in human cancer cells without affecting normal cells (Kumar & Mandal, 2019a, 2019b).

The strong antioxidant characteristic of sericin due to the high content of hydroxy amino acids also inhibits the activity of the enzyme tyrosinase, responsible for melanin production in the skin (Kato et al., 1998). Another complementary study evaluated the inhibitory effect on skin damage caused by UVB radiation in mice, indicating the photopreventive property of silk protein (Zhaorigetu et al., 2003). Therefore, sericin can also be applied in cosmetic products with the potential to prevent skin cancer.

Furthermore, sericin-based formulations can be used as carriers for targeted delivery of chemotherapy drugs (Kumar Dan et al., 2022). Recent studies explore nanoparticles (Gao et al., 2021; Mandal & Kundu, 2009; Shirangi et al., 2022), microcapsules (Yang et al., 2017), and nanomicelles (Guo et al., 2018; Guo et al., 2019) produced from this protein in order to overcome limitations of chemotherapeutic drugs such as solubility, stability, toxic effect, and side effects.

5.3.3 Other applications

Sericin has also recently attracted the attention of scientists in the electronic field. Devices created to monitor human health can take advantage of the binding characteristic of silk protein to improve the electrical properties of various sensors. Although carbon materials are more frequently used for this purpose due to its good conductivity and flexibility, their modification with sericin contributes to a more homogeneous dispersion and stable matrix, in addition to providing biocompatibility with the human body (Lin et al., 2022). Researchers developed wearable electronic devices from the combination of carbon-based and sericin, which significantly improved the electromagnetic shielding performance, hydrophilicity, and sensitivity, allowing applications in echocardiogram, breathing sensors, sweat loss sensors, and ink for printed electronics (Duan & Lu, 2021; Liang et al., 2020; Ma et al., 2022).

As discussed before, sericin is a globular protein that cannot be digested by our body, which justifies its antitumor action mainly in the colon area. Thus, oral intake of this protein may also act as a regulator of obesity (Zhaorigetu et al., 2001). Studies performed in mice indicate increased excretion of lipids through feces, inhibition of lipogenesis, and restoration of jejunal morphometry, which resulted in reduced body weight and regulation of cholesterol and triglyceride levels (Kunz et al., 2020; Seo et al., 2011). Furthermore, sericin can reduce blood sugar and help in the treatment of type 2 diabetes. Studies indicate stability in glucose levels of mice and rats through different mechanisms such as increased expression of the PI3K/AKT insulin receptor (Dong et al., 2020; Song et al., 2018), inhibition of gluconeogenesis (Wei et al., 2022) and improvement of disorders in growth hormone in the diabetic hippocampus (Chen et al., 2013), being considered a potential additive mainly in hypoglycemic foods.

The antioxidant potential of sericin is so remarkable that evidence has already been developed in the fight against Alzheimer's. Alzheimer's is a disease that affects older people and may reach about 82 million people worldwide by 2030, according to estimates by Alzheimer's Disease International, 2020 (Alzheimer's Disease International. Numbers of People with Dementia around the World, 2020). This disease still has no cure, despite recent advances in science, and patients often suffer from cognitive disorder and memory loss. Silk protein was able to reduce oxidative stress by increasing the presence of antioxidant enzymes and reducing the expression of acetylcholinesterase (AChE) activity in rats, which creates protection for the cholinergic areas of the brain and improves cognitive behavior (Peera & Yellamma, 2015; Peera & Yellamma, 2016). Another more recent study proved the reduction of memory loss episodes and the improvement of social behavior in older mice by suppression of apoptosis in the hippocampus and improvement in antioxidant and

anti-inflammatory properties (Seyedaghamiri et al., 2021). In general, sericin can be considered a potential asset in the treatment of Alzheimer's and other cognitive diseases.

Another advantage of sericin that is worth mentioning is its use in supplementing culture media, with the aim of replacing components such as serum, due to its high cost and low biosafety. Although some serum-free media exist commercially, the growth rate and cell density are greatly affected, which makes their use unfeasible depending on the culture (Cao & Zhang, 2017; Sahu et al., 2016). According to scientific researches, the addition of sericin in culture media was able to accelerate the proliferation of mammalian cells with performance similar to bovine serum albumin (BSA) media, which is also a serum-free supplement, but because it is derived from mammals' proteins, runs the risk of contamination with pathogens and subsequent retroviral infection (Terada et al., 2002). According to these same authors, lower-molecular-weight sericin (5−100 kDa) showed better proliferation results than medium-molecular-weight sericin (50−200 kDa) (Terada et al., 2005). The silk protein also showed good behavior in the proliferation of rat islet cultures, used for the treatment of diabetes (Ogawa et al., 2004), improved the attachment of cultured human skin fibroblasts (Tsubouchi et al., 2005), and was considered a viable and safe alternative for the supplementation of bovine and sheep embryo cultures through increased production of blastocyst cells (Aghaz et al., 2016; Inaba et al., 2010).

5.4 Food industry

Since 2001, sericin and its derivatives have been on the Generally Recognized as Safe (GRAS) list approved by the Food and Drug Administration (FDA), which enables the commercialization of products based on this protein (Barajas-Gamboa et al., 2016). The vast majority of sericin applications in the food industry are aimed at supplementing a daily diet due to the various benefits of oral consumption of this protein, such as the reduction of glucose, triglyceride, and cholesterol levels, in addition to improving bowel function and consequent increase in weight loss (Aznar-Cervantes et al., 2021; Yang et al., 2023; Kunz et al., 2020; Limpeanchob et al., 2010). The addition of sericin can also be indicated for the stabilization of formulations for showing affinity with food emulsions, avoiding the use of animal or synthetic derivatives (Padamwar & Pawar, 2004; Züge et al., 2017).

Other applications of silk protein in the food industry involve the production of eco-friendly packaging/coatings with the aim of postponing the oxidation reaction and maintaining food freshness for a longer time. Due to its antioxidant and biodegradable properties, and because it has antibacterial evidence, sericin has been increasingly explored in this area (Fan et al., 2009; Kumar & Mandal, 2017; Mei et al., 2022; Oh et al., 2021; Senakoon et al., 2009). However, as sericin has high hydrophilicity and unstable mechanical properties, film formation (coating) in the presence of watery foods is limited, which can be overcome with the addition of other materials such as nanocellulose fibrils and carbon dots or even through chemical modification of sericin itself (Seo et al., 2023; Yang et al., 2023). Studies indicate that the hydrolyzed sericin in film production reduces the solubility and water vapor permeation, increasing the

antioxidant property and tensile strength, which can also be considered a viable alternative in food preservation (Meerasri et al., 2022).

Sericin is an interesting biomaterial with great potential for application in the food industry, mainly due to its antioxidant and edible film-forming characteristics, ideal for preserving food and increasing shelf life, in addition to having a considerable nutritional value that helps in combating food-related illnesses.

5.4.1 Additives

The investigation of oral consumption of sericin-containing foods is already widespread. In fact, some research shows that a diet with this protein as an additive presents a greater bioavailability and absorption of the minerals iron, zinc, magnesium, and calcium by the intestine (Sasaki et al., 2000). Silk protein can be used as a food stabilizer and solution emulsifier due to the hydrophilic and hydrophobic amino acid chains in its structure, which induces a reduction in surface tension between oil/water mixtures. According to studies, high-molecular-weight sericin can maintain an emulsion for up to 24 h and has the potential to replace other natural emulsifiers such as casein and egg white, which may present allergy risks. Thus, high-molecular-weight sericin can be used as an additive to creams and mayonnaise, while low-weight sericin can be used in salad dressing and lighter emulsions, for example (Takechi et al., 2011; Züge et al., 2017).

An effective way to improve the emulsifying property of sericin is through modification by the Maillard reaction, which consists of nonenzymatic glycation between carbonyl and amino groups. Wang and Zhang (2023) reported a glycated sericin that improved not only the water solubility and consequent emulsifying property, but also the antioxidant activity and the pupal odor of silk protein, allowing wider applications in the food industry.

Matran et al. (2023) developed a prebiotic dessert with 1% of sericin and other natural products, sugar-free and low energy value, for consumption by people with dysphagia, diabetes, or who would like to maintain a healthier diet. In addition to the health benefits that sericin can offer, the authors also took advantage of sericin's gelling property, claiming that other gelatinous products can be developed from this protein. However, as the recipe does not contain food preservatives, the dessert needs to be kept refrigerated to preserve its properties and last longer.

Another study also verified the antihardening effect of sericin peptides produced from silk protein hydrolysis in high protein nutritional bars (Zhu et al., 2023). The addition of this protein promoted an improvement in water mobility, reducing phase separation. In this way, hardening was reduced in up to 72 h of storage, and the final product showed enhanced texture.

A bread containing sericin was created by (Takechi & Takamura, 2014) with the aim of stimulating the consumption of silk protein and verifying changes in physical−chemical characteristics. The authors reported that the addition of sericin made the crust darker and dough growth was inferior, but with no deep impacts. In general, the addition of 2 g of sericin to each 1 kg of flour provided approximately 330 mg of protein per slice, and because it maintained palatability and quality, the

food was considered quite effective in sericin intake, which can bring many benefits for the consumer.

5.4.2 Packaging and coating

Due to the increasing concern about hunger by the world population, preserving food for longer is a way to avoid waste and price increases, in addition to avoiding contamination and foodborne diseases. In this sense, silk sericin has also been reported as a preventive agent against the oxidation of fruits, vegetables, and other perishable foods, significantly increasing their shelf life (Seo et al., 2021; Yang et al., 2023).

To overcome the limitations of sericin itself and enable its application in coatings and packaging, the Maillard reaction can be performed through a crosslinking between sericin and glucose to develop a film with better mechanical structure, antioxidant activity, and UV-blocking (Oh et al., 2021). The addition of bamboo-derived cellulose nanofibrils to sericin was also found in the literature with the aim of improving the tensile properties (Kwak et al., 2018). More structured films have broader applications in industry and are less susceptible to moisture, being considered good substitutes for petroleum derivatives or synthetic products often used for this purpose.

As in the packaging production, edible coatings formed by sericin directly on the food itself usually use other compounds to reinforce the mechanical property in film formation. For example, (Tarangini et al., 2022) prepared a dip-coating on tomatoes based on sericin, chitosan, aloe vera, and glycerol to verify its preservative action after 40 days at controlled humidity and temperature. The authors reported reduced weight loss and firmness compared to uncoated tomatoes, in addition to showing no signs of deterioration or wrinkling up to 21 days. In another study, lychee fruits were coated with a thin layer composed of sericin, chitosan, and carbon dots, which significantly delayed the browning and opacity of the product, in addition to losing fewer nutritional components compared to fruit without the treatment (Mei et al., 2022). Moreover, other foods covered with sericin-based edible films were also found in the literature showing the inhibition of the enzyme polyphenol oxidase, responsible for the browning of fruits and vegetables (Chimvaree et al., 2019; Puangphet et al., 2015; Thongsook & Tiyaboonchai, 2011).

5.5 Environmental application

Sericin has various applications in the environmental field due to its properties, composition, and biodegradability. Its composition makes some sericin-based materials effective in capturing metals, chemical compounds, and pollutants present in aqueous media. Applications are also reported in soil remediation, preservation of agricultural soils, biodegradable films to replace synthetic plastic films, and nanoparticles for disease vector control, among other applications.

The removal, recovery, and remediation of aqueous media loaded with metals is an environmental concern, given the persistence and toxic effects that these compounds impose on the environment and human health. Sericin-based materials have been developed to address this challenge.

Kwak and Lee (2018) manufactured polyethylenimine-modified silk sericin beads for chromium removal. The authors reported a removal capacity of 365.3 mg/g for hexavalent chromium when the initial pH was 2.0 and, simultaneously with the removal process, there was a reduction of Cr^{6+} to Cr^{3+}. The reduction phenomenon was attributed to the presence of hydroxyl and amine groups on the surface of the solid.

Particles produced from sericin and alginate by ionotropic gelation in Ca^{2+} solution were evaluated for copper and zinc removal (da Silva et al., 2016). In this work, different concentrations of the polymers were evaluated in the blend, which was gelled in aqueous and alcoholic (ethanol) Ca^{2+} solution and then dried at different temperatures. It was observed that the solubility of the dried particles was lower when prepared in alcoholic solution, which is related to the lower solubility of sericin and alginate in ethanol and to changes the structure of proteins since ethanol induces β-sheet formation in sericin protein. Thermal crosslinking at 100°C (drying temperature) proved to be more effective in reducing the solubility of the adsorbent particles, 7.5% in particles prepared in aqueous solution, and 5.0% in ethanolic solution. Despite the differences in physical characteristics, the particles prepared in aqueous Ca^{2+} solution had superior or very similar results to the particle produced in ethanol, being the gelation process in aqueous medium the most suitable to produce solid for metal removal. The results demonstrate that physical and chemical processes lead to materials with different characteristics and properties.

Other works used the sericin and alginate blends to produce particles (cross-linked with Ca^{2+}) for the removal of toxic metals. de Andrade et al. (2018) investigated the removal of Cr^{3+} and Cr^{6+} and observed that the maximum adsorptive capacities (q_{max}) for Cr^{6+} increased from 0.08 mmol/g at 20°C to 0.76 mmol/g at 55°C, the endothermic process occurred with the ion exchange with the calcium of the particle. Silva et al. (2021) evaluated sericin and alginate particles crosslinked with poly(ethylene glycol) diglycidyl ether for recovery of palladium (in chloro-complexes forms). q_{max} of 0.25 mmol/g was obtained involving chemisorption and physisorption, with best fit of the pseudo-second-order model to the kinetic data and with external mass transfer resistance being the limiting step of the adsorption process. Santos et al. (2020) used proanthocyanidin to crosslink the sericin/alginate blends for gold recovery, obtaining q_{max} of 238 mg/g at 30°C. In the regeneration of the adsorbent, 84% of the metal was eluted using thiourea/hydrochloric acid solution. The recovery of noble metals is part of the context of minimizing environmental impacts because mining process has a high polluting potential, and often noble metals are present together with heavy metals.

Costa et al. (2022) evaluated the affinity of particles produced with sericin/alginate/PVA by ionotropic gelation (SAPVA particles) in the recovery of rare earth metals. They observed that the particles are able to recover the metals in the order Ytterbium (Yb^{3+}) > Dysprosium (Dy^{3+}) > Neodymium (Nd^{3+}) > Cerium (Ce^{3+}) > Lanthanum (La^{3+}). In another study (da Costa et al., 2022), they reported the recovery efficiency of ytterbium in a continuous packed-bed column. They observed an exhaustion adsorption capacity of 128 mg/g. Regeneration cycles led to recovery higher than 97%, concentrating the metal in the eluent solution to 3870 mg/g (concentration of the eluted metal in solution), 44 times higher than input concentration.

Singh et al. (2018) evaluated the conjugate of chitosan and sericin crosslinked by glutaraldehyde for removal of hexavalent chromium (Cr^{6+}) and methyl orange dye (MO). The maximum capacities (Langmuir) were 139 mg/g for Cr^{6+} and 385 mg/g for MO, and the process was influenced by the pH of the medium. With increasing pH, the capacities decreased from 95.6 to 92.9 mg/g for Cr^{6+}, and from 78.4 to 50.4 mg/g for MO, a reduction attributed to the competition of OH^- ions for the active sites of the adsorbent.

Verma and Subbiah (2019a, 2019b) investigated sericin-coated polypropylene membrane for drug removal in a multicomponent system. The observed removal efficiency was ibuprofen > diclofenac > amoxicillin > ciprofloxacin > estrone > β-estradiol (nonsteroidal anti-inflammatory and antibiotics drugs were completely removed at concentrations of 20 μg/L), and desorption was achieved effectively by changing the pH of the membrane-cleaning solution. The amine functional groups present in the membrane can act as hydrogen bond donors or acceptors by establishing bonds with the carboxyl, ketone, and hydroxyl groups of the drugs evaluated. The study using continuous adsorptive membrane filtration was predicted by the Bohart-Adams model.

Chauhan et al. (2023) used silk sericin extract as a green reducer agent for zinc oxide nanoparticles production, coated with stabilizer chitosan polymer, for removal of methylene blue dye by photocatalysis (under UV light−664 nm). The proposed system was able to remove 90% of the dye in 135 min. Comparing the results with other nanoparticles produced with the extract of shiitake mushrooms (*Lentinula edodes*), the nanoparticles manufactured with sericin showed a greater catalytic effect because it led to a greater production of −OH radicals in the oxidative system to degrade the dye.

Jaramillo-Quiceno et al. (2023) developed hydrogels of sericin, carboxymethylcellulose, and polyvinyl alcohol for the production of films that were applied to soils to increase moisture retention. The films produced had a porous structure and the incorporation of 1% of the material produced in the soil increased water retention by 44.7%. The loss of soil moisture leads to the loss of nutrients, notably NPK fertilizers (nitrogen [N], phosphorus [P], and potassium [K]), through leaching, evaporation/volatilization, and/or degradation. Within the environmental context, this raises concern because it is directly related to soil degradation, water eutrophication, and global warming, among other problems. Still, given the projection of population growth in the coming decades, the rational and optimized use of these nutrients is important for the preservation of natural resources (N and P are considered critical elements) and to meet the world demand for food.

Summer et al. (2023) studied the larvicidal activity of sericin-based silver nanoparticles (Se−AgNP) for the control of the dengue vector (*Aedes aegypti*). The *Aedes aegypti* mosquito is one of the main vectors of diseases such as dengue, Zika, chikungunya, and urban yellow fever. From an environmental perspective, effective control techniques imply the minimization of negative impacts related to the use of toxic substances released into the environment focused on the control of this type of pest (Silvério et al., 2020). In the study, Se−AgNPs were produced using sonication and heat. It was observed that sericin acts as a reducing/stabilizing agent for silver nanoparticles and that larvicidal activity is inversely proportional to the size of the nanoparticles.

Other examples of applications include: the production of sericin-coated polyester filter for the removal of particulate matter and volatile compounds from the air (Verma & Subbiah, 2019a, 2019b), pellets made of sericin crosslinked with poly(ethylene glycol) diglycidyl ether for Cu^{2+} biosorption (Marques et al., 2022), sericin/functionalized graphene nanocomposite for phenolic compounds adsorption (Abdolmaleki & Mahmoudian, 2020), sericin-coated magnetite nanoparticles synthesized from ferric and ferrous salts, and sericin in alkaline conditions for the adsorption of methylene blue dye from water (Chamchoy et al., 2021), among others.

The various examples presented demonstrate the versatility of sericin to produce materials aimed at the environmental area. The chemical composition of sericin and auxiliary polymers, as well as the crosslinking processes, have produced materials with great affinity to organic and inorganic pollutants. Also, from a comprehensive point of view, the use of the protein in materials for agriculture and remediation of environmental impacts demonstrates the potential of the material in various fields of the environmental area.

5.5.1 Life cycle assessment of sericin and carbon footprint

The life cycle of a material is a critical factor in assessing its sustainability and environmental impact. The recovery of resources from wastewater is particularly significant within the framework of the circular economy (Hernández-Chover et al., 2023). When considering sericin, it is essential to evaluate each step of its cycle, from extraction to end-of-life disposal, to ensure that the processes involved are environmentally friendly and aligned with the principles of minimizing waste and maximizing resource efficiency.

Capar et al. (2022) conducted a life cycle assessment (LCA) study on the recovery of sericin from silk degumming wastewaters at an industrial plant in Bulsa, Turkey. In a 100 kg batch of silk yarn, approximately 25 kg corresponds to the protein sericin, which is typically discarded into the wastewater during the degumming process. The study compared two main scenarios: one without sericin recovery and another considering all steps necessary for sericin recovery to assess the feasibility of implementing this process in industry. According to the authors, the recovery of sericin has greater impacts than just treatment and disposal. In relation to the equivalence in kg of CO_2, the recovery of sericin has impacts of 2000 to 2650 times greater on the effect of global warming than the scenario without recovery due to the number of steps. However, a study carried out by (Giacomin et al., 2017) states that the agricultural cultivation of the mulberry tree (*Morus alba*), the main source of food for the silkworm (*Bombyx mori*), has a broad capacity to mitigate its carbon footprint by sequestering CO_2 from the atmosphere, reducing total greenhouse gas emissions. Using data from average cocoon production in Brazil, the authors estimated that mulberry trees attenuate around 81,650 tons of CO_2e (carbon dioxide equivalent) per hectare per year, which corresponds to more than 735 times the weight of the silk fiber produced per cultivated area. Therefore, there is a positive correlation that encourages the recovery of this bioproduct.

Among the sericin recovery processes, the electrical energy consumption of nanofiltration and sericin degumming had the greatest environmental impact. The energy requirement for sericin recovery is 1700 to 2300 times higher compared to conventional end-of-line treatment of sericin wastewater, clearly indicating the importance of utilizing renewable energy sources to minimize the effect on the global warming. However, regardless of sericin recovery, the textile industry must still carry out the degumming process. Therefore, it is important to emphasize the need for new, more environmentally friendly sericin extraction methods that offer similar performance to current soap and soda treatment at alkaline pH. Furthermore, the current cost of recovering sericin from wastewater is higher than that of purchasing low-purity sericin from a commercial supplier, justifying the indispensability of these new methods being cost-competitive (Capar & Pilevneli, 2024).

Regarding the incorporation of sericin into blends, eco-friendly techniques and simple processes are generally used to minimize emissions and waste, such as mixing in solution followed by evaporation to form the blend. The choice of polymers to blend and solvents also plays a significant role, as some may require more resources and produce more greenhouse gases than others. Transportation of raw materials and final products further adds to the carbon footprint. To minimize these impacts, it is crucial to optimize each step of the process, use renewable energy sources, and select eco-friendly materials (Sharma & Bhende, 2024). Conducting a thorough LCA can help identify the most carbon-intensive stages and guide efforts to reduce the overall carbon footprint of sericin blend production. At the end of their life cycle, sericin-based composites contribute to a lower environmental impact, as these materials decompose naturally, reducing landfill waste and associated methane emissions, further lowering their carbon footprint (Ho et al., 2012; Zhao & Zhang, 2020). Compared to synthetic polymers, sericin generally exhibits a lower carbon footprint due to its renewable origin and biodegradability. However, no reference was found in the literature addressing an LCA specifically referring to the production of sericin blends.

The scarcity of LCA studies represents one of the significant challenges for industry and the transition from laboratory-scale processes to industrial-scale production. This lack of studies can affect decision-making and the implementation of more sustainable practices. Collecting detailed and accurate data for all stages of the LCA is a time- and resource-intensive process, which often becomes unfeasible (Moutik et al., 2023). Despite its complexity, LCA provides invaluable insights that can help industries make informed decisions to enhance sustainability and minimize environmental footprints.

6. Challenges and opportunities

Characteristics such as biocompatibility, biodegradability, and nontoxicity give sericin an advantageous and extensive potential, covering various fields such as biomedicine, pharmaceuticals, the food industry, and environmental protection. However, sericin-based composites face several challenges in terms of application and performance.

A significant challenge is the amorphous structure of sericin, which leads to poor mechanical performance due to auto-degradation of the protein. Incorporating materials to form films, sponges, hydrogels, or particles in an optimized way can improve the mechanical strength and flexibility of these materials, while balancing mechanical properties with other desired attributes such as compatibility and degradability (Wu et al., 2024; Zhang et al., 2017).

Strategies such as the formation of nanocrystals that permeate the composite hydrogel network and the integration of silver nanoparticles into sericin-based composites improve antimicrobial properties, but often at the expense of mechanical stability, requiring further refinement of the synthesis processes (Boonpavanitchakul et al., 2020). For example, hydrogels composed of alginate/sericin/cellulose nanocrystal interpenetrating networks were developed to improve the low mechanical strength of single-component hydrogels. However, balancing mechanical performance with other desired properties such as biocompatibility and biodegradability remains a complex task (Wu et al., 2024).

Similarly, the integration of silver nanoparticles into sericin-based composites enhances antimicrobial properties, but often compromises mechanical stability, which requires further refinement of the synthesis processes (Boonpavanitchakul et al., 2020). In addition, process variables such as temperature, concentration, and agitation vary depending on the composition of the desired composite, adding another layer of complexity to the production process. Overall, while sericin-based composites hold significant promise across various industries, optimizing their mechanical properties without compromising other desirable characteristics is a critical area of ongoing research and development.

Another challenge is to ensure the stability and biocompatibility of sericin composites so that they retain their functional properties (Wu et al., 2024). The addition of silver nanoparticles, polysaccharides, and cross-linking agents into sericin composites demonstrated antibacterial activities and sufficient biocompatibility. However, achieving consistent and controlled release of antimicrobial agents without compromising the structural integrity of the material remains a challenge (He, Cai, et al., 2017; Wu et al., 2024; Zhang et al., 2017). For biomedical applications, sericin composites must ensure the promotion of cellular activities such as wound healing, nerve regeneration, and inflammation reduction (Wang et al., 2024). However, the preparation process requires careful control to prevent adverse effects on cells and tissues. In addition, maintaining the balance between mechanical strength and biological functions is critical for these applications.

In addition to applications in the medical and pharmaceutical fields, sericin fiber composites promise to significantly improve the thermal insulation of building materials due to their ability to reduce heat transfer. However, for this application, the durability, mechanical, and chemical resistance of the material must be guaranteed, and it must meet environmental requirements to minimize impact (Pakdel & Alemi, 2022). Sericin-based electrospun nanofibers are being investigated for their potential in filtration and smart textiles, where their ability to incorporate nanosized bioactive materials and metals can confer new functional properties such as antibacterial activity and improved mechanical strength (Mowafi & El-Sayed, 2023).

These advances emphasize the versatility and potential of sericin-based composites in the production of sustainable, high-performance materials for diverse applications. However, the optimization of process parameters, stability, and durability of materials remain limiting factors in their application. Further research and development are needed to overcome these challenges and fully harness the benefits of sericin-based composites.

6.1 Scale-up

Large-scale production of sericin-based composites faces various challenges in meeting industrial demand. The environmental impact of increasing the scale of production must also be considered. Although the process involves the use of a biodegradable protein that is more sustainable than synthetic components currently available on the market, the industrial processes involved can pose environmental risks. The development of environmentally friendly extraction processes that minimize waste and reduce energy consumption is essential for sustainable sericin production (Pakdel & Alemi, 2022, 2023). A relevant obstacle is the standardization of the sericin extraction and purification process to produce an efficient product. Conventional extraction methods using hot or chemical degumming require significant energy and are harmful to the environment. More innovative methods, such as the use of enzymes and ultrasound, have been investigated to ensure reproducible and scalable extraction (Wang et al., 2024).

Achieving batch uniformity of sericin composites with other materials (polymers, metals, clays) with consistent properties is a challenge in the scale-up phase. Electrospinning and 3D printing techniques for integrating sericin with polymers, metals or natural fibers are promising for producing sericin-based composites with more precision. However, scaling these methods to ensure control of the properties, distribution, and uniform bonding of components while maintaining mechanical strength and flexibility remains a limiting factor (Mowafi & El-Sayed, 2023). Strict quality control is necessary to ensure that composites meet the standards required for different applications, especially in the biomedical field, which requires critical material performance. Increasing production volume and consistency is essential for commercializing sericin composites. To achieve large-scale production without compromising material quality and performance, advanced technologies in automated production and robust supply chain management for quality monitoring are crucial (Boonpavanitchakul et al., 2020; Zhang et al., 2017). The research and development phase is critical to optimize and validate process parameters to ensure successful production ramp-up.

In conclusion, although sericin-based composites are promising, several challenges must be faced to increase their production in a sustainable and efficient way. Innovations in extraction methods, precise integration techniques, and strict quality control are essential to meet industrial demands. Collaborative efforts between researchers and industry stakeholders will be vital in developing the technologies and processes needed to overcome these challenges and fully realize the potential of sericin-based composites.

7. Final considerations

Innovative devices and economically viable nanotechnologies based on sericin have been widely reported. This is mainly due to the use of a residue from the silk industry that is biocompatible and has inert biological properties, which enable the use of bioproducts in biomedicine, regenerative medicine, drug delivery systems, cosmetics, and environmental field. This chapter described the use of sericin for the preparation of composites with improved physicochemical and structural properties through different methods for obtaining of the films, membranes, beads, nanoparticles, and 3D structures (hydrogels and sponges) for several applications. Sericin is a natural polymer whose properties enable it to perform a wide range of materials with applicable functions in different fields of knowledge. The composition of sericin and its high capacity to polymerize, form blends and crosslink allows the production of materials with different functions, given its interaction with organic and inorganic contaminants, its biological responsiveness that gives it numerous attractive properties for the biomedical and cosmetic area. Recent reports have shown relevant results on the effects of sericin on pH-dependent systems, on cell adhesion and proliferation, on bone matrix and skin regeneration, on immunomodulation and therapies of some cancers, as well as on antioxidant, anti-inflammatory effects, and protection against UV irradiation, all related to protein extraction conditions and structure (molecular weight and purity). However, the development and application studies of sericin composites have not overcome the barrier of in vitro assays. Therefore, in vivo investigations are needed to improve clinical applications and further steps.

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Medical applications of sericin: A molecular perspective

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Thitima Wattanavijitkul[1], *Sarocha Cherdchom*[2] *and Pornanong Aramwit*[1,3,4]
[1]Chulalongkorn University, Department of Pharmacy Practice, Faculty of Pharmaceutical Sciences and Center of Excellence in Bioactive Resources for Innovative Clinical Applications, Bangkok, Thailand; [2]Chulalongkorn University, Department of Anatomy, Center of Excellence in Nanomedicine, Bangkok, Thailand; [3]The Academy of Science, The Royal Society of Thailand, Bangkok, Thailand; [4]Silpakorn University, Faculty of Pharmacy, Nakhon Pathom, Thailand

1. Introduction

Silk is a natural polymer composed mainly of hydrophobic fibroin and hydrophilic sericin. This material is produced by the silkworm (*Bombyx mori*). In the past, sericin was considered to be merely a byproduct or waste in silk production, particularly in countries such as China, India, and Brazil (Kunz et al., 2016). However, sericin actually plays a vital role in the silk extraction process, which involves various physical, biological, and chemical extraction techniques. Due to its biocompatibility and diverse bioactivities, sericin has become an attractive candidate for biomedical and pharmaceutical research (Liu et al., 2022).

Over the past 2 decades, there has been a notable increase in sericin-related research and innovation. Early in this period, the numbers were relatively modest, reflecting initial exploratory studies and foundational research. However, as the unique properties and potential applications of sericin have become more apparent, there has been a marked rise in scholarly articles and patents. This surge is particularly noticeable in the past decade, indicating a growing recognition of sericin's versatility in medical, cosmetic, and biotechnological applications. The trend suggests a robust and expanding interest among researchers and innovators, driven by advancements in extraction techniques, formulation methods, and the exploration of novel applications such as wound healing, tissue engineering, and drug delivery systems.

Sericin can be applied for numerous medical purposes due to its distinctive molecular properties and therapeutic activities, ranging from its antioxidant activity to its contributions in wound healing, antimicrobial efficacy, and potential applications in treating various diseases. The exploration of the molecular mechanisms underlying sericin's therapeutic activities has tremendous potential to advance treatments and to improve patient outcomes.

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2. Stability, biodegradability, and reusability of sericin in biomedical applications

2.1 Sericin extraction methods and influential factors

The stability of sericin is significantly influenced by the extraction methods (Table 8.1) employed and various external factors such as the addition of other chemicals (Seo et al., 2023). Sericin can be extracted using hot water extraction, acid or alkaline extraction, and urea extraction, each of which affects its stability differently (Noosak et al., 2022). Hot water extraction, a commonly used method, generally yields sericin with moderate stability, retaining most of its functional properties (Seo et al., 2023; Silva et al., 2022). Acid or alkaline extraction can alter the protein structure, potentially reducing stability but enhancing certain bioactive properties (Aramwit, Kanokpanont, et al., 2010). Urea extraction, known for producing highly purified sericin, can improve stability by minimizing denaturation (Aramwit, Kanokpanont, et al., 2010). However, chemical extraction methods require an additional step to remove the chemical impurities (Lamboni et al., 2015; Silva et al., 2022). Enzymatic extraction of sericin has garnered significant attention due to its ability to preserve the protein's stability and functional properties. Unlike traditional methods that may involve harsh chemicals or extreme conditions, enzymatic extraction leverages the specificity and mild nature of enzymes to hydrolyze silk fibroin selectively, releasing sericin in a more intact and bioactive form. One of the primary benefits of enzymatic extraction is the maintenance of sericin's structural integrity. This preservation is crucial as the structural integrity of sericin is directly related to its functional properties, including its binding capacity, film-forming ability, and biocompatibility. External factors such as pH, temperature, and storage conditions also play crucial roles; the effects vary by study (Noosak et al., 2022; Rahman et al., 2021; Zhang, 2002). Optimal stability is often achieved under neutral pH and controlled temperatures, preventing hydrolysis and aggregation of sericin. Understanding the influence of these factors is vital to ensure sericin's stability is sufficient for specific biomedical applications.

Table 8.1 Methods used to extract sericin.

Methods	Approach
Conventional	Detergents/soaps (e.g., Marseille) and sodium bicarbonate
Physical	Hot water
Chemical	Alkaline solutions
	Acidic solutions
	Urea
Enzymatic	Proteolytic enzymes

2.2 Biodegradability of sericin and sericin-related materials and products

Sericin's biodegradability is a key attribute that makes it highly desirable for biomedical applications. As a natural protein, sericin is broken down by proteolytic enzymes (e.g., protease XIV, α-chymotrypsin, proteinase K, papain, matrix metalloproteinases [MMPs], and collagenase) in the body (Silva et al., 2022) into nontoxic, absorbable amino acids, and peptides (Cao & Zhang, 2016; Zhang et al., 2024). This biodegradability is advantageous for temporary implants and scaffolds in tissue engineering, where the material needs to support tissue growth and then be resorbed gradually without causing harm. Sericin-based hydrogels, films, and nanoparticles also exhibit excellent biodegradability, making them suitable for drug delivery systems where they can provide sustained release of therapeutics followed by safe degradation (Lamboni et al., 2015). The degradation rate of sericin can be controlled by modifying its physical structure or blending it with other biocompatible polymers, allowing its use in specific medical applications (Cao & Zhang, 2016; Silva et al., 2022). This tunable biodegradability ensures that sericin-related materials and products are both effective and safe for long-term medical use.

2.3 Recycling sericin: Innovations in reuse and reusability in biomedical applications

Sericin's potential for reuse and reusability is an emerging area of interest in biomedical research, offering both economic and environmental benefits. Recycling sericin has become a focal point in sustainable biomaterial research due to its potential to minimize waste and to create value-added products. Several recycling methods have been developed, including aqueous extraction, enzymatic hydrolysis, and the use of environmentally friendly solvents. These methods aim to recover sericin from silk production waste efficiently while maintaining its bioactive properties (Table 8.2) (Cao & Zhang, 2016). However, the cost of sericin recovery is high. A previous study reported a new degumming/refining method using strongly alkaline electrolyzed water (pH 11.50) in combination with sericin recycling by ultrafiltration and nanofiltration from the degumming solution. Nevertheless, the approach requires further development to reduce the high cost, to improve the low processing efficacy, and to achieve industrial-scale recovery (Wu & Zhang, 2014). Aqueous extraction, utilizing water or mild solvents, is favored for its simplicity and minimal environmental impact. Enzymatic hydrolysis employs specific enzymes to selectively break down silk fibroin, releasing sericin in a highly functional form. Emerging technologies such as microwave- and ultrasound-assisted extraction are also being explored for their ability to enhance yield and reduce processing time.

The future of sericin recycling looks promising, with advancements in green chemistry and biotechnological processes paving the way for more efficient and sustainable methods. Integrating sericin recycling into a circular economy framework could significantly reduce the environmental footprint of the silk industry. Innovations in nanotechnology may further enhance the functionality of recycled sericin, broadening its

Table 8.2 Methods to recycle sericin from silkworm cocoons, silk fiber, or raw silk.

Type of recycling method	Name	Degumming conditions	Yield (%)	Application
Physical	Film filtration	Micro- and nanofiltration, room temperature	>90	Laboratory
	Electrolysis	25 V_{DC}; 40−60 min	20−75	Research
	Freezing−thawing	−20−30°C; 5 h 2	>80	Laboratory
Chemical	pI-centrifuge	~ pH 8.0; 0.1% HACC	76	Laboratory
	Coagulation	pH 8.0; 75°C; 1:30 (w/v); 480 min; 1 time	95	Research
	Denaturation in solvents	90% (v/v) ethanol	>90	Research

Adapted from Cao, T. T., Zhang, Y. Q. (2016). Processing and characterization of silk sericin from *Bombyx mori* and its application in biomaterials and biomedicines. *Materials Science and Engineering: C, 61*, 940−952, https://doi.org/10.1016/j.msec.2015.12.082.

application in biomedicine, cosmetics, and food preservation. Collaborative research between academia and industry is crucial to develop scalable and economically viable recycling processes.

3. Sericin and skin wound treatment

Sericin has shown great potential for wound-healing treatment, and there has been increasing research interest in this topic. Inflammatory responses occur during the initial stages of wound healing, playing a role in the removal of debris and the initiation of tissue repair processes (Eming et al., 2007). Sericin has anti-inflammatory properties that can influence various molecular pathways involved in the inflammatory response. It can regulate the activity of key inflammatory mediators such as cytokines and chemokines, leading to a controlled and balanced inflammatory environment around the wound area. Researchers demonstrated that sericin contributes to wound healing by reducing the wound size and inflammatory cytokines in male Sprague−Dawley rats (Aramwit et al., 2009). The authors conducted an in vitro experiment using mouse monocyte and alveolar macrophage cell lines to investigate the impact of sericin on the levels of interleukin (IL)-1β and tumor necrosis factor (TNF)-α. The cells were exposed to different concentrations of sericin (0.2−1.0 mg/mL). The amount of TNF-β and IL-1β generated by both cell lines corresponded to the sericin concentration in the culture medium. However, wounds treated with sericin exhibited significantly lower levels of both inflammatory cytokines. In another experiment, full-thickness rat excisions were subjected to dermatotomy, and the wounds were treated with a cream base, normal saline, or sericin. After 15 days, the wounds treated

with the cream base and normal saline were not yet fully epithelized and showed some ulcers. In contrast, the wounds treated with sericin showed complete epithelization, and there had been a more pronounced wound size reduction (Aramwit et al., 2009).

Sericin has positive effects on repairing damaged corneal epithelium. Sericin promoted corneal wound healing in normal and diabetic rats by enhancing the proliferation of corneal epithelial cells (Nagai et al., 2009a, 2009b). Therefore, sericin could be effective for the treatment of corneal wounds. In fact, when a human corneal epithelial cell line (HCE-T cells) was treated with sericin, the growth of the cells increased significantly by 1.7-fold compared with the vehicle-treated HCE-T cells. In an in vivo study using rat debrided corneal epithelium, sericin instillation also enhanced the corneal wound healing rate. Interestingly, this enhancement was attenuated by instillation of a nonspecific extracellular signal-regulated kinase (ERK) inhibitor. Moreover, the corneal wound healing rate in rats co-instilled with sericin, and the ERK inhibitor was similar to that following the instillation of the ERK inhibitor alone (Nagai et al., 2024).

In a clinical study, the authors found that the use of silver zinc sulfadiazine cream with sericin is both safe and effective in treating burn wounds. The treatment reduced the wound size and healing time without any adverse reactions (Aramwit et al., 2013). The use of sericin in wound treatment requires further investigation through clinical studies to translate promising laboratory findings into practical and evidence-based medical applications. Despite the extensive history of silk and its applications in traditional medicine, the limited number of studies conducted on the effects of silk in wound healing in humans represents a significant gap in our understanding of this potential therapeutic avenue. The lack of clinical investigations makes it difficult to evaluate comprehensively the efficacy and safety of silk-based wound treatments for medical use. Addressing this gap is crucial to unlock the full therapeutic potential of silk-based wound treatments. This will provide evidence-based insights into the molecular mechanisms and clinical outcomes associated with silk use. Clinical studies are crucial to evaluate the potential of silk-based wound treatments and to translate the promising laboratory findings into practical medical applications.

3.1 Sericin-based dressings for enhanced wound healing

The biocompatibility and bioactivity of the sericin contribute to a supportive microenvironment for wound healing. It promotes cell adhesion and migration while also regulating the expression of growth factors and cytokines. These mechanisms collectively enhance wound closure, reduce scar formation, and contribute to overall tissue regeneration. Hence, sericin can be incorporated in wound dressings, films, or hydrogels, making it a promising and natural solution for improving the efficiency and efficacy of wound management (Du et al., 2023; Xue et al., 2016). It is necessary to improve the mechanical strength and stability of sericin extracted from silk cocoons during processing so that is can be utilized as a biocompatible natural biopolymer in biomedical applications. A crosslinked sericin membrane was prepared using glutaraldehyde as the crosslinking agent. It showed improved physical and structural characteristics,

cytocompatibility, and supported the growth of AH927 cells (a feline fibroblast cell line) (Nayak et al., 2012).

Materials for wound dressing, such as sericin hydrogel film, have been developed to treat chronic wounds. In one study, researchers developed agar-glycerol-sericin hydrogel films as potential dressing materials to treat chronic wounds (Tyeb et al., 2018). The authors fabricated flexible agar-sericin-glycerol hydrogel films (03:01, 05:01, and 10:01) with sericin as a minor component to improve collagen production and to reduce free radical species, ultimately promoting chronic wound healing. The films demonstrated improved collagen production across all three concentrations. Concerning free radical scavenging, the 03:01 and 05:01 films demonstrated superior performance based on Sirius red staining and the 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay. These films displayed adequate tensile strength of around 35 MPa along with elongation at break of >25%. Finally, the films showed satisfactory swelling behavior of around 320% in simulated wound fluid, which is important for maintaining a moist wound environment that promotes healing. Overall, these findings suggest that agar-sericin-glycerol hydrogel films could be a promising material to treat chronic wounds (Tyeb et al., 2018).

In a diabetic mouse models where delayed wound healing is a concern, sericin-based hydrogels have demonstrated notable attributes such as antioxidant and anti-inflammatory properties that contributed to improve wound healing (Baptista-Silva et al., 2022; Tyeb et al., 2020). The combination of carboxymethyl cellulose (CMC) and sericin has shown great potential as a treatment for diabetic wound healing. This CMC/sericin-based hydrogel showed a high level of swelling; had a porous structure; and possessed good antibacterial and antioxidant activities and hemocompatibility. In vivo evaluations of diabetic wounds treated with CMC-sericin hydrogel revealed significant improvements in wound healing. On day 21, the wounds treated with the CMC-sericin hydrogel showed full restoration. In addition, these wounds had significantly lower levels of proinflammatory cytokines (IL-1, IL-6, and TNF-α) compared with those treated with CMC-sericin or insulin. This indicates that the CMC-sericin hydrogel not only promotes wound healing but also has anti-inflammatory properties (El-Samad et al., 2022).

Sericin hydrogel has also been used as a wound dressing for the delivery of exogenous growth factors to facilitate wound healing. Researchers developed a novel heparin-based sericin hydrogel that encapsulates basic fibroblast growth factor (bFGF-HS) to facilitate wound healing and skin regeneration with retention of exogenous growth factor. This hydrogel has a unique three-dimensional (3D) microporous structure, which provides a large surface area for cells to attach and proliferate, is highly biodegradable, and can sustainably release the encapsulated bFGF at the wound site for a few days. bFGF-HS showed better support for the growth of double-layered construct cells and enabled deeper migration and a higher number of cells in the hydrogels. Moreover, bFGF-HS significantly promoted vascularization and re-epithelialization and improved collagen deposition, ultimately accelerating wound healing in vivo in mice (Du et al., 2023).

In another study, researchers found that hydrogels made from sericin-chitosan-glycosaminoglycans and containing growth factors such as vascular endothelial growth

factor (VEGF) and transforming growth factor (TGF)-β can promote skin tissue repair both in vitro and in vivo. The hydrogel released TGF-β and VEGF slowly and continuously, leading to enhanced cellular functions such as growth, collagen production, and MMP production, which help reconstruct lost dermal tissue and repair skin. When implanted in animals, the hydrogel led to skin tissue repair, angiogenesis, and a minimal immune response (Sapru et al., 2021).

Scaffolds are a type of drug delivery technology that helps release molecules at a targeted site. They act as a template and provide physical support to guide cell proliferation and differentiation (Agrawal & Ray, 2001). Moreover, a scaffold protects wounds, maintains an optimum microenvironment, and facilitates cellular signaling (Okabayashi et al., 2009). Researchers developed a sericin/poly(vinyl) alcohol (PVA) scaffold using freeze-drying and subsequent precipitation in various ethanol concentrations. The scaffold possessed excellent properties and exhibited the highest potential for promoting cell proliferation in mouse fibroblasts using 70% (v/v) ethanol precipitation. Furthermore, the authors evaluated the efficacy of these scaffolds in full-thickness wounds in rats compared with control scaffolds without sericin. The sericin/PVA scaffold significantly reduced the wound size, increased the extent of type III collagen formation, and facilitated epithelialization compared with the control scaffold (Siritienthong et al., 2012). These findings suggest that a sericin/PVA scaffold could have promising applications in wound healing and tissue regeneration.

The potential therapeutic role of sericin in wound healing, particularly in the context of skin disorders such as psoriasis, holds promise for innovative approaches to managing these conditions. Psoriasis is a skin disease that results from an overactive immune response. It causes skin cells to grow rapidly and excessively, leading to the formation of thick, red, and scaly patches (Garg et al., 2014). These patches can also result in open wounds, especially if the affected areas are scratched or irritated. The chronic inflammation caused by psoriasis can delay wound healing, increase the risk of infection, and form nonhealing or persistent wounds (Ellis et al., 2018). Therefore, it is necessary to address both the underlying skin condition and to promote optimal wound healing when managing psoriasis-associated wounds. In one study, researchers highlighted the therapeutic potential of sericin in a skin-psoriasis rat model, revealing its capacity to modulate epidermal immunity and mitigate excessive cell proliferation (Rujimongkon et al., 2021). In another study, researchers synthesized a sericin-based PVA (SS/PVA) hydrogel that could relieve plaque and epidermal lesions in psoriasis. The hydrogel modulated inflammation, apoptosis, and antioxidative properties to reduce the severity of psoriasis in both gross and microscopic skin lesions (Tuentam et al., 2023). The results of the study indicate that sericin-based dressings are safe and may be effective in to manage wounds and skin disorders due to their physical, chemical, and biological characteristics. Furthermore, sericin has great potential in the treatment of skin disorders in human peripheral blood mononuclear cells (hPBMCs) from patients with psoriasis, due to its anti-inflammatory and antiproliferative properties (Deenonpoe et al., 2019).

3.2 Molecular mechanisms of sericin in wound healing

Sericin is involved in wound healing at the molecular and cellular levels. Its properties make it a promising candidate for developing new wound-healing strategies. Sericin exerts anti-inflammatory effects that help reduce inflammation by suppressing proinflammatory cytokines. It also has antioxidant activity, which helps mitigate oxidative stress and create a favorable environment for wound healing (Aramwit et al., 2009; Deenonpoe et al., 2019; El-Samad et al., 2022; Kumar & Mandal, 2017). During the inflammatory phase of wound healing, immune cells generate reactive oxygen species (ROS) to eliminate pathogens and to initiate tissue repair. However, excess ROS can lead to prolonged inflammation and tissue damage. Antioxidants help regulate this process by neutralizing excessive ROS, thereby mitigating inflammation and supporting the transition to the proliferative phase of wound healing. Studies have shown that sericin has free radical scavenging activity, which effectively reduces the levels of ROS and prevents oxidative damage (Baptista-Silva et al., 2022). The molecular structure of sericin includes amino acids with antioxidant properties that play a crucial role in neutralizing free radicals and protecting cells from oxidative stress. According to the proteomic results, sericin has the ability to reduce cytokine production by Th17 cells by regulating the expression of signaling proteins in the Janus kinase/signal transducer and activator of transcription (JAK/STAT) signaling pathway. The positive effects of sericin on psoriatic skin are attributed to its ability to decrease epidermal cell proliferation and immune responses associated with immune cell trafficking to the inflammatory site (Rujimongkon et al., 2021).

Sericin stimulates cell proliferation and migration by promoting the expression of growth factors and influencing extracellular matrix remodeling. Its role in fibroblast activation and collagen synthesis contributes to the structural integrity of healing tissue. In a rat model, sericin exerted positive effects on wound healing and exerted antioxidant activity. The sericin-treated group exhibited an increase in epidermis thickness and induction of vascularization. The biochemical results showed significantly higher activities of the antioxidant enzymes glutathione peroxidase (GPx), superoxide dismutase (SOD), and catalase (CAT) in the sericin group compared with the placebo group (Ersel et al., 2016). Sericin also increased nuclear factor erythroid 2-related factor 2 and IL-10 while decreasing TNF-α and IL-20 (Tuentam et al., 2023). Furthermore, sericin treatment promoted corneal wound healing via the mitogen-activated protein kinase (MAPK)/ERK signaling (Nagai et al., 2024).

The antioxidant activity of sericin makes it a viable option for various medical and cosmetic applications, including wound dressings, skincare formulations, and other therapeutic interventions where protection against oxidative stress is beneficial (Cherdchom et al., 2021; Dash, Acharya, et al., 2008; Deori et al., 2016; Kumar et al., 2018; Kumar & Mandal, 2017; Manosroi et al., 2010; Seyedaghamiri et al., 2021; Takechi et al., 2014). Table 8.3 summarizes the mechanisms by which sericin modulates wound healing.

Table 8.3 Summary of the mechanisms by which sericin modulates wound healing.

Model	Mechanism	References
Human corneal epithelial cell line (HCE-T cells)	• Activates cell proliferation via phosphorylation of proteins in the mitogen-activated protein kinase/extracellular signal-regulated kinase pathway	Nagai et al. (2024)
Fibroblast cell line (NIH 3T3 cells)	• Improves collagen production • Activates anti-inflammatory properties	Tyeb et al. (2018)
Rat	• Reduces inflammatory cytokines including interleukin 1β and tumor necrosis factor-α	Aramwit et al. (2009)
Rat	• Reduces malondialdehyde levels • Activates superoxide dismutase, catalase, and glutathione peroxidase	Ersel et al. (2016)
Rat	• Downregulates Nme2, involved in skin psoriasis, and reduces epithelial cell proliferation • Reduces cytokine production from Th17 cells via the Janus kinase/signal transducer and activator of transcription signaling pathway	Rujimongkon et al. (2021)
Rat	• Upregulates nuclear factor erythroid 2-related factor 2 and interleukin 10 • Suppresses tumor necrosis factor-α and interleukin 20 expression • Downregulates psoriasis-related genes including S100a7a and S100a14	Tuentam et al. (2023)

4. Sericin and antimicrobial properties

A substance or material has antimicrobial properties when it can inhibit the growth or survival of microorganisms, including viruses, bacteria, fungi, and other pathogens. Substances with antimicrobial properties can act through several mechanisms, such as disrupting the cell membranes of microorganisms, interfering with their metabolic processes, and/or inducing oxidative stress, ultimately leading to inhibition of their growth or death. The importance of antimicrobial properties also extends beyond medicine and healthcare, finding applications in areas such as textiles, food preservation, and environmental hygiene. Natural compounds are considered to be potential alternatives because of the increasing threat of antibiotic resistance and the limitations of current antibiotic therapies (Kouidhi et al., 2015).

Sericin has antimicrobial properties (Jassim, 2010; Noosak et al., 2022), including the ability to reduce spore colonies and to inhibit the growth of *Micrococcus luteus*, and the extraction method affects its antimicrobial properties (Aramwit et al., 2020). In an in vitro study, researchers determined the effectiveness of using sericin extracted

through various methods to inhibit biofilm formation and to disrupt already formed biofilms. Sericin extracted using the urea method showed the highest antibiofilm activity at all tested concentrations (12.5, 25, 50, and 100 mg/mL). Moreover, it demonstrated superior efficacy in both inhibition and disruption compared with sericin extracted through the heat, acid, or alkaline method. The heat and acid extraction methods also showed some dose-dependent reduction in biofilm formation. In contrast, sericin extracted through the alkaline method did not produce any inhibitory or disruptive effects on bacterial biofilm. These findings emphasize the importance of the extraction method in determining sericin's biofilm-modulating properties and highlight the potential of urea-extracted sericin as an effective antibiofilm agent (Aramwit et al., 2020).

In another study, the authors utilized a chemical-free boiling method to extract sericin and found that the extracted sericin possessed biological activity. When compared with the untreated control, the extracted sericin increased the proliferation of osteoblasts by up to 135%. The antibacterial activity of sericin increased against *Staphylococcus aureus* clinical isolates and the reference strain ATCC 29213. Additionally, at the minimal inhibitory concentration, the extracted sericin significantly reduced the biofilm formation of *S. aureus* by up to 95%. Based on these findings, sericin could be utilized as a dual-functional bioactive material to support bone regeneration and to treat bone infections (Noosak et al., 2022).

Sericin and the sericin-derived peptide F5-SP exerted antiviral activity in vitro and in vivo against RNA virus infections of the respiratory tract. Sericin inhibited glycolysis and decreased lactate production, thereby promoting the activation of interferon (IFN) and enhancing the antiviral response (Li et al., 2021).

4.1 Sericin nanoparticles for controlled antimicrobial delivery

4.1.1 Sericin nanoparticles

Sericin nanoparticles (SNPs) have recently been developed and have shown notable antimicrobial properties. These nanoscale particles ensure the stability, controlled release, and enhanced interaction of sericin with microorganisms. Because of its inherent biocompatibility and functional groups, sericin is an ideal candidate for controlling the size, shape, and stability of nanoparticles. Various techniques, such as chemical reduction, green synthesis, and coprecipitation, are used to synthesize nanoparticles using sericin. The nanoparticles coated with sericin show enhanced biocompatibility, which makes them suitable for drug delivery systems in antimicrobial application.

Sericin extract was separated into three fractions based on molecular size: fraction 1 (50−300 kDa), fraction 2 (30−50 kDa), and fraction 3 (10−30 kDa). These fractions were used to prepare SNPs with different surface potentials. The authors tested the antibacterial activity of SNPs against *S. aureus* and *Escherichia coli* at three concentrations (50, 100, 200 μg/mL). The positively charge fraction 2 SNPs showed significantly greater antibacterial activity than the negatively charged SNPs. Furthermore, the positively charge SNPs induced the generation of ROS which was found to be

nontoxic to HaCaT cells (a keratinocyte cell line) (Dutta et al., 2020). Although SNPs are very promising for their antimicrobial properties, their stability and the controlled release of sericin need to be considered, and clinical studies should be performed.

4.1.2 Metal-sericin nanocomposites

Nanoparticles, particularly silver nanoparticles (AgNPs) and gold nanoparticles (AuNPs), are important in the field of nanotechnology and have a variety of applications. AgNPs are known for their potent antimicrobial properties. Because of their small size and large surface area, they interact effectively with microbial membranes, disrupting cellular functions and ultimately resulting in microbial death (Bruna et al., 2021; Tang & Zheng, 2018). AgNPs are used in proper applications such as wound dressings (Kalantari et al., 2020; Tian et al., 2007) or medical coatings (Knetsch & Koole, 2011).

A novel, simple, and one-step biosynthesis method has been developed to prepare a sericin−AgNP composite in solution. Sericin reduces silver ions and acts as a dispersant and stabilizer for the prepared composite. The sericin−AgNP composite showed prolonged stability at room temperature and demonstrated potent antibacterial activity against *S. aureus*. In addition, the composite was biocompatible with NIH/3T3 cells at a concentration of 25 mg/L (He, Tao, et al., 2017). AgNPs synthesized in a 0.3 mg/mL sericin solution showed an average diameter of only 3.78 ± 1.14 nm. These nanoparticles were conjugated with sericin, which is an organic phase. The sericin-conjugated AgNPs exhibited strong anti-HIV-1 activity against both JR-FL (a CCR5-tropic strain) and HxB2 (a CXCR4-tropic strain). They also demonstrated effective suppression of Gram-negative (*E. coli*) and Gram-positive (*S. aureus*) bacteria. Importantly, there was no significant cytotoxicity toward VK2/E6E7 cells (a human ectocervix epithelial cell line) compared with free silver ions, which are known for their potent antimicrobial properties (Lv et al., 2018). Similarly, sericin was used as a reducing and capping agent for nanoparticle synthesis. Sericin-conjugated AgNPs significantly inhibit the growth of *E. coli*, *S. aureus*, and *Klebsiella pneumoniae*, with stability at wide temperature and pH ranges (Tahir et al., 2020). In another study, the authors aimed to examine the antibacterial and antifungal properties of sericin-conjugated AgNPs at various concentrations (5−20 mg/mL) and three temperatures (8, 40, and 50°C). Interestingly, sericin-conjugated AgNPs were stable at all temperatures, with maximum growth inhibition at 8°C against all pathogenic strains, namely *Clostridium difficile*, *Proteus mirabilis*, and *Bacillus licheniformis*. Furthermore, these AgNPs showed antifungal activity against the pathogenic fungi *Candida albicans*, *Aspergillus niger*, and *Mucor mycetes* (Mumtaz, Ali, Kazmi, et al., 2023).

The integration of sericin with AuNPs or magnesium oxide nanoparticles (MgONPs) produces compounds with notable antioxidant capacity and the ability to inhibit pathogenic bacteria (Das et al., 2023; Shankar et al., 2023). AuNPs possess unique optical and electronic properties, which make them useful in imaging and diagnostic technologies. Additionally, their surface chemistry can be tuned to create drug-delivery systems. In one study, researchers biosynthesized AuNPs using waste sericin solution as both the reducing and capping agent. The sericin-AuNPs were 54.82 nm

according to the particle size analyzer, and the zeta potential was −19.8 mV. These sericin-AuNPs demonstrated antioxidant activity based on the DPPH, 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS), and reducing power assays. In addition, they demonstrated significant antibacterial activity against the foodborne pathogenic bacteria *E. coli*, *Enterococcus faecium*, *Salmonella typhimurium*, and *Salmonella enterica* (Das et al., 2023). In another study, researchers generated sericin-MgO-NPs that could inhibit the formation of *Pseudomonas aeruginosa* and *Bacillus cereus* biofilm in a dose-dependent manner. Furthermore, these sericin-MgO-NPs presented antioxidative properties, which are advantageous for the targeted antioxidant delivery system (Shankar et al., 2023).

One significant limitation regarding the use of SNPs is the inherent instability of sericin, particularly in aqueous solutions and under certain environmental conditions (Cho et al., 2003). Modifications in processing techniques, crosslinking with other polymers, or encapsulation within protective matrices, could be used to overcome these limitations.

4.1.3 Sericin-based dressings for enhanced antimicrobial activity

Sericin can be incorporated into films to create antimicrobial barriers that prevent infection. An AgNP-sericin/PVA blend film was created using an ultraviolet (UV)-assisted green synthesis method. This film had excellent mechanical performance, hygroscopicity, water retention capacity, and a low mass losing ratio. The blending of PVA and sericin helped to form a hydrogen bond network between them, which enhanced the mechanical performance and stability of sericin, as well as the hygroscopicity and water retention capacity of the film. Additionally, the film exhibited a significant inhibitory effect on the growth of both *E. coli* and *S. aureus*, indicating its strong antibacterial activity (He, Cai, et al., 2017). Sericin/agar films modified with AgNPs and polyelectrolyte membrane (PEM) were developed using the layer-by-layer adsorption method and ultraviolet-assisted AgNPs synthesis technique to create a potential biomaterial with antibacterial properties. The resulting AgNP-PEM-sericin/agar film exhibited excellent mechanical strength, high hydrophilicity, and remarkable water absorption capacity. The antibacterial activity of the film against *E. coli* and *S. aureus* was due to the release of bound silver or AgNPs into the environment (Liu et al., 2018).

Zinc oxide nanoparticles (ZnONPs) synthesized through green chemistry have a significant antibacterial effect, inhibiting the growth of both Gram-positive and Gram-negative bacteria. ZnONPs are relatively easy to synthesize and have good biocompatibility and biodegradability. Researchers generated sericin/PVA film by blending sericin with PVA, soaking the composite film in PDA solution to coat its surface with PDA, and then immersed the resulting PDA-SS/PVA film in a ZnONP solution to obtain a ZnONP-PDA-sericin/PVA composite film. The composite film presented improved mechanical performance and antibacterial activity against *E. coli* and *S. aureus* (Ai et al., 2019).

The integration of sericin and AgNPs in the form of a hydrogel resulted in a powerful product with antimicrobial activity and wound-healing properties. The

antimicrobial activity of the sericin-AgNP hydrogel is attributed to the silver released from the hydrogel. In vivo, the researchers used *S. aureus* to infect the wound and assessed the bactericidal ability of the hydrogel in Sprague−Dawley Wistar rats. The hydrogel effectively reduced the number of bacterial colonies and promote wound healing (Tao et al., 2021).

Researchers developed a cryogel called SMC@Ag (sericin-methacryloyl/Ag cryogel) by freezing polymerization of methacryloyl-modified sericin and in situ sericin reduction of silver ions. This cryogel promoted hemostasis and had antibacterial activity. In their in vitro study, blood-clotting tests showed that SMC@Ag decreased whole blood coagulation due to the introduction of AgNPs. The bleeding time and blood loss were reduced in the SMC@Ag-treated group, demonstrating the hemostatic property of SMC@Ag. Moreover, SMC@Ag exhibited antibacterial effect in both in vitro and in vivo studies and did not trigger significant inflammatory responses. These results indicate that AgNPs provide significant antibacterial activity, especially against drug-resistant *S. aureus* (Zhu et al., 2022).

In another study, the authors aimed to develop a wound dressing that could accelerate wound healing while also being multifunctional and efficient. To achieve this, they combined curcumin and AgNPs due to their well-known properties that promote healing and inhibit bacterial growth, respectively. However, curcumin has limited dispersibility and stability in water, which can reduce its efficacy in a wound dressing. To overcome this limitation, the researchers strategically decorated the two active agents with sericin. After sericin decoration, the two active agents were incorporated into a hydrogel matrix made from silk fibroin (SF), which is known for its biocompatibility and biodegradability. The resultant SF/Ag/C hydrogel was biologically safe and nontoxic, making them ideal for wound-healing applications. The researchers evaluated the efficacy of the hydrogels by testing their ability to promote the migration of human umbilical cord vein endothelial cells (HUVECs) and L929 cells, which are important for wound healing and tissue regeneration. The SF/Ag/C hydrogel facilitated the migration of HUVECs and L929 cells, leading to accelerated wound healing and improved cell colonization. Additionally, the hydrogels were found to have inhibitory effects against two common wound infection-causing bacteria, *S. aureus* and *E. coli*. These findings suggest that the SF/Ag/C hydrogels have great potential for use as an effective wound dressing that promotes healing while also preventing infection (Yan et al., 2023).

A new SS/PVA hydrogel was developed using a simple and environmentally friendly synthesis method, which makes it highly desirable for use in various applications. The hydrogel could also be loaded with gentamicin to provide antibacterial properties. In tests carried out on NIH3T3 and HEK293 cells, the hydrogel demonstrated high cytocompatibility, with no negative impact on cell viability. The authors also evaluated the immunotoxicity of the hydrogel by using murine macrophage-like cells (RAW 264.7); it was safe as it did not increase the protein levels of the proinflammatory cytokines TNF-α and IL-1β. The gentamicin-loaded SS/PVA hydrogel demonstrated effective antibacterial properties against Gram-negative (*E. coli*) and Gram-positive (*S. aureus* and *P. aeruginosa*) bacteria (Tao et al., 2019).

Sericin-based scaffolds support cell proliferation and tissue regeneration and have antimicrobial properties. By incorporating sericin, the functionality of these scaffolds is further enhanced, making them particularly valuable for wound healing and other medical applications. The sustained release of antimicrobial agents from sericin scaffolds ensures their efficacy for a relatively long period of time. Researchers developed chitosan/sericin microsphere−embedded PVA/gelatin scaffolds for wound-healing applications. The scaffold showed sustained release of sericin and effective antimicrobial activity. Additionally, in a mouse model, the wound size was reduced significantly after treatment with the scaffold as compared to a clinically used wound dressing (Allevyn) (Aramwit et al., 2016). In another study, investigators developed a 3D porous scaffold made of chitosan and sericin (CHT/SS) for use as a wound dressing material. To enhance its antimicrobial activity, they incorporated lauric acid (LA) and ZnONPs, both with strong antimicrobial properties, into the CHT/SS scaffold. The scaffold was safe for use as a wound dressing material, as it was not toxic to HaCaT cells. Moreover, the LA-CHT/SS scaffold demonstrated significantly greater antibacterial activity against Gram-negative (*E. coli*) and Gram-positive (*S. aureus*) bacteria than the pure and ZnONP-CHT/SS scaffolds (Karahaliloglu et al., 2017).

Sericin-based dressings represent a new approach for wound care that utilizes the unique properties of sericin. These dressings are designed to provide an effective, multifaceted solution for wound management by enhancing antimicrobial efficacy. The antimicrobial activity of sericin, combined with its biocompatibility, promotes an environment that is conducive to wound healing. Additionally, different forms of sericin-based dressings have been designed to serve as carrier matrices for delivering other antibacterial agents such as nanoparticles or antibiotics. These materials offer a protective barrier against infections and contribute to the overall improvement of wound closure. This innovative application of sericin underscores its potential to revolutionize wound care by providing a platform for enhanced antimicrobial effectiveness in dressing formulations.

4.1.4 Mechanisms of antimicrobial action by sericin

Sericin's antimicrobial ability is attributed to its ability to engage in complex molecular interactions with microbes. Sericin can disrupt the cell membranes of microbes, leading to an increase in permeability and leakage of intracellular content (Xue et al., 2016). This effect is due to the amphiphilic nature of sericin, which allows it to interact with lipids in the microbial membrane (Shitole et al., 2020). Sericin also activates ROS generation within bacterial cells, causing damage to the bacterial membrane (Dutta et al., 2020). Sericin can function as a versatile carrier or matrix for the delivery of antimicrobial agents such as nanoparticles or other bioactive compounds. For example, sericin-based materials, such as metal-sericin nanocomposites, release antimicrobial agents like metal ions, which induce oxidative stress and cellular damage in microorganisms Fig. 8.1 (Chopra et al., 2022; Aramwit et al., 2016). Furthermore, sericin can obstruct microbial adhesion and biofilm formation, thus preventing the establishment of colonies on surfaces (Aramwit et al., 2020; Shankar et al.,

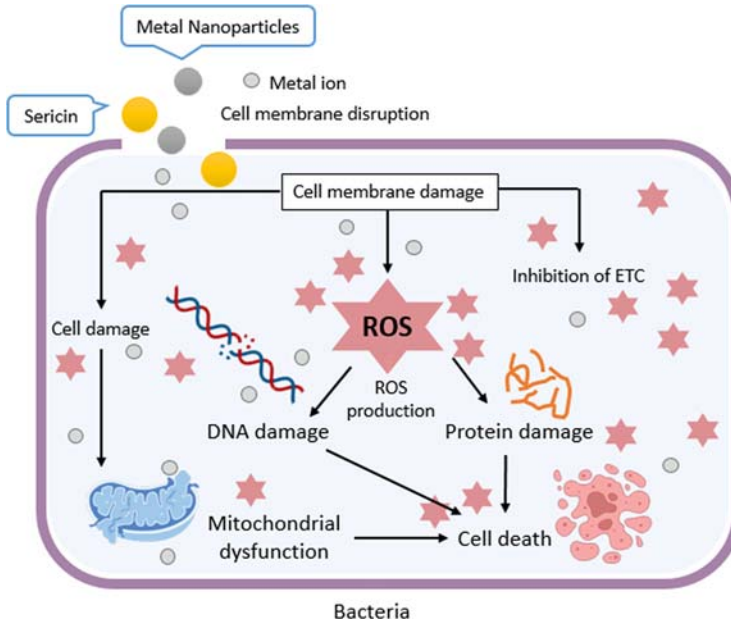


Figure 8.1 A schematic illustration of the antibacterial mechanisms of sericin and metal-sericin nanocomposites. Sericin and sericin-based materials exhibit the ability to disrupt cell membranes, resulting in increased permeability and the leakage of intracellular contents. Additionally, these materials have the capacity to release metal ions, facilitating the activation of ROS production. This process induces oxidative stress, ultimately causing cellular damage in microorganisms. ROS: reactive oxygen species, ETC: electron transport chain.

2023). In particular, sericin has been found to significantly inhibit the formation of biofilms by a range of microorganisms.

Research on the molecular interactions of sericin that underlie its antimicrobial activity have provided valuable insights into the development of targeted strategies for microbial control. Additional studies are being conducted to elucidate the specific mechanisms involved and to optimize the use of sericin in various antimicrobial applications, ranging from wound dressings and medical textiles to coatings for medical devices. The versatility of sericin in interacting with microbial entities at the molecular level underscores its potential for innovative solutions in the ongoing fight against infections and antimicrobial resistance. Table 8.4 summarizes the mechanisms of sericin antibacterial activity.

5. The antiaging properties of sericin

Aging is a complex physiological and biological process that occurs naturally and involves the gradual deterioration of organs and leads to a decline in overall well-being.

Table 8.4 Summary of antimicrobial mechanism of sericin and sericin-based materials.

Type of sericin	Type of bacteria	Mechanism	References
Sericin	Vesicular stomatitis virus and enterovirus 71	• Enhances RIG-I-MAVS signaling to boost the interferon-dependent antiviral effect by attenuating the glycolytic rate and repressing cellular lactate production	Li et al. (2021)
Poly-L-lysine-coated sericin nanoparticles	*Escherichia coli* and *Staphylococcus aureus*	• Disrupts bacterial membrane integrity through reactive oxygen species generation	Dutta et al. (2020)
Sericin−magnesium oxide nanoparticles	*Pseudomonas aeruginosa* and *Bacillus cereus*	• Disrupts bacterial membrane integrity through reactive oxygen species generation	Shankar et al. (2023)
Silver nanoparticle−polyelectrolyte membrane−sericin/agar film	*Escherichia coli* and *Staphylococcus aureus*	• Bound silver ions/silver nanoparticles released into the environment, resulting in bacterial inhibition	Liu et al. (2018)
Sericin−silver nanoparticle hydrogel	*Escherichia coli*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa*	• Disrupts bacteria cell membrane by releasing silver ions to cause bacterial lysis and death	Tao et al. (2021)
Chitosan/sericin scaffolds combined with lauric acid and zinc oxide nanoparticles	*Escherichia coli* and *Staphylococcus aureus*	• Releases lauric acid and zinc oxide nanoparticles into the environment	Karahaliloglu et al. (2017)

The effects of aging are most visible in the skin, which becomes wrinkled, less elastic, and dull. The skin aging process is influenced by genetics, lifestyle, and environmental factors such as exposure to sunlight (Kammeyer & Luiten, 2015), which can lead to skin damage, wrinkles, age spots, and a loss of elasticity. In recent years, researchers have focused on sericin, which has a wide range of therapeutic properties that make it a promising avenue for antiaging applications.

Sericin has excellent moisturizing properties that help the skin to retain hydration and to prevent moisture loss. This is important for maintaining skin supple and resilient. According to research, sericin contains amino acids (serine, aspartic acid, glycine, and threonine) that contribute to the production of collagen and elastin (Jena et al., 2018; Miyamoto et al., 2012; Padamwar et al., 2005). These proteins are crucial for skin structure and elasticity (Kitazawa et al., 2005; Nigdelioglu et al., 2016). Recent studies have shown that sericin can be converted from the α-random coil to β-sheet structure, resulting in gelation (Zhu et al., 1995). This makes it a biocompatible and biodegradable material that has wide applicability in the pharmaceutical and cosmetic industries.

Researchers evaluated the moisturizing properties of sericin gels by applying them to the skin of healthy human volunteers. They measured the efficiency of the sericin gels by evaluating the skin hydroxyproline content, impedance, and transepidermal water loss (TEWL). The study showed that sericin gel−treated skin had a significant increase in hydroxyproline content, indicative of a substantial stratum corneum. It also showed a significant reduction in skin impedance and TEWL, and the upper layer of the skin was smooth (Padamwar et al., 2005). Sericin can reduce the formation of free radicals, which are a common cause of aging-related skin damage. Hence, it could be added to skincare products that aim to prevent premature aging and to improve overall skin health (Kumar & Mandal, 2017; Rinnerthaler et al., 2015).

Beyond its direct impact on skin health, sericin's role in promoting wound healing has significant implications to address age-related skin concerns. By fostering an environment conducive to tissue repair and regeneration, sericin may contribute to the restoration of skin integrity. The development of innovative sericin-based antiaging solutions shows great promise for novel cosmetics and skin products.

5.1 Antioxidant properties of sericin and its impact on aging

Maintaining the antioxidant status is crucial to ensure an optimal intracellular environment and to slow down or even prevent the aging process. Both intrinsic and extrinsic factors can contribute to skin damage by generating free radicals. The antioxidant capacity of a cell contributes to neutralize these free radicals, preventing harm to the cells and ultimately reducing oxidative damage that causes aging.

Researchers use induced free radical production in *in vitro* systems to evaluate antioxidant activity. Specifically, in one study, sericin treatment exerted a cytoprotective effect on hydrogen peroxide (H_2O_2)-treated keratinocyte HaCaT cells. Sericin treatment effectively attenuated oxidative stress−induced ROS generation and decreased oxidative stress−induced inflammatory factors such as cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), TNF-α, and IL-1β. To confirm the possible

role of sericin in antiaging properties, the researchers evaluated skin regeneration under oxidative stress. They found that an imbalance between MMP-1 and procollagen type (PCOL1) reduced collagen and elastin production, which in turn reduced skin regeneration. However, sericin treatment activated PCOL1 and elastin and suppressed MMP1. Therefore, sericin could potentially be used in the development of antiaging products due to its ability to neutralize free radicals, reduce oxidative damage, and promote skin regeneration (Choi et al., 2023).

In another study, researchers examined the effects of sericin on liver damage in aged mice. The mice were given sericin orally for 14 days. This treatment decreased the activity of the liver enzymes alanine transaminase (ALT) and aspartate transaminase (AST), which were higher in the aged control group than in the young control group. Sericin administration reduced oxidative stress markers of lipid peroxidation; increased SOD, CAT, and GPx activities; and increased reduced glutathione and the total antioxidant capacity. Sericin treatment also showed antiapoptotic properties by decreasing the expression of Bax and cleaved caspase-3, which are proapoptotic proteins, and increasing the expression of B cell lymphoma-2 (Bcl-2), an antiapoptotic protein. Moreover, treatment with sericin suppressed phosphorylation of JNK (p-JNK) and the p-JNK/JNK ratio. JNK can activate certain signaling pathways that can lead to cell death (Bagheri et al., 2021).

In a D-galactose-induced mouse model of aging, sericin presented potential anti-inflammatory and antioxidant properties. Sericin treatment reduced cortisol and total cholesterol levels and increased T3 levels. Telomeres are repetitive DNA sequences that protect the ends of chromosomes from degradation, and telomere shortening is associated with aging. Telomerase reverse transcriptase (TERT) gene and protein expression was significantly downregulated in the D-galactose-treated group compared with the normal saline—treated group. However, there was a significant increase in telomere length in the sericin-treated group. Additionally, sericin prevented histopathological changes induced by D-galactose in the liver and brain of aged mice (Mumtaz, Ali, Qureshi, et al., 2023). Overall, sericin has potential as an antiaging agent due to its anti-inflammatory and antioxidant properties, its ability to regulate hormone levels, and its effect on telomere length and histopathological changes.

5.2 Sericin-loaded nanoparticles to produce advanced antiaging formulations

Sericin-loaded or conjugated nanoparticles, or a combination of sericin with other antiaging compounds, have shown potential for antiaging formulations. The combination of sericin and MgONPs produced SS-MgONPs, which showed great potential in scavenging free radicals and exhibited dose-dependent antibacterial activity. The researchers also investigated the antiaging activity of sericin by measuring the activity of several predictive biomarkers such as hyaluronidase, collagenase, elastase, and tyrosinase. These enzymes play a crucial role in the aging process by breaking down important molecules in the skin such as collagen and elastin. The results showed that both sericin and SS-MgONPs are effective in inhibiting the activity of all these

enzymes. This suggests that the combination of sericin and MgONPs could be a promising strategy in developing antiaging products. Additional studies are required to evaluate the long-term safety and efficacy of SS-MgONPs (Shankar et al., 2023).

5.3 Sericin and sun protection: Ultraviolet protection and antiaging properties

Sun exposure is a significant external factor that contributes to the aging process, known as photoaging. UV radiation causes the formation of ROS within skin cells, leading to oxidative stress. Researchers have generated numerous formulations with biocompatible, UV shielding, and antioxidant properties to protect against UV-induced skin damage.

UV-B radiation from the sun can cause harmful effects on the skin, including premature aging (Fisher et al., 1997). Sericin can provide photoprotection against UVB-induced apoptosis in human skin keratinocytes. Pretreatment with sericin inhibited UVB-induced apoptosis by reducing toxicity and DNA fragmentation, downregulating Bax, and upregulating Bcl-2, leading to the inhibition of apoptosis. The activation of caspase-3 and cleavage of poly (ADP-ribose) polymerase (PARP), which are associated with apoptosis, are also reduced by pretreating UVB-induced HaCaT cells with sericin (Dash, Mandal, et al., 2008). In a hairless mouse model, an experiment was conducted to investigate the photoprotective effects of sericin. Two groups of mice were exposed to UVB light (180 mJ/cm^2) once daily for either 1 or 7 days. The mice treated with sericin had reduced expression of these markers compared with the control group. Specifically, sericin treatment suppressed the expression of 4-hydroxynonenal, COX-2, and proliferating cell nuclear antigen (PCNA). These results support the photoprotective effects of sericin for antiaging applications (Zhaorigetu et al., 2003).

Sericin hydrogel has emerges as a valuable tool in antiaging skincare regimens. When sericin is formulated into a hydrogel, it demonstrates exceptional moisturizing capabilities, helping to enhance skin hydration and elasticity (Padamwar et al., 2005). Researchers developed a sericin hydrogel that contains purple waxy corn (*Zea mays* L.) cob extract (PWCC) rich in anthocyanins for UV protection and antiaging benefits. Anthocyanins have been recognized for their potential role in mitigating skin aging. These compounds possess antioxidant properties, which play a crucial role in protecting the skin from oxidative stress caused by free radicals (Diaconeasa et al., 2024). The study showed that PWCC-sericin hydrogel enhanced the amount of anthocyanin that permeated the skin and inhibited tyrosinase activity, leading to a reduction in melanin pigment in melanocytes (B16F10 melanoma cell line). In a study of UV-irradiated keratinocytes, cells exposed to UV with PWCC-sericin hydrogel significantly inhibited collagenase and elastase and increased collagen type I production (Kanpipit et al., 2023). The potential mechanism by which sericin exerts antiaging benefits is shown in Fig. 8.2. These findings suggest that sericin has potential as a natural ingredient in skin care products to protect against the harmful effects of UV radiation.

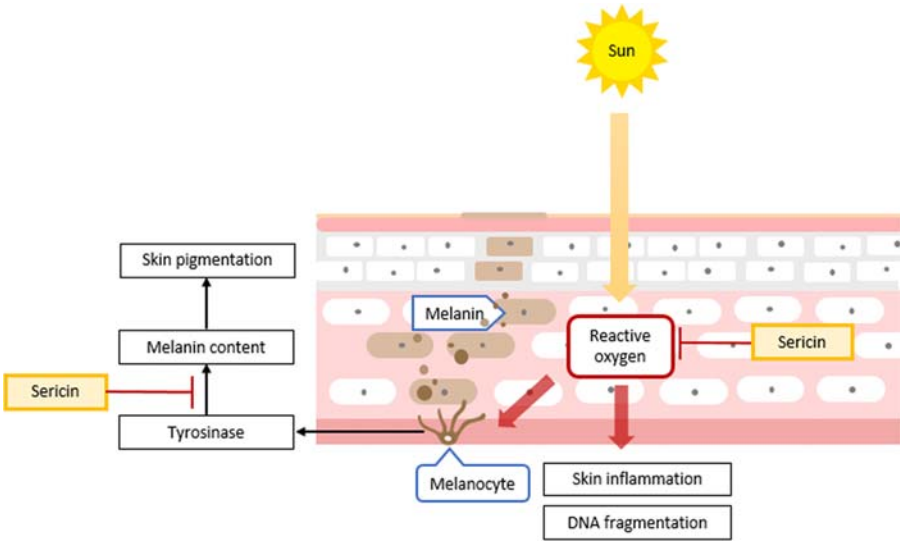


Figure 8.2 The potential mechanism by which sericin protects against ultraviolet radiation. Sericin exerts its inhibitory effects on reactive oxygen species (ROS), thereby suppressing the expression of inflammatory cytokines such as COX-2, iNOS, IL-1β, and TNF-α, as well as DNA fragmentation. This multifaceted action contributes to the attenuation of the inflammatory microenvironment. Additionally, sericin demonstrates the ability to inhibit melanin production by suppressing tyrosinase activity, resulting in a reduction of skin pigmentation. The combined impact of these mechanisms positions sericin as a versatile agent with antiaging applications.

5.4 *Molecular mechanisms by which sericin exerts antiaging benefits*

Chronic inflammation is a significant contributor to aging and age-related diseases. Sericin could attenuate the inflammatory markers, including COX-2, iNOS, IL-1β, and TNF-α, and modulate inflammatory pathways, helping to create a more balanced and less inflammatory microenvironment (Choi et al., 2023; Zhaorigetu et al., 2003). This anti-inflammatory action is crucial for mitigating age-related skin conditions and supporting overall tissue health.

Apoptosis, or programmed cell death, is a natural process that occurs during aging. Excessive or accelerated apoptosis can lead to tissue degradation and aging-related changes. Sericin has been shown to inhibit proapoptotic Bax and enhance antiapoptotic Bcl-2 (Dash, Mandal, et al., 2008). This promotes cell survival and contributes to tissue integrity, which is particularly beneficial for maintaining skin health and delaying the aging process.

Combining sericin with other compounds, or modifying sericin, could result in additional mechanisms or synergistic effects, further enhancing its antiaging activity. These strategies capitalize on the diverse properties of different ingredients, offering

Table 8.5 Summary of the antiaging effects of sericin.

Formulation	Model	Antiaging properties of sericin	References
Sericin	L929 cells (a mouse fibroblast cell line)	Scavenges reactive oxygen species Protects cells from oxidative stress Suppresses lipid peroxidation	Kumar and Mandal (2017)
Sericin	HaCaT cells	Antioxidant activity Suppresses inflammatory factors Skin regeneration effects	Choi et al. (2023)
Sericin	HaCaT Hairless mice	Ultraviolet protection effect	Dash, Mandal, et al. (2008), Zhaorigetu et al. (2003)
Sericin	Aged mice	Hepatoprotective effect on aging-induced liver damage in mice Antioxidant activity Antiapoptotic activity	Bagheri et al. (2021)
Sericin	D-galactose-induced aged mice	Antioxidant activity Prevents telomere shortening Hormone regulation	Mumtaz, Ali, Qureshi, et al. (2023)
Sericin—magnesium oxide nanoparticles		Suppresses aging enzymes including hyaluronidase, collagenase, elastase, and tyrosinase	Shankar et al. (2023)
Sericin gel	Humans	Reduces skin impedance and TWEL Increases hydroxyproline Improves the smoothness of the upper layer of the skin	Padamwar et al. (2005)

comprehensive solutions for addressing various aspects of aging skin. Table 8.5 summarizes the antiaging effects of sericin in various models.

6. Sericin and neurological conditions

Researchers are interested in exploring potential therapeutic interventions for neurological conditions, which are quite challenging to treat, and sericin has emerged as a promising candidate. Although sericin is widely used in other fields, its potential in

neurological disorders has not been fully explored. Nevertheless, studies have shown that sericin has potential neuroprotective effects and biocompatibility, highlighting its potential to improve cognitive function and to reduce neuronal damage in neurodegenerative disorders. Its neuroprotective effects, as evidenced by reduced inflammation and improved cognitive function in experimental models, suggest a promising avenue for therapeutic intervention. Moreover, the integration of sericin in tissue engineering for neuroregeneration holds immense significance, providing innovative approaches to treat neurological conditions.

6.1 Stroke

A stroke is a severe medical emergency that occurs when blood flow to a part of the brain is interrupted or reduced. This interruption can lead to damage or death of brain cells. Sericin hydrogel has been shown to carry neurons for neuronal tissue repair. Studies using animal models have demonstrated the neuroprotective potential of sericin (Vatandoust et al., 2023; Wang, Li, et al., 2021; Wang et al., 2015). A novel genipin-cross-linked sericin hydrogel was developed to create a matrix that can help improve the survival of transplanted cells and to reduce the loss of neurotrophic cytokines as part of the treatment of ischemic stroke. This hydrogel was compatible for primary cortical neurons, allowing these cells to attach to and grow on it for up to 17 days. The hydrogel also demonstrated significant protective effects for neurons submitted to oxygen glucose deprivation. It reduced the release of lactate dehydrogenase (LDH) from neurons, which is a sign of damage, and promoted axon growth and branching in vitro. Transplanted cells in the hydrogel could proliferate after transplantation in mice (Wang et al., 2015).

An injectable scaffold made of sericin was developed and tested in a mouse model of ischemic stroke (middle cerebral artery occlusion [MCAO]). The scaffold, with a degradation period of 56 days, offered prolonged structural support crucial for the regeneration of new neural tissues, a vital aspect in repairing damaged brain tissues. Additionally, the gradual degradation of the scaffold creates space for the formation of new tissues, facilitating the repair process. The scaffold effectively filled the lesion resulting from MCAO and delivered bone marrow mesenchymal stem cells (BMSCs) into the brain, which could differentiate into neuronal cells (Wang, Li, et al., 2021).

Overall, sericin has a great potential to be used as an effective biomaterial for the treatment of ischemic stroke. It has been found to improve the survival of transplanted cells in the body and reduce the loss of neurotrophic cytokines. This can help enhance patient outcomes and provide a solution to this medical condition.

6.2 Neurodegenerative diseases

Parkinson's disease is a progressive neurodegenerative disorder that primarily affects movement. Sericin administration prevented movement failure in a rotenone-induced Parkinson's disease model by reducing the inflammatory factors IL-6 and TNF-α. The authors found that brain-derived neurotrophic factor (BDNF)/TrkB signaling can be regulated through the activation of BDNF, c-fos, and TrkB expression (Salari et al., 2023).

Extended exposure to high temperatures can lead to physiological changes and cellular stress that affect the central nervous system, resulting in anxiety-like behavior and memory impairment. Researchers developed a heat stress model by exposing adult male mice to heat stress (43°C for 15 min a day) for 14 days. At the same time, they treated these mice with 100−200 mg of sericin per kg body weight per day through oral gavage. Sericin improved the spatial memory of heat stress−exposed mice. Furthermore, sericin decreased the levels of corticosterone and lipid peroxidation while increasing the SOD, GPx, and TAC levels. Sericin also suppressed hippocampal heat shock protein 70 kDa (HSP70) expression in the heat stress−exposed mice. These findings suggest that sericin's protective effects against cognitive dysfunction and anxiety-like behavior induced by heat stress may be attributed to the inhibition of HSP70, oxidative stress, and apoptosis (Mahmoudi et al., 2021). Additional studies are needed to understand the underlying mechanisms of sericin's protective effects and its potential clinical applications in this clinical setting.

6.3 Brain metabolism

Researchers fed sericin to mice and observed notable effects on the neurochemical composition of the brain. Specifically, there were elevated levels of L-serine and L-tyrosine, amino acids that play crucial roles in neurotransmitter synthesis and neuronal function. Moreover, sericin intake enhanced noradrenaline metabolism in the cerebral cortex. The amino acids the comprise sericin can be degraded in the blood and then efficiently transported into the brain via the blood−brain barrier (Kawano et al., 2020). Based on these findings, consuming sericin may regulate neurotransmitter precursors and their turnover in the brain. This potential could be explored further in other neurological conditions such as anxiety, depression, and neurological disability.

7. Sericin and nonneurological conditions

7.1 Obesity and diabetes

Obesity is a serious global health problem that is characterized by an excessive accumulation of body fat. The condition is associated with a range of chronic diseases, including cardiovascular disorders, diabetes, and certain types of cancer (Bhupathiraju & Hu, 2016; Louie et al., 2013; Verma & Hussain, 2017). Sericin may have therapeutic benefits for obesity management due to its antioxidant, anti-inflammatory, and antiapoptotic properties. Researchers investigated the effect of sericin on mice fed a high-fat diet and found that it effectively reduced body weight and lowered triglyceride and total cholesterol plasma levels (Seo et al., 2011). Sericin presented significant hypolipidemic action based on its ability to inhibit hepatic and adipocyte lipogenesis and to regulate adipokine production (Okazaki et al., 2010; Seo et al., 2011). On the other hand, at the end of the experiment, the body weight, carcass weight, and retroperitoneal and periependymal fat deposits were not significantly different compared

with the group fed a high-fat diet, but there was increased lipid excretion in the feces in obese mice (Kunz et al., 2020).

Individuals with obesity show structural and functional changes in their adipose tissue, which affect the secretion of adipokines and inflammatory cytokines. These changes contribute to insulin resistance, a precursor to type 2 diabetes, and result in elevated blood glucose levels (Chait & den Hartigh, 2020). Moreover, chronic inflammation, which is related to both obesity and diabetes, causes insulin resistance and promotes the progression of diabetes (Ellulu et al., 2017).

A high-glucose environment in cell culture is a commonly employed experimental condition in studies on diabetes. Sericin exerted a cytoprotective effect on AML12 cells, a murine hepatocyte cell line, by reducing oxidative stress caused by a high-glucose environment (Jing et al., 2022). The hypoglycemic potential of sericin was examined in streptozotocin (STZ)-induced diabetic mice; oral sericin administration improved pathological abnormalities and decreased fasting blood glucose, fasting plasma insulin, and glycosylated serum protein levels through the phosphoinositide 3-kinase (PI3K)/P-AKT/AMP-activate protein kinase (AMPK) pathway (Dong et al., 2020; Song et al., 2018). There was also reduced expression of MKK6, p-p38MAPK, NF-κB, IL-1β, IL-6, NLRP3, and caspase-1. Sericin also inhibited p38MAPK signaling and NLRP3-associated inflammation, suggesting that it can protect against kidney damage caused by type 2 diabetes (Liu et al., 2020). Sericin has also been observed to have hepatoprotective properties in diabetic rats by effectively inhibiting inflammatory proteins such as NF-κB, IL-6, and TNF-α (Wei et al., 2022). The hypoglycemic effect is linked to a reduction in fat deposition in hepatocytes and improvement of mitochondria and endoplasmic reticulum integrities (Ampawong et al., 2017).

Sericin administration could improve the antioxidant and anti-inflammatory properties in mice with STZ-induced diabetes (Dong et al., 2020). Sericin possesses notable antioxidant properties that can effectively counteract the oxidative stress induced by hypercholesterolemia (Deori et al., 2016). Oral administration of sericin markedly reduced blood glucose levels by improving the abnormal glucose tolerance in a rat model of type 2 diabetes (Wang, Zhong, et al., 2021). Another mechanism for the hypoglycemic effects of sericin treatment involves the modulation of neurofilament protein expression in the sciatic nerve and nerve growth factor (NGF) expression in spinal ganglion and anterior horn cells in diabetic rats (Song et al., 2013).

In recent years, the potential of sericin to modulate the gut microbiome and to improve intestinal health in individuals with diabetes has emerged as a research hotspot. Sericin could alter the composition of the gut microbiota in diabetic rats, particularly increasing the presence of *Lactobacillus gasseri* (Zhou et al., 2023). Although sericin may have a positive impact on intestinal health and could be a promising therapeutic strategy for managing complications related to diabetes, additional research is needed to fully understand the interactions between sericin, the gut microbiome, and diabetes.

There have been only a few studies and clinical trials that have used diverse simulation models to assess sericin's safety, efficacy, and sustained impact in combating obesity. Therefore, more extensive research is needed to evaluate comprehensively

sericin's potential in antiobesity interventions. By addressing these limitations, we can gain a better understanding of sericin's potential and create a strong foundation for future research and therapeutic applications.

7.2 Cardioprotective potential of sericin

Cardiovascular diseases remain a leading global health concern. There has been an intense search for natural compounds with cardioprotective properties, including increased interest in sericin. The term "cardioprotective effect" refers to the ability of a substance to protect the heart from damage and maintain its optimal function. In one study, researchers found that a dietary supplement of silk cocoon extract had cardioprotective potency in an isoprenaline-induced myocardial infarction rat model (Srivastav et al., 2013). Further evaluation of sericin demonstrated that its oral administration improved myocardial activity and reduced cardiac damage after myocardial ischemia via its antioxidant activity and ability to reduce inflammation (Ahsan et al., 2022). When rats were given sericin before being subjected to isoproterenol-induced myocardial injury, the level of a nonenzymatic antioxidant marker decreased, but the amount of glutathione, vitamin E, and vitamin C increased with the enzymatic antioxidant marker, mitochondrial enzymes, and protein (Ahsan et al., 2022). Preventing mitochondrial dysfunction is an important therapeutic strategy for cardioprotection (Ramachandra et al., 2020). Sericin had a positive effect on recovering cardiac muscle and improving the structure of mitochondria; it was associated with fatty acid oxidation, the electron transport chain, pyruvate metabolism, and mitochondrial structural proteins (Rujimongkon et al., 2022).

As mentioned previously, sericin has inherent properties that make it an ideal candidate for nanoscale formulations. A recent study developed a nanoformulation comprising sericin and carvedilol to evaluate its cardioprotective activity in rats with doxorubicin (DOX)-induced cardiotoxicity. The developed nanoparticle formulation could counteract DOX-induced cardiotoxicity. Sericin suppressed oxidative stress and inflammatory reactions caused by DOX, leading to improved myocardial activity and attenuation of heart damage after myocardial ischemia (Shariq et al., 2023).

The cardioprotective effects of sericin involve a complex interplay between its antioxidant properties that counteract oxidative stress, anti-inflammatory actions that mitigate inflammation, and antiapoptotic effects that prevent cell death. Additional research is required to examine the molecular mechanism of the cardioprotective effect of sericin, which should include the evaluation of physical, biochemical, and histopathological parameters.

7.3 Sericin as a potential anticancer agent

Extensive research has been conducted to explore the potential benefits of sericin in cancer treatment. Sericin exhibits properties that could contribute to anticancer effects (Mumtaz et al., 2024). Sericin suppressed ROS and cancer cytokines and presented a protective effect against colon cancer cells. Sericin caused cell death by inducing cell

apoptosis through caspase-3 activation and downregulation of Bcl-2 expression (Kaewkorn et al., 2012).

One promising avenue of research has focused on sericin nanocarriers loaded with DOX, a chemotherapeutic drug commonly used to treat breast cancer. These nanocarriers have been found to effectively reduce the viability of MCF-7 cells, a breast cancer cell line (Radu et al., 2021), suggesting that sericin could be an effective drug delivery agent for breast cancer treatment. Another study explored the potential anticancer properties of sericin, specifically its ability to inhibit MDA-MB-468 breast cancer cells (Niu et al., 2021). Sericin affected the cell cycle and induced apoptosis. The mechanism involved downregulation of the PI3K/Akt signaling pathway, which is known to play a role in breast cancer development and progression.

Researchers recently developed sericin-AgNPs to alleviate dimethylbenzanthracene (DMBA) toxicity, which is associated with cancer due to its long-term accumulation in tissues. In the DMBA-induced group, sericin-AgNP treatment resulted in effective recovery based on blood chemistry and histopathology (Mumtaz et al., 2024). In another study involving a UVB-induced tumor animal model, the application of sericin significantly reduced tumor incidence by reducing oxidative stress, COX-2, and cell proliferation (Zhaorigetu et al., 2003). Although these findings suggest that sericin could be a promising candidate for cancer therapy, more research is needed to fully understand the mechanisms underlying its anticancer properties and to determine its potential as a cancer treatment in humans.

7.4 Sericin and alcoholic/nonalcoholic fatty liver disease

Alcoholic liver disease (ALD) is a range of disorders caused by excessive alcohol consumption, leading to liver dysfunction due to inflammation and oxidative stress. ROS production increases with heavy ethanol intake, leading to enhanced peroxidation of lipids, protein, and DNA (Lindros, 1995). Sericin has been shown to exert hepatoprotective effects in animal models (Bagheri et al., 2021). In one study, researchers administered various concentrations of sericin dissolved in distilled water to mice via oral gavage 1 h before alcohol treatment every day for 30 days. Sericin administration decreased the serum alcohol concentration and increased its excretion via urine. Chronic alcohol administration increased AST, ALT, and MDA levels, and reduced GSH, GPx, CAT, and SOD levels in the serum and liver. Hepatic triglyceride levels also increased. Intriguingly, high doses of sericin (0.75 and 1.50 g/kg body weight) restored serum antioxidant enzyme levels to normal, indicating a potential mitigating effect (Li et al., 2008). Additional investigations are warranted to understand the mechanisms underlying sericin's influence on alcohol-induced oxidative stress and liver function.

The prevalence of nonalcoholic fatty liver disease (NAFLD) has increased markedly in recent years (De Chiara et al., 2018). Ammonia is removed from the body through the urea cycle, a metabolic pathway that occurs predominantly in the liver. Dysregulation of the urea cycle can lead to hyperammonemia, which can further damage the liver and cause fibrosis (De Chiara et al., 2018; Gallego-Durán et al., 2022). Researchers examined the effect of sericin on the urea cycle enzyme CPS-1 and

ornithine transcarbamylase (OTC), as well as proteins such as MAPK, caspase recruitment domain-containing protein 9 (CARD-9), and microtubule-associated protein light chain 3 (LC-3). Sericin promoted ammonia detoxification by increasing CPS-1 and OTC gene expression and enhancing hepatic autophagy (downregulating CARD-9) via the CARD-9/MAPK pathway (Ampawong et al., 2023). This study highlights the beneficial properties of sericin as a potential treatment to alleviate ammonia toxicity and to improve liver function.

7.5 Ulcerative colitis

Ulcerative colitis is a chronic disease that affects the lining of the colon and rectum, causing inflammation and ulcers (Gajendran et al., 2019). Given its anti-inflammatory, antioxidant, and tissue-regenerative properties, researchers have examined whether sericin could be useful for people with ulcerative colitis. They extracted and purified different types of sericin, including silk degumming water (SS), tussah sericin (TS), and castor silk sericin (CSS) and evaluated their effectiveness in treating ulcerative colitis in mice, based on their antioxidant and anti-inflammatory capacity, wound-healing activity, and biocompatibility. Sericin was biocompatible and exhibited antioxidant and anti-inflammatory properties, as well as wound-healing activity. Moreover, these three types of sericin activated innate immune and ROS detoxification responses in *Caenorhabditis elegans*, which could lead to health benefits and longer lifespan. The disease activity index (DAI) increased in the dextran sulfate sodium (DSS)-treated group, which was used to generate an ulcerative colitis model. However, the sericin-treated DSS group showed the lowest DAI value among all treatment groups, indicating positive therapeutic outcomes in treating ulcerative colitis (Ma et al., 2021). Overall, the study provided promising evidence for the potential therapeutic effects of sericin on ulcerative colitis. Further research is needed to fully understand how sericin works and how it can be used to treat this chronic disease. Table 8.6 summarizes the effects of sericin on neurological and nonneurological conditions.

8. Other applications

Cryopreservation is an essential technique in cell biology as it allows cells to be frozen at low temperatures for a long time. During the freezing and thawing processes, high levels of ROS can harm sperm motility, cause DNA damage and chromatin decondensation, and even make sperm cells incapable of fertilizing oocytes. Sericin is suitable for cryopreservation solutions used for diverse cell types, including neurons, stem cells, oocytes, and sperm cells, due to its antioxidant properties and stabilizing effects (Cao & Zhang, 2017). Indeed, researchers have reported the cryoprotective benefits of sericin on human sperm. Sperm freezing and thawing media containing 5% sericin showed excellent outcomes (Aghaz et al., 2020). The study revealed that cumulus–oocyte complexes (COCs) cultured with 1.0% sericin showed a higher rate of germinal vesicle breakdown, reaching metaphase II, compared with control COCs that were

Table 8.6 Effects of sericin on neurological and nonneurological conditions.

Disease	Main effects	References
Neurological conditions		
Stroke	• Sericin hydrogel or scaffold serves as a supportive matrix for cellular activities, providing the growth and proliferation of cells	Wang, Li, et al. (2021), Wang et al. (2015)
Neurodegenerative disease	• Improves anxiety-like behavior and cognitive impairment • Reduces motor impairment, inflammatory cytokines, and disruption of the brain-derived neurotrophic factor/TrkB signaling pathway	Mahmoudi et al. (2021), Salari et al. (2023)
Brain metabolism	• Modulates neurotransmitters	Kawano et al. (2020)
Nonneurological conditions		
Obesity and diabetes	• Antiobesity properties • Glucose regulation • Lipid metabolism • Anti-inflammatory effects • Antioxidant activity • Regulation of adipokines • Insulin sensitization • Gut microbiota modulation	Ampawong et al. (2017), Dong et al. (2020), Jing et al. (2022), Kunz et al. (2020), Liu et al. (2020), Okazaki et al. (2010), Seo et al. (2011), Song et al. (2018), Song et al. (2013), Wang, Zhong, et al., 2021, Wei et al. (2022), Zhou et al. (2023)
Cardiovascular diseases	• Antioxidant activity • Anti-inflammatory effect • Improved cardiac muscle • Myocardial infarction protection	Ahsan et al. (2022), Rujimongkon et al. (2022), Ramachandra et al. (2020), Shariq et al. (2023), Srivastav et al. (2013)
Cancer	• Apoptosis induction • DNA damage protection • Reduces tumor size • Antioxidant activity • Anti-inflammatory effects	Kaewkorn et al. (2012), Mumtaz et al. (2024), Niu et al. (2021), Radu et al. (2021), Zhaorigetu et al. (2003)
Alcoholic/ nonalcoholic fatty liver disease	• Anti-inflammatory effects • Improvement in antioxidant defense • Regulates enzyme levels • Ammonia detoxification • Reduces triglyceride levels	Ampawong et al. (2023), Bagheri et al. (2021), Li et al. (2008)
Ulcerative colitis	• Antioxidant effects • Anti-inflammatory action • Tissue repair and regeneration • Immunomodulation	Ma et al. (2021)

matured without sericin (Do et al., 2014). To assess maturation and fertilization rates, COCs were cultured in TCM-199 medium supplemented with varying concentrations of fetal bovine serum (FBS). Following in vitro maturation with FBS, the sericin-cultured COCs exhibited a significantly greater mean size of the perivitelline space compared with those cultured with FBS. Despite these differences, the rate of oocyte development in terms of nuclear maturation, fertilization, and blastocyst formation did not differ significantly between the in vitro maturation conditions (Do et al., 2014). The findings underscore the potential of sericin supplementation to improve the in vitro maturation of oocytes, with implications for refining assisted reproductive techniques in both animals and humans.

Neurons are vulnerable to environmental changes and susceptible to damage during cryopreservation. The use of serum-free freezing solutions supplemented with sericin, maltose, and 10% dimethyl sulfoxide (DMSO) using slow freezing for undifferentiated and differentiated neuronal cells represents new possibilities for preserving neuronal cells for various applications (Yamatoya et al., 2022).

Adipose-derived stem cells (ADSCs) are a type of mesenchymal stem in the adipose tissue. These cells are abundant, easily accessible, and can be harvested through minimally invasive procedures such as liposuction. ADSCs are recognized for their unique regenerative properties, capable of differentiating into various cell types, including adipocytes, chondrocytes, and osteocytes. Due to their versatility and accessibility, they are considered a valuable resource for regenerative medicine and tissue engineering applications (Sterodimas et al., 2010). In addition to their potential in reconstructive and esthetic procedures, ADSCs also play a crucial role in ongoing research to develop therapies for various medical conditions, such as musculoskeletal disorders, cardiovascular diseases, and neurodegenerative disorders. A recent study showed that human ADSCs could be cryopreserved more effectively by using a cryopreservation medium that contains sericin. There was enhanced cell survival and differentiation capabilities were maintained after thawing (Miyamoto et al., 2012). The cryopreservation medium used in the study was CELLBANKER 2, and DMEM/Ham's F-12 medium (serum-free) + 10% DMSO, 0.1 mol/L maltose, and 1% sericin. The viability rate of ADSCs frozen in this medium exceeded 95%. Interestingly, the proliferation rate of human ADSCs frozen in the specified serum-free medium with sericin was higher than that of the cells frozen in the maintenance medium +10% DMSO. To assess the adipogenic/osteogenic differentiation capabilities, the authors examined frozen human ADSCs with oil red O staining and Von Kossa's method. ADSCs frozen using the specified serum-free medium with sericin exhibited positive results, indicating their preserved potential for adipogenic and osteogenic differentiation postcryopreservation. This study highlights the importance of using a cryopreservation medium containing sericin for the successful cryopreservation of human ADSCs (Miyamoto et al., 2012).

In addition to its use as a cryoprotective agent, sericin is added to food products (Seo et al., 2023). The future prospects of sericin in food preservation are highly promising, given its multifunctional properties and the increasing demand for natural and sustainable preservation methods. This natural protein can be used to develop biodegradable, nontoxic coatings that maintain the freshness; nutritional value; and sensory

qualities of fruits, vegetables, and other perishable items. This application leverages sericin's safety and biodegradability for use in food packaging. A previous study explored a sericin-based edible coating material for postharvest shelf-life extension and preservation of tomatoes. The coating, composed of sericin (1.5%), chitosan (1.0%), aloe vera (1.0%), and glycerol (1.5%) in water, was applied using a dip-coating method. The results indicated that the coating reduced weight and firmness losses in tomatoes. As storage time increased, the titratable acid content in the fruit rose, while pH, total soluble solids, the lycopene content, the total phenolic content, and the TAC remained lower compared with uncoated tomatoes (Tarangini et al., 2024). Continued research and development, along with advancements in sustainable production methods, will be crucial in realizing the full potential of sericin in the food industry.

9. Sericin from the laboratory to industrial development

Studying sericin at the laboratory level involves extensive research into its biochemical properties and potential applications. Researchers have focused on the extraction and purification of sericin from silk, ensuring the protein's integrity and activity are preserved. Various methods, such as water extraction, urea extraction, and enzymatic methods, have been explored to yield highly pure and functional sericin (Aramwit, Damrongsakkul, et al., 2010; Aramwit, Kanokpanont, et al., 2010; Muindi et al., 2022; Yun et al., 2013). Laboratory studies have also delved into understanding sericin's molecular structure, its interactions with other biomolecules, and its biological activities, such as antioxidant, anti-inflammatory, and antimicrobial properties. Researchers employ a range of analytical techniques, including spectroscopy, chromatography, and electrophoresis, to characterize sericin and assess its potential in various biomedical applications, such as wound healing, tissue engineering, and drug delivery systems. These foundational studies are crucial to establish sericin's efficacy and safety, setting the stage for further development and application.

The transition from laboratory-scale research to industrial development involves overcoming several challenges related to the scalability, consistency, and cost-effectiveness of sericin. The focus shifts to optimizing extraction processes that can be scaled up without compromising the quality of sericin. This endeavor involves pilot studies to refine methods that ensure reproducibility and efficiency on a larger scale. This phase also involves the development of formulations that incorporate sericin into various products, such as hydrogels, films, and nanoparticles. Moreover, it is important to perform clinical studies to assess safety, efficacy, and stability. Collaborations between academic institutions and industry players will be crucial, combining research expertise with industrial capabilities. Successful industrial development will result in the production of sericin-based products that can be manufactured consistently, meeting the stringent standards required for commercial distribution.

10. Sericin marketing trends

There has been growing recognition of and demand for sericin across various industries. In recent years, there has been a notable increase in the commercialization of sericin-based products, particularly in cosmetics and personal care products, where its skin hydration, antiaging, and UV-protection properties are highly valued (Giovannelli et al., 2021). Sericin is an ideal ingredient in various skincare formulations due to its unique properties such as biocompatibility, biodegradability, hydration, and film-forming abilities. It helps maintain skin moisture by creating a protective barrier that prevents water loss, making it particularly effective in moisturizing creams and lotions (Padamwar et al., 2005). Moreover, sericin is used as a component in foundation creams, eyeliners, and sunscreen products as a coating agent (Giovannelli et al., 2021). As a natural and sustainable ingredient, sericin aligns with the growing consumer demand for ecofriendly and effective skincare solutions, leading to the growth of sericin the future of cosmetic product development. Moreover, continuous innovation and positive research outcomes sustain and expand sericin's market presence, driving further growth and diversification of its applications.

11. Life cycle analysis and carbon footprint

11.1 Life cycle analysis of sericin

A life cycle analysis (LCA) is a systematic method used to evaluate the environmental impacts associated with all stages of a product's life, from raw material extraction through production, use, and disposal. It provides a comprehensive view of its environmental footprint, helping to identify areas for improvement and sustainable practices. For sericin, the assessment begins with its extraction from silk, which involves degumming and purification. These steps consume energy, water, and various chemicals. Sericin must also be transported and processed for its various applications, such as in cosmetics, pharmaceuticals, and textiles. The LCA for sericin, including greenhouse gas emissions, resource depletion, and waste generation, aids in developing strategies to minimize negative environmental effects and enhance the sustainability of sericin production and use. A published LCA for sericin based on pilot- and lab-scale data indicates that sericin's recovery is significantly impacted by climate change (50%), natural resource depletion (34%), and human health impacts (15%). Nanofiltration and sericin degumming are particularly detrimental, though spray drying is a more sustainable alternative to centrifugation. Despite the importance of resource recovery for a circular economy, its environmental impacts necessitate careful decision-making. Renewable energy use could mitigate adverse effects. The study's reliance on pilot- and lab-scale data highlights the need for full-scale assessments and recommends incorporating techno-economic analysis and uncertainty analysis for more comprehensive insights (Capar et al., 2022) (Fig. 8.3).

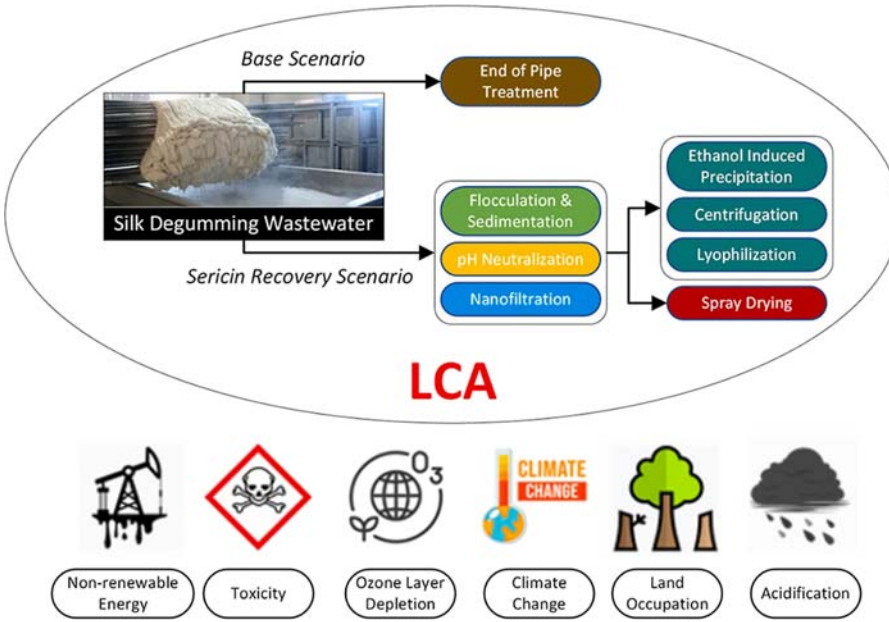


Figure 8.3 Life cycle analysis of sericin recovery from silk degumming wastewater. The LCA diagram of sericin recovery from silk degumming wastewater illustrates the environmental impacts at various stages of the recovery process. It highlights the significant increase in environmental impacts when resources are processed for recovery instead of treatment and discharge. The recovery scenario involves a series of steps to recover sericin, including silk degumming, sedimentation, nanofiltration, precipitation, and lyophilization. As an alternative to the precipitation and lyophilization steps, spray drying was also considered. From Capar, G., Pilevneli, T., Yetis, U., & Dilek, F. B. (2022). Life cycle assessment of sericin recovery from silk degumming wastewaters. *Sustainable Chemistry and Pharmacy, 30*. https://doi.org/10.1016/j.scp.2022.100889.

11.2 Carbon footprint of sericin

The carbon footprint of sericin refers to the total amount of greenhouse gases, particularly carbon dioxide, emitted throughout its life cycle. This encompasses emissions from the cultivation of silkworms and the production of silk, as well as the extraction, processing, and transportation of sericin. The key contributors to the carbon footprint include the energy-intensive processes of boiling and degumming silk to extract sericin, the use of chemicals in its purification, and fuel consumption during transportation. Evaluating the carbon footprint is essential to understand the environmental impact of sericin and identifying opportunities to reduce greenhouse gas emissions. Efforts to mitigate the carbon footprint of sericin can include optimizing energy efficiency in production processes, utilizing renewable energy sources, and improving waste management practices. Additionally, advancements in green chemistry and sustainable extraction methods can further lower the carbon footprint. By addressing these

aspects, the sericin industry can move toward more ecofriendly practices, contributing to global efforts to reduce climate change impacts.

12. Future directions and emerging trends in sericin research

One potential direction for sericin research involves investigating the potential synergies between sericin and biomaterials or therapeutic agents to amplify therapeutic benefits. This approach could significantly enhance the efficacy of sericin to address complex medical challenges, such as wound healing, tissue regeneration, and neuroprotection. The combination of sericin with pharmaceutical agents, natural compounds, and/or other biomolecules could offer novel and effective therapeutic strategies across diverse medical fields. The therapeutic potential of sericin has already been demonstrated in preclinical studies, where it has shown promising results in the treatment of various medical conditions, including skin conditions, cardiovascular diseases, and neurological disorders. However, to optimize the treatment outcomes of sericin-based therapies, experts need to explore these combination therapies for specific medical conditions and gain a thorough understanding of the intricate interactions between sericin and other compounds. Future research in this field should focus on identifying the ideal conditions for combining sericin with other compounds to maximize its therapeutic potential.

The utilization of sericin in biocompatible materials has immense promise for the advancement of tissue engineering. The unique molecular properties and biocompatibility of sericin, as well as its availability as a byproduct of silk production, make it an attractive candidate to enhance the functionality of biomaterials. Incorporating sericin into biocompatible scaffolds, hydrogels, or nanomaterials could lead to the development of advanced platforms for tissue-engineering applications. To ensure optimal results, future research could focus on optimizing the fabrication techniques to ensure the proper distribution and stability of sericin within these materials. This approach could enable the design of scaffolds that mimic the natural extracellular matrix, promoting cellular adhesion, proliferation, and differentiation. By mimicking the natural extracellular matrix, sericin could help to create a suitable microenvironment that promotes tissue regeneration. The exploration of sericin-incorporated materials in targeted tissue regeneration, such as bone, skin, or cartilage, could revolutionize the field by offering sustainable and effective solutions for regenerative medicine. Sericin has been shown to promote cell proliferation and differentiation, which could prove useful in the regeneration of damaged tissues. To achieve the full potential of sericin in advancing the frontiers of biocompatible materials and tissue engineering, rigorous studies and collaborations between materials scientists, biologists, and clinicians are crucial. Bringing together experts from different fields should help develop innovative strategies that could lead to breakthroughs in tissue engineering.

Sericin has the potential to revolutionize the functional food, nutraceutical, and cosmetics industries. Its impressive antioxidant and anti-inflammatory properties make it

an attractive candidate for developing functional foods and nutraceuticals that promote overall well-being. For example, sericin-enriched formulations could be developed to address specific health concerns, leading to the growing trend of personalized nutrition. In the cosmetics industry, sericin's moisturizing and skin-conditioning attributes could lead to the formulation of new skincare products that provide natural alternatives with potential antiaging benefits. As consumer preferences shift toward sustainable and bioactive ingredients, sericin's biocompatibility and ecofriendly sourcing as a byproduct of silk production align well with industrial trends. Moreover, sericin has low allergenicity, so it does not cause allergic reactions.

The use of sericin in clinical trials and drug development shows promise, but there are certain limitations to consider. One challenge is the variability in sericin extraction methods and the composition of silk sources, which can make it difficult to compare the results from different studies. In addition, it can be challenging to determine the molecular mechanisms behind sericin's effects in different clinical contexts due to the complexity of biological systems. There have been limited large-scale clinical trials, which makes it difficult to understand sericin's safety profile and potential side effects in diverse patient populations. Furthermore, the lack of standardized dosage regimens and administration protocols is a hurdle in establishing optimal treatment parameters. To provide robust evidence for the efficacy and safety of sericin-based therapies in humans, more rigorous and well-designed clinical trials are necessary. As these trials progress, we can expect to gain more knowledge, which will contribute to refine sericin's applications in disease treatment and drug development, ultimately leading to its integration into mainstream medical practices.

In the future, we can advance the use of sericin by improving its extraction methods, developing new formulations, and conducting thorough studies to ensure the safety and effectiveness of sericin-based products. With more research in this field, we can unlock the full potential of sericin and establish a path toward a healthier and more sustainable future.

13. Conclusions

Sericin is a protein derived from silk that has potential applications in various biomedical fields. It has multiple beneficial activities and is thus a promising candidate for various therapeutic purposes. Its biocompatibility, biodegradability, and functional groups make it an ideal material for nanomaterial development. When combined with nanotechnology and biomaterial formulations, sericin has opened up new avenues for drug delivery systems, tissue engineering, and regenerative medicine. Combining sericin with other agents, such as antioxidant and anti-inflammatory agents, produces synergistic therapeutic effects, making it a valuable tool in addressing complex healthcare challenges. The extensive research on sericin's mechanisms of action has provided valuable insights and a solid foundation for future development of targeted and efficient medical interventions. Additional research exploring combination

therapies and the integration of sericin into biocompatible materials as well as clinical trials is needed to fully unlock the potential of sericin.

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Stimuli-responsive and self-assembled sericin materials for various applications

9

Nihan Arabaci[1], *Ayse Demirbas*[2], *Seyma Dadi*[3], *Fatma Dogan*[4] *and Ismail Ocsoy*[4]

[1]Department of Biology, Faculty of Arts and Sciences, Cukurova University, Adana, Turkey; [2]Department of Seafood Processing and Technology, Faculty of Fisheries, Recep Tayyip Erdogan University, Rize, Turkey; [3]Department of Nanotechnology Engineering, Abdullah Gul University, Kayseri, Turkey; [4]Department of Analytical Chemistry, Faculty of Pharmacy, Erciyes University, Kayseri, Turkey

1. General introduction of sericin with physical, chemical, and biological properties

Silk is an industrially valuable natural polymer synthesized in nature by epithelial cells of silkworms (*Bombyx mori, Antheraea mylitta*) (Dash et al., 2008; Sehnal & Sutherland, 2008) and spiders (*Araneus diadematus*, *Nephila clavipes*, etc.) (Gün Gök et al., 2019; Silva et al., 2022). Silkworm cocoon structurally has two main proteins called fibroin and sericin. Fibroin is a fibrous protein consisting of two strands linked by disulfide bonds and surrounded by layers of sericin, which make them stick together in a cocoon. Fibroin constitutes >70% of the weight of the cocoon (Onder et al., 2022). Sericin is a globular protein synthesized by the expressions of Ser1, Ser2, and Ser3 genes (Silva et al., 2022). It makes up 25%−30% of the weight of the cocoon structure and is referred to as "silk glue" because it combines two fibroin units (Onder et al., 2022). The cocoon's structural integrity is maintained by sericin, which acts as a sticky binding layer that envelops the fibroin fibers, effectively holding them together (Cao & Zhang, 2016). Degumming, the process of removing sericin from raw natural silk, is commonly carried out to enhance the softness and smoothness of the resulting silk filaments (Hong et al., 2019). Numerous degumming techniques have been documented, employing a variety of reagents, including boiling water, soap, alkalis, acids, and enzymes (Hu et al., 2019).

Sericin, separated from cocoon fibroin by the degumming process of silk fabric, is discarded as waste material. Also, it is removed as a by-product or waste in the processing of silk dental floss or silk biomaterials (Cao & Zhang, 2016). About 50 tons of sericin are annually discharged into the effluent as a byproduct of degumming over 400,000 tons of cocoons (Hong et al., 2019). The remaining fibroin is used in the production of silk fabric and yarn. In the silk industry, sericin is removed from

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the structure of fibroin during the gumming process to provide the silk's whiteness, softness, and smoothness and also to make it dyeable (Gupta et al., 2013).

Sericin, which comes out of tons of cocoons produced worldwide and thrown into nature as waste, contaminates natural resources (e.g., waters), causes the need for chemical and biological oxygen, and pollutes the environment (Gün Gök et al., 2019). Evaluating and using discarded sericin in various fields will provide important environmental and economic contributions, especially in countries where silkworm breeding is common (Kunz et al., 2016).

A natural biomolecule sericin with excellent physical, chemical, and biological properties has significant potential to be used in pharmacology, food, cosmetics, biomaterials, biotechnology applications, and the biomedical field (Kunz et al., 2016; Liu et al., 2022). Sericin has various physical properties such as solubility, gel formation ability, isoelectric point, and sol−gel transition ability. This protein is completely soluble in hot water and partially soluble in cold water. It differs according to its solubility, structural properties, and molecular weights and thus is classified into three basic sections (Wang & Zhag, 2011; Cao & Zhang, 2016; Dong et al., 2020; Kumar Dan et al., 2022).

The solubility of sericin in water differs according to the position of sericin in silk fiber. The solubility of sericin (α-sericin) in the outer layer in hot water is higher than that of sericin (β-sericin) in the inner layer that comes into contact with fibroin (Mondal et al., 2007). Random coils and β-sheets correspond to the amorphous and crystalline regions in the secondary structure of the globular sericin protein (Lamboni et al., 2015). It is brittle in a dry state because it contains random coils. The strength and brittleness of sericin-based materials can be controlled by temperature, moisture absorption, and chemical modification (Liu et al., 2022). Sericin becomes soluble in water at temperatures of 50°C and above. While the temperature increase destroys the β layers in the structure, chemical cross-linking enables the formation of these structures. Thus, the crystallinity and durability of the sericin increase, the solubility decreases, the random coil structure turns into β-sheets, and gel formation occurs (Kunz et al., 2016; Liu et al., 2022). Another physical property that affects the use of sericin as a biomaterial is the isoelectric point value. Sericin has an isoelectric point in the range of 5.5−5.8. This is because sericin contains more acidic amino acids than neutral or basic (Boonpavanitchakul et al., 2020; Crivelli et al., 2018; Kumar Dan et al., 2022).

Sericin is a glycoprotein consisting of 62.16% hydrophilic and 37.84% hydrophobic amino acids (Silva et al., 2022; Kumar Dan et al., 2022) (Fig. 9.1). 45.8% of the protein structure is formed by polar hydroxyl amino acids (serine and threonine), 42.3% of polar amino acids, and 12.2% of nonpolar amino acids. Serine (32%), aspartic acid (18%), and glycine (16%) in the amino acid composition are essential amino acids (Chouhan & Mandal, 2020; Fatahian et al., 2021; Lamboni et al., 2015). The fluorescent property of the aromatic tyrosine and phenylalanine amino acids in sericin's structure makes it a valuable biomaterial for biological detection and in vivo monitoring, with chemical modification and physical cross-linking (Cao & Zhang, 2016). Polar hydroxyl, carboxyl, and amino groups in the protein chain provide cross-linked network formation and allow the combinations with various polymers to form biodegradable materials (Elahi et al., 2021; Rupesh Dash et al., 2006).

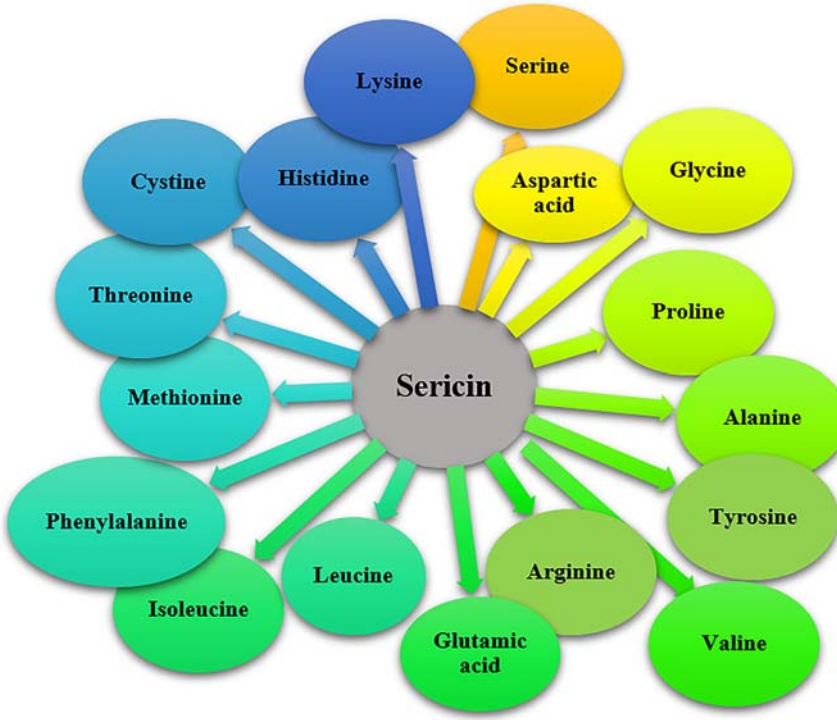


Figure 9.1 Amino acids in the structure of sericin. The amino acid composition of sericin protein is indicated.
Adapted by the authors.

Various functional groups resulting from the diversity of amino acids in the structure of the sericin polymer allow it to be chemically modified to occur in the formation of structures that will be used as a matrix in biomedical applications (Liu et al., 2022). Polar groups in the structure of the sericin allow interaction with other polymers through blending, crosslinking, or copolymerization in the production of sericin-based biomaterials (Lamboni et al., 2015). Its biochemical properties give sericin many important biological characteristics such as biodegradability, biocompatibility, immunocompatibility, moisturizing, anti-inflammatory, antibacterial, antioxidant, and photoprotective activities (Fig. 9.2).

In research, from an immunological point of view, sericin protein is considered a material with high biocompatibility since it has an inert character. Sericin did not show cytotoxic properties for cells when incorporated into the culture medium. This indicates that sericin is a reliable material for cells (Silva et al., 2022). According to various studies, sericin is a suitable and biocompatible natural protein for different biomedical applications (Aramwit et al., 2009; Mandal et al., 2009; Chlapanidas et al., 2013; Holland et al., 2019; Silva et al., 2022).

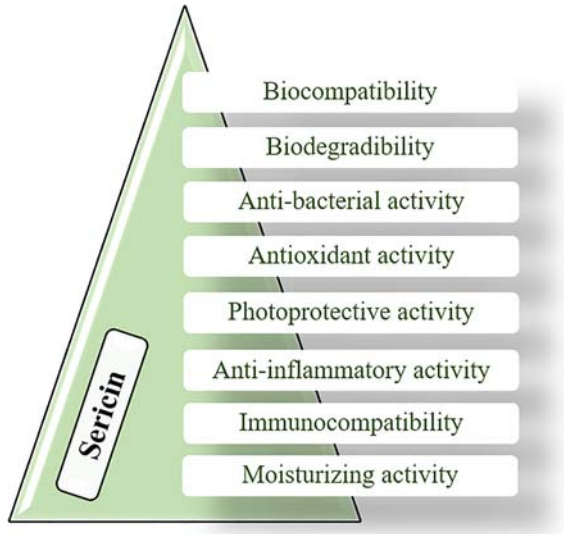


Figure 9.2 Various features of sericin. Advantageous properties of sericin are listed in figure. Adapted by the authors.

The biomaterial is expected to be capable of suppressing the growth of bacteria or killing them. Microorganisms, which are the source of infectious diseases, cause the formation of serious infections or sepsis in wounds during the wound healing period. The bacteria in the wound area prolong the healing process or cause serious complications. For these reasons, biomaterials with antibacterial properties are used in the production of biomedical products (Silva et al., 2022). Sericin contains methionine groups, which accelerate the epithelialization process of the wound by activating collagen synthesis and play a role in the healing mechanism of the sericin by contributing to the reduction of the wound size (Verma et al., 2017). A study reported by Verma et al. (2017) showed that the wound-healing property and antibacterial nature of sericin can be utilized in the development of novel wound dressing biomaterial for the treatment of wounds. According to studies, sericin is a polymer with antimicrobial activity. It has been reported that this feature is due to the fact that sericin contains cysteine, an uncharged polar amino acid containing sulfhydryl groups. Sulfhydryl groups also affect the enzymatic reactions and metabolic activities of microorganisms by producing reactive compounds and forming weak hydrogen bonds with oxygen and nitrogen (Silva et al., 2022). Sericin has antibacterial activity as well as being an antibiofilm agent. Aramwit et al. (2020) reported that sericin prevents the biofilm formation and disrupts the biofilm structure formed by *Streptococcus mutans*.

Sericin has antioxidant activity, which is responsible for many of its biological activities. Thanks to its antioxidant activity, sericin increases the activity of antioxidant enzymes such as catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GPx) (Dong et al., 2020; Lamboni et al., 2015). The antioxidant properties are due to the oxygen species (ROS) scavenging activity of sericin, inhibition of lipid peroxidation, antityrosinase, and antielastase activities (Kato et al., 1998; Silva et al., 2022). These properties are due to the high amount of serine and threonine in its amino

acid composition. The hydroxyl groups of these amino acids contribute to the antioxidant activity of sericin by chelating trace elements such as copper, iron, and zinc (Lamboni et al., 2015; Rosena et al., 2018; Fatahian et al., 2021; Liu et al., 2022). Sericin with photoprotective activity can absorb ultraviolet radiation and prevent oxidative damage by maintaining the redox balance. Absorbing UV light wavelengths below 200 nm owes its presence to various amino-based groups rich in hydrogen, oxygen, and nitrogen (Dash et al., 2008; Gore et al., 2019; Silva et al., 2022).

Silk, one of the most valuable materials of the textile industry, also has important properties that are desired for applications in many fields such as cosmetics, pharmaceuticals, drug distribution, medicine, bioengineering, wound healing, tissue engineering, etc. The value-added applications of silk in these areas offer various opportunities to the industry in terms of being sustainable and providing health, environmental, and economic benefits. Cost is one of the leading parameters for applications and efficiency in industrial processes. In industrial production, low cost, environmental friendliness, and clean production methods are among the factors that contribute to the sustainability of the process (Pradhan et al., 2022). For this reason, determining the technical and economic feasibility of the product to be recycled from waste, which is a by-product of industrial production, and determining the applicability of recovery methods are also important in terms of economic sustainability (Capar & Pilevneli, 2024).

Silk sericin was often discarded as a by-product of the silk production process because its potential use was high, but its advantages were not well understood. However, especially with the research conducted in recent years, the unique biological properties, composition, and use of the spreader in many industrial areas have been discovered. There is an increasing trend around the world to recycle waste and bring it into industry and as a result, to prevent environmental pollution and to develop products that will contribute to the economy of countries. In this regard, sericin is a very valuable biopolymer in terms of being both a waste product and being a natural protein that can be used in areas where humanity's most fundamental problems are faced, such as health, food, tissue engineering, and wound healing.

Various methods such as enzymatic hydrolysis and freeze-thaw, ethanol precipitation, infrared (IR) technology, and membrane filtration are used in the recovery processes of silk. Various optimum processes have been developed for cocoon cooking wastewaters (containing silk protein) and silk degumming wastewaters (containing sericin and soap). The economic feasibility of recovering the sericin after these methods was evaluated (Capar & Pilevneli, 2024). The recycling processes of sericin, which is the waste of the textile industry, may have various effects on nature. In this context, conducting analyzes determined as life cycle assessment (LCA), which supports the technical, environmental, and economic determination of the effects of processes involving the recovery of waste by-products, will provide better information on the subject (Finnveden et al., 2009).

LCA is a standard framework that defines analyzes for the quantitative and systematic determination of the environmental impacts of a product, its production process, and the entire cycle of raw material supply (Bitar et al., 2024). Although there is LCA data on primary production in the textile industry, LCA data on the processing processes of the textile industry are limited (Astudillo et al., 2014). According to

the LCA of the recovery of the sericin, it has been observed that environmental impacts increase in the process of further processing of a resource for recovery instead of treatment. In this respect, environmental impacts should be taken into account in resource recovery as well as improving the economy. It has been determined that the biggest impact on the recovery process is on climate change, natural resources, and human health. For example, increasing renewable energy sources to meet the energy demand in the recovery process will contribute to reducing climate change and global warming problems and therefore strengthen the recovery process procedures. As a result, LCA data provide an important decision-making aid in the recovery of the sericin (Capar et al., 2022; Peydayesh, 2024).

We anticipate that this study, which emphasizes the recovery of the source of sericin, which is released annually in large amounts worldwide, how it can be evaluated technically, and its economic contributions, will make a great contribution to the existing literature in an up-to-date and innovative way. Our study, in which we emphasize the methods and importance of developing stimuli-responsive and self-assembled sericin materials, brings to the attention of researchers who will work in this field that their biological and physicochemical effects are invaluable in fields such as biomedicine, food, textile, medicine, and pharmacology, which constitute the most basic factors of human life. In addition, this study, which will be an insightful reference for the development of sericin-based biomaterials, summarizes that synthesizing silk sericin, which has a large waste potential, as biomaterials in various structures will contribute to human health, the solution of global environmental pollution problems and the world economy. Research, publications, and patents on sericin-based biomaterials, which have progressed at an increasing rate, especially in the last 20 years, show how important a recycling material this valuable protein is Fig. 9.3.

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https://www.sciencedirect.com/search?qs=sericin%20materials&date=2005-2024&lastSelectedFacet=articleTypes&articleTypes=REV

https://www.sciencedirect.com/search?qs=sericin%20materials&date=2005-2024&lastSelectedFacet=articleTypes&articleTypes=CH

https://patentscope.wipo.int/search/en/result.jsf?query=FP%3A%28sericin+materials%29&sortBy=-score.

2. Stimuli-responsive and self-assembled sericin materials

In recent years, materials prepared as self-assembled have been used as a very effective method in various fields (Elahi et al., 2021). Spontaneous formation of more functional and larger complexes through molecular self-assembly processes occurs frequently in various natural systems. Weak noncovalent interactions aid the process of assembling supramolecular structures from small building blocks. There are various applications for collecting these small particles to form larger clusters. Different biomolecular

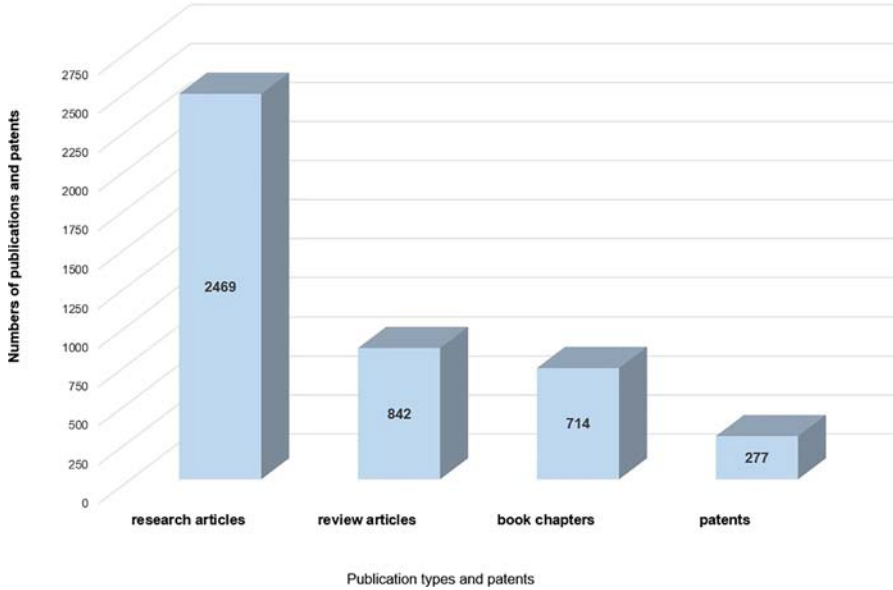


Figure 9.3 A graph indicating the number of publications and patents for the last 20 years in the field of "sericin materials." Each column shows the number of research articles, review articles, book chapters, and patents on "sericin materials" between 2005 and 24. Adapted by authors. (Accessed on July 23, 2024).

aggregation systems such as colloid and gel formation are among these applications (Kurland et al., 2012).

Self-assembly is a mechanism based on the principle that molecular units form regular structures spontaneously and reversibly through noncovalent interactions. These interactions occur spontaneously without any external guidance and form the nanostructure. The most fundamental feature of the self-assembled system is that this self-assembly function occurs spontaneously (Mandal & Kundu, 2009; Kumar Dan et al., 2022). The self-assembly mechanism occurs through the cross-linking method. In this way, biological polymers contribute to the production of new materials that can be used in various application areas by creating new structures through self-assembly (Zhang et al., 2019).

The self-assembly mechanism of natural precursors finds a wide range of applications in materials engineering. Thanks to this mechanism, new biomaterials can be created by spontaneously assembling disordered components into ordered complexes. New and functional biomaterials formed by the self-assembly mechanism provide great benefits in many industrial application fields such as medicine, bioengineering, drug delivery, tissue engineering, food, and textiles (Kurland et al., 2012). The technique of self-assembly of these molecular units has been frequently used in research in bioanalytical and biomedical (Ocsoy et al., 2015; Mingying Yang et al., 2015; Celik

et al., 2018; Celik et al., 2020; Seyma Dadi et al., 2020; Rizzo & Kehr, 2021; Dadi et al., 2023).

The self-assembly technique is a bottom-up approach used especially in the preparation of nanoparticles (NPs). The most obvious benefit of the mechanism of spontaneous and reversible assembly of particles through noncovalent bonding is that the assembly of NPs can occur without external influence (Kumar Dan et al., 2022). Sericin protein, which constitutes an important part of the silk macrostructure, exhibits important properties regarding self-assembly via multiple aggregation mechanisms (Kurland et al., 2012). For example, in a study by Huang et al. (2016), DOX−sericin conjugates self-assembled to form NPs. This is achieved, thanks to the hydrophilic structure of sericin and the hydrophobic structure of DOX. Thanks to this mechanism, it ensured the release of DOX inside the cell and increased the antitumor effect of sericin NPs. Folate-sericin-DOX (FA-SND)-based NPs produced by this mechanism have been used as carriers for drug transfer in cancer therapy.

Stimuli-responsive polymers are smart materials that can change their properties when triggered by external stimuli such as physical (temperature, light, mechanical force, magnetic field, electric interaction, etc.), chemical (pH, redox, molecules, supramolecular interaction, etc.), or biological (enzyme, etc.) factors. Smart polymers such as films, NPs, and hydrogels have been applied in various fields such as drug carriers, molecular sensing, coatings, thermoelectric materials, and artificial muscles (Png et al., 2023). Stimuli-responsive and self-assembly of natural precursors are of great importance in the field of biomaterial production. The creation of natural and synthetic systems through self-assembly processes has a valuable place in biomaterials research (Kurland et al., 2012).

Low−molecular-weight gels (LMWGs) can form soft materials through noncovalent interactions. These materials retain the properties of both the solution and the solid phase, as well as temperature, solvents, etc. They adjust the effects of various factors such as. LMWGs are preferred in many areas, thanks to their self-assembling structure. For example, fluorescent LMWGs, which have extraordinary detection capabilities with multiple sensing approaches (gel, solution, etc.) and signal modes (fluorescence, color, etc.), thanks to their photophysical properties, are used as sensors in biological and environmental applications. For example, fluorescent chemosensors are capable of detecting gases and organic compounds (Cao et al., 2021; Png et al., 2023).

Sericin helps cell attachment, proliferation, and differentiation in sericin-based materials, owing to its biocompatibility, biodegradability, and bioactivity features (natural adhesive to cells, nonimmunogenicity, oxidation resistance, antiapoptosis) (Lamboni et al., 2015; Tao et al., 2019). It is also attractive due to its good hydrophilicity and excellent affinity for biomolecules (Tao et al., 2019). With sericin polymer, which has these properties, biomaterials whose morphology, dimensions, flexibility, and durability can be controlled and stable can be prepared (Kunz et al., 2016; Kurland et al., 2012; Liu et al., 2022). Due to all these specific features, sericin protein is involved in various biomaterials such as films, hydrogels, scaffolds, conduits, fibers, and devices used in tissue engineering and regenerative medicine (Liu et al., 2022). It is quite easy to prepare sericin-based biomaterials such as hydrogels, scaffolds,

fibers, and films by cross-linking (Fig. 9.4) because these materials have abundant polar groups (Yang et al., 2023).

2.1 Sericin-based hydrogels

Hydrogels are three-dimensional physically or chemically crosslinked viscoelastic polymer networks, which are insoluble but swollen in an aqueous medium (Hoffman, 2012; Onder et al., 2022). In chemical crosslinking, covalent bonds formed by crosslinking agents exist between different polymer chains. In physical crosslinking, the hydrogel possesses hydrophobic, ionic interactions, and hydrogen bonding (Ullah et al., 2015). Hydrogels can adsorb high amounts of water due to having hydrophilic groups such as amino, hydroxyl, carboxyl, and amido (Samchenko et al., 2011). The insolubility of hydrogels in aqueous medium is due to cross-links between network chains (Ahmed, 2015). The large amounts of water adsorption capabilities of hydrogels give them a good degree of flexibility. Thanks to the highly elastic structure of hydrogels, they can adapt to environmental conditions (Annabi et al., 2014; Omidian et al., 2006). Additionally, chemical and physical modification of the polymeric chains allows for the production of various types of hydrogels including shape-memory, self-healing, and environment-responsive hydrogels (Taylor & in het Panhuis, 2016; Gyarmati et al., 2017). These properties of hydrogels make them preferred in many different fields, especially biomedical applications, tissue engineering, and drug delivery (Onder et al., 2022).

Hydrogels can be classified based on source, synthesis route, physical structure, size, configuration, and ionic charge (Mahinroosta et al., 2018). The main classification is based on their polymer source and the source of hydrogels can be categorized into natural, synthetic, and semi-synthetic (Khansari et al., 2017; Yanyu Zhang & Huang, 2021). Natural hydrogels can be obtained by adding synthetic parts to proteins or carbohydrates (Ahmed, 2015). Biodegradability, biocompatibility, bioactivity, and nontoxicity of natural hydrogels assure a safe, biologically friendly, and renewable environment for different applications (Peppas et al., 2000). Sericin-based hydrogels have been particularly attracted to attention due to their excellent properties such as antioxidant activity, oxygen and water vapor permeability, biocompatibility, and

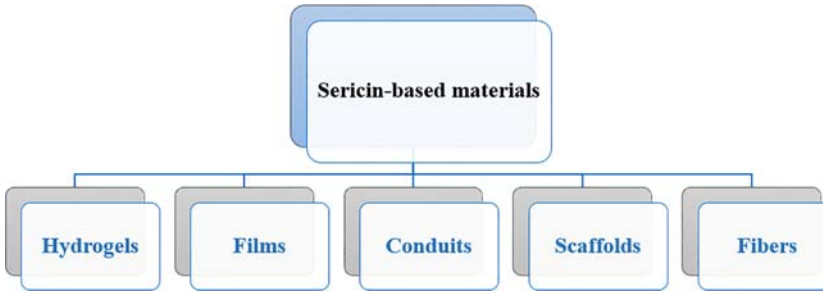


Figure 9.4 Sericin-based materials. Main materials prepared with sericin were shown. Adapted by authors.

enzymatic degradability. Owing to these properties, sericin-based hydrogels can be used in various biomedical and biotechnological applications (Baptista-Silva et al., 2021; Han et al., 2023; Zahoor et al., 2023). For instance, Yang et al. (2017) developed nano clay lithium magnesium silicate hydrate (LMSH) cross-linked semi-IPN sericin/poly(NIPAm/LMSH) (HSP) nanocomposite hydrogels. They demonstrated the efficiency of the hydrogel as a wound dressing. The sericin-based nanocomposite hydrogels had better mechanical and antimicrobial properties. The embedding of the sericin structure into the polymer network led to an increase in the pore size of the polymer network, adsorption of the bacteria by the charge interaction, and destruction of their physiological activities.

The self-assembly of proteins enables the formation of hydrogels that resemble natural extracellular matrix, have high biocompatibility against cells, and are controllable for drug release and tissue engineering applications (Li et al., 2012). Protein-based hydrogels are preferred as systems that provide controlled drug release because of their ability to mimic extracellular matrices, stabilize bioactive molecules, be biocompatible, and have adjustable self-assembly properties (Rizzo & Kehr, 2021). Hydrophobic/hydrophilic balance is the most effective force in the self-assembly of proteins. The hydrophilic protein contains ionic units such as amines and carboxylic acids. These components regulate self-assembly, water solubility, and pH (Ghosh et al., 2019). Additionally, stimuli-responsive polymers can be incorporated into sericin hydrogels to produce stimuli-responsive sericin-based hydrogels. Sericin-based hydrogels have been developed for pH-responsive (Kurland et al., 2014), drug delivery systems (Al-Tabakha et al., 2021), invasive repairing cartilage (Qi et al., 2018), and wound healing (Verma et al., 2017).

In a study, silk sericin−based hydrogel was generated via horseradish peroxidase (effective cross-linking agent) mediated cross-linking. As shown in Fig. 9.5, first silk sericin was extracted from *Bombyx mori* cocoon. The addition of peroxidase enzyme and H_2O_2 generated sericin-based hydrogels. In this process, peroxidase catalyzes the oxidation of sericin phenolic hydroxyl groups in the tyrosine amino acid residues in the presence of H_2O_2, forming an amorphous hydrogel. The amorphous structure of hydrogel enabled a high degree of transparency and wound visualization. The generated sericin-based hydrogels demonstrated antioxidant activity and high potential for the regeneration and treatment of wounds (Baptista-Silva et al., 2021).

The wound-healing property and antimicrobial activity of sericin-based hydrogels can be enhanced by the addition of various NPs and natural bioactive agents. For example, Munir et al. (2023) produced silk sericin-based hydrogels with Ag NPs by the physical method using banana peel extracts and curcumin without adding any chemicals. The wounds treated with this hydrogel combination with Ag NPs and plant extracts healed more efficiently in 11 days compared to control groups.

The chemical and physical crosslinking of the hydrogel makes the hydrogel insoluble, leading to enhancing drug loading efficiency. Thus, sericin-based hydrogels can be used in drug delivery systems (Al-Tabakha et al., 2021). In a study, Tao et al. (2019) synthesized a gentamicin-loaded sericin/polyvinyl alcohol hydrogel (Fig. 9.6). This hydrogel, which has excellent mechanical performance and the ability

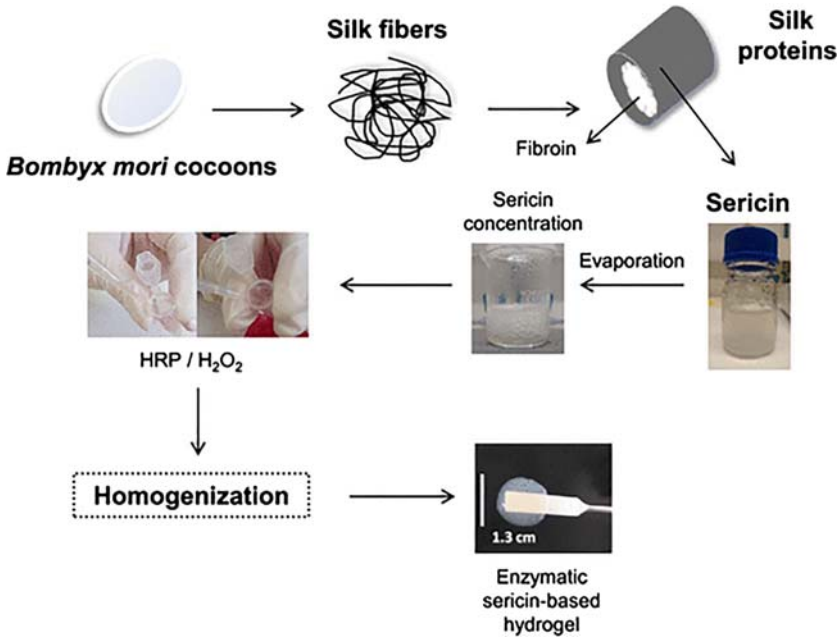


Figure 9.5 The generation of sericin-based hydrogels. The main production steps of a sericin-based hydrogel.
Reprinted (adapted) with permission from Baptista-Silva, S., Borges, S., Costa-Pinto, A.R., Costa, R., Amorim, M., Dias, J.R., Ramos, O., Alves, P., Granja, P.L., Soares, R., Pintado, M., & Oliveira, A.L. (2021). In situ forming silk sericin-based hydrogel: A novel wound healing biomaterial. *ACS Biomaterials Science and Engineering, 7*(4), 1573−1586. https://doi.org/10.1021/acsbiomaterials.0c01745. Copyright (2021) American Chemical Society.

to load/release drug molecules, inhibited the growth of *Staphylococcus aureus*, *Escherichia coli*, and *Pseudomonas aeruginosa*.

2.2 Sericin-based films

Polymeric films can be defined as thin films, which are composed of natural, synthetic, and composite polymers. Polymeric films can be clear, opaque, semitransparent, smooth, and rough and the thickness of the polymeric films can be up to 200 μm (Drobny, 2020, pp. 1−314). Synthetic polymers have provided a better option to industry and consumers in terms of mechanical strength, cost-effectiveness, and shape stability. However, nonbiodegradable synthetic polymers pose a threat to the environment because they originate from petroleum resources. Natural polymers have advantages over synthetic polymers through eco-friendliness, biocompatibility, and biodegradability (Abdullah & Dong, 2019; Gowthaman et al., 2021, pp. 351−372). Natural polymers such as polysaccharides (starch, cellulose, etc.) and proteins (collagen, gelatin, etc.) are often utilized as polymeric films for use in different applications (Kaushik et al., 2016).

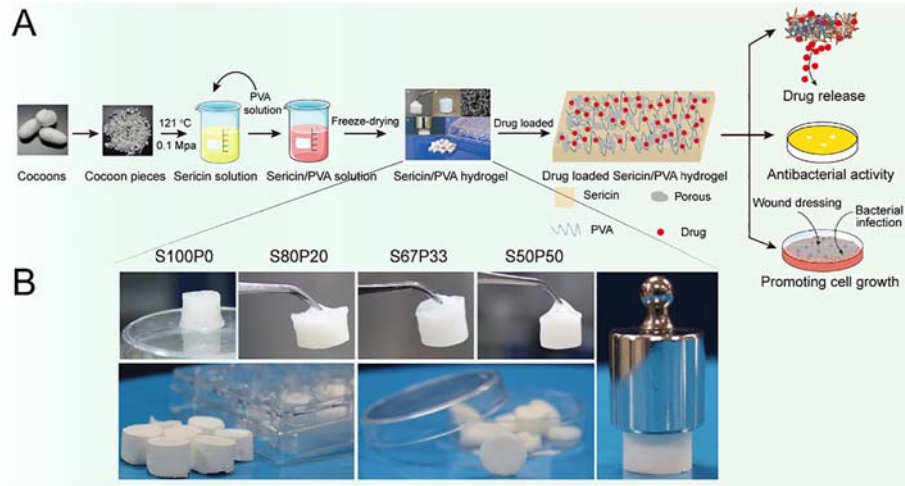


Figure 9.6 The gentamicin-loaded sericin/polyvinyl alcohol hydrogel. (a) Sericin extraction and the preparation of drug loaded SS/PVA hydrogels, (b) SS/PVA hydrogel with different ratios of sericin and PVA (v/v).
Reprinted from Tao, G., Wang, Y., Cai, R., Chang, H., Song, K., Zuo, H., Zhao, P., Xia, Q., He, H. (2019). Design and performance of sericin/poly (vinyl alcohol) hydrogel as a drug delivery carrier for potential wound dressing application. *Materials Science and Engineering: C, 101*, 341−351. https://doi.org/10.1016/j.msec.2019.03.111. Copyright (2019), with permission from Elsevier.

Since sericin is brittle in a dry environment due to its amorphous structure, sericin-based films are not suitable for biotechnological and biomedical applications (Cai et al., 2017). Therefore, sericin is usually blended with a polymer or cross-linked to improve the performance of films for relevant applications (He et al., 2017; Nayak et al., 2012). The researchers prepared bamboo-derived cellulose nanofibrils and used a reinforcer to enhance the mechanical properties of sericin-based films (Kwak et al., 2018). They reported that the antioxidant activity of sericin was well maintained even though it was used as a matrix in cellulose nanofibrils.

In another study, the blending of sericin and polyvinyl alcohol enhances the mechanical performance, hygroscopicity, and water retention capacity of the film (He et al., 2017). They generated sericin/polyvinyl alcohol blend film and in situ formed Ag NPs on blend film. The mechanical performance, swellability, and water retention capacity of the film were investigated. They reported that the hydrogen bonds between the hydroxyl groups of polyvinyl alcohol and polar amino acid residues of sericin enhanced the mechanical performance and the stability of sericin. Additionally, the blend film had excellent antimicrobial activity against *E. coli* and *S. aureus*. In another study, sericin was blended with agar film to enhance mechanical properties. The composite film showed good mechanical performance, hydrophilicity, hygroscopicity, and stability (Wang et al., 2018).

Zhang et al. (2011) developed a sericin film with glycerol a green substance. The stability and tensile strength of the sericin film decreased with the addition of glycerol to the structure. Because glycerol causes the formation of an amorphous structure in sericin films. The flexibility of sericin film was greatly improved with the incorporation of glycerol. These results showed that developed sericin/glycerol film can be used in application in tissue engineering. Nayak et al. (2012) reported the production of crosslinked sericin film using glutaraldehyde as the crosslinking agent. Crosslinking of sericin with glutaraldehyde provided the film superior stability, mechanical strength, swelling ratio, and resistance to hydrolytic degradation.

In another study, sericin NPs and pectin were added to improve the mechanical properties and the antioxidant activity of the sericin film. This caused lower solubility, higher water permeability, and improved thermal stability. While the incorporation of pectin enhanced the mechanical properties of sericin film, NPs enabled the film to show better antioxidant activity. It was reported that the developed nanocomposite-based sericin films can be used in food packaging or biomedical applications (Meerasri et al., 2023).

2.3 Sericin-based conduits

Nerve guidance conduits (NGCs) mimic the physical and biological properties of native nerve tissue for repairing peripheral nerve injury. NGSc are generally a hollow cylinder shape produced from natural materials, synthetic materials, or a combination of both (Parker et al., 2021). To develop efficient NGCs, the material should be biodegradable and biocompatible and promote cellular growth and proliferation (Carvalho et al., 2021). Researchers have worked to develop NGCs using various materials such as collagen, hyaluronic acid, polyvinyl alcohol, and poly-ε-caprolactone (Entekhabi et al., 2016; Yao et al., 2010). Among these polymers, sericin has a good potential for producing NFCs due to its excellent biocompatibility and biodegradability. Additionally, sericin's neurotrophic and neuroprotective effects make it a suitable substrate for the repair of injured nerves (Lei Zhang et al., 2017; Xie et al., 2015).

A research team reported the development of a carbon nanotube/sericin-based nerve conduit for transected nerve injury repair (Li et al., 2020). The incorporation of carbon nanotube into sericin enhanced mechanical and electrical conductive properties of conduits that promote peripheral nerve injury repair. In another study, sericin/silicone conduits effectively promoted functional recovery of peripheral nerves of 5 mm gap defects close to that of the autologous nerve graft (Xie et al., 2015).

2.4 Sericin-based scaffolds

Scaffolds, characterized as solid, porous, three-dimensional biomaterials, are specifically engineered to establish a favorable environment that supports, stimulates, and enhances the growth and development of new tissue (Liverani et al., 2019). Scaffolds, when fabricated with polymeric materials, offer improved control and reproducibility, owing to their ability to incorporate optimal characteristics such as resistance,

degradation rate, porosity, microstructure, and precisely defined shapes and sizes (Dhandayuthapani et al., 2011).

Biocompatibility of the scaffold is vital for tissue regeneration, as it prevents adverse reactions, inflammation, and rejection while facilitating proper cell signaling and healing mechanisms (O'Brien, 2011). Biodegradability of the scaffold is crucial in tissue engineering as it allows for the gradual replacement of the scaffold by native tissue over time. The controlled degradation of the scaffold, concurrent with tissue formation, requires the promotion of inflammatory responses and the infiltration of cells, such as macrophages or leukocytes, to facilitate the production of an extracellular matrix by the cells themselves (Arango et al., 2021).

An optimal scaffold in tissue engineering should have suitable pore size and architecture to support cell signaling, act as a barrier against microorganisms, allow for waste molecule diffusion, and regulate nutrient exchange. Cell−scaffold interactions depend on ligands on the scaffold surface, with ligand density influenced by the available pore surface for cell adhesion. The average pore size within the scaffold significantly affects cell adhesion and overall scaffold functionality (O'Brien, 2011).

Sericin is an important protein polymer used as a scaffold material. Various fabrication methods, including foam processing, solvent casting, and freeze-drying, have been employed to prepare sericin-based scaffolds (Liu et al., 2022). Sericin-based scaffolds offer considerable potential in tissue engineering, stemming from their advantageous characteristics including biocompatibility, bioactivity, mechanical properties, and biodegradability. The multifaceted nature of sericin-based scaffolds makes them a promising avenue for advancing tissue engineering strategies (skin regeneration, bone tissue engineering, wound healing) and addressing clinical challenges in regenerative medicine (Lamboni et al., 2019; Arango et al., 2021; Bhoopathy et al., 2023).

The role of sericin's bioactivity in wound healing is highly significant. Incorporating sericin into skin repair and wound healing scaffolds holds significant potential as a biomaterial. It fosters better adhesion, migration, and growth of fibroblasts and keratinocytes, boosts collagen production, and facilitates enhanced re-epithelialization in skin wounds (Kunz et al., 2016). In the study reported by Siritientong et al. (2014), an evaluation was performed to investigate the efficacy of an ethyl alcohol-precipitated silk sericin/polyvinyl alcohol scaffold as a wound dressing. The study also compared its effectiveness with Bactigras, a commercially available wound dressing. The sericin biomaterial is proven to have excellent properties and can be applied safely and effectively, surpassing the performance of Bactigras. During the clinical evaluation, there was no indication of skin irritation observed. Additionally, the use of sericin biomaterial resulted in faster healing and decreased pain compared to wounds that were treated with Bactigras.

Researchers utilized a combination of sericin and extracellular matrix from the human placenta to create freeze-dried scaffolds to treat skin wounds. The scaffolds, a combination of sericin and placenta-derived extracellular matrix (SPEM), were tested using in vitro MTT and scratch wound assays with HaCaT cells. Results showed that the scaffolds were both nontoxic and effective in promoting wound healing. Studies conducted on Wistar albino rats indicate that using SPEM scaffolds to treat open

excision wounds leads to a significant reduction in wound size, along with increased collagen deposition (Bhoopathy et al., 2023).

Siritienthong et al. (2012) used freeze-drying and EtOH precipitation methods to produce sericin/PVA scaffolds (Fig. 9.7). Compared to nonprecipitated scaffolds, the EtOH-precipitated ones had denser structures, stronger compressive moduli, and lower water swelling capacity. EtOH-precipitated scaffolds released their sericin over time. In trials involving murine fibroblasts L929, the 70% EtOH-precipitated sericin/PVA scaffolds displayed the greatest potential for encouraging cell proliferation. As per the research, sericin/PVA scaffolds that are precipitated using 70% EtOH are found to be more efficacious in promoting wound healing than PVA scaffolds that are precipitated using EtOH alone. Moreover, they stimulated the production of type III collagen and enhanced epithelialization. It has been observed that the sustained release from scaffolds is aided by sericin, and it also can attract and mobilize macrophages, which are essential in repairing wounds.

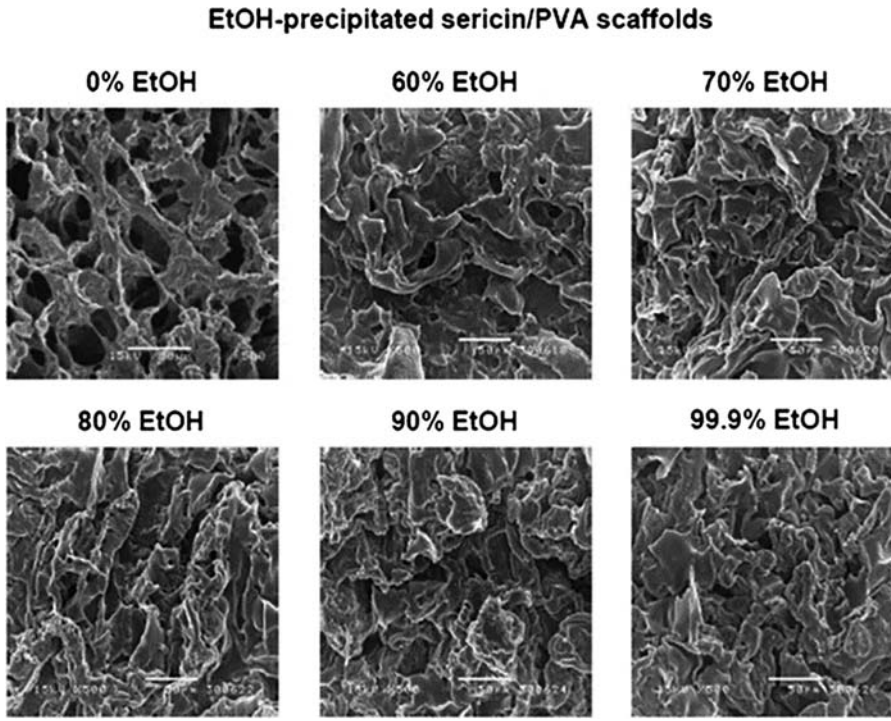


Figure 9.7 The cross-sectional morphology of ethanol-precipitated sericin/PVA scaffolds, as observed using SEM. EtOH concentrations of 0%, 60%, 70%, 80%, 90%, and 99.9% were used.

Reprinted from Siritienthong, T., Ratanavaraporn, J., Aramwit, P. (2012). Development of ethyl alcohol-precipitated silk sericin/polyvinyl alcohol scaffolds for accelerated healing of full-thickness wounds. *International Journal of Pharmaceutics, 439*(1−2), 175−186. https://doi.org/10.1016/j.ijpharm.2012.09.043. Copyright (2012), with permission from Elsevier.

A team of researchers has designed a targeted solution for chronic nerve compression by creating a specialized nerve growth factor (NGF)-loaded chitosan/sericin composite scaffold. This cutting-edge scaffold was carefully crafted to enhance the adhesion and proliferation of Schwann cells. The NGF-loaded scaffold demonstrated significant advancements in promoting nerve regeneration and facilitating functional recovery during a preclinical study conducted using a rat model with chronic nerve compression (Fig. 9.8). The NGF-loaded scaffold effectively relieved neuralgia, enhanced nerve conduction velocity, accelerated microstructure recuperation, and ameliorated gastrocnemius muscle dystrophy (Zhang et al., 2017).

Wang et al. (2021) successfully developed an injectable scaffold known as the carbon-nanotubes-doped sericin scaffold (CNTs-SS) with programmable shape-memory properties, specifically designed for treating ischemic stroke. One notable feature of CNTs-SS is its ability to be custom-shaped according to personalized stroke damage, allowing precise injection into the affected area in mice for repair. Moreover, the CNTs-SS scaffold effectively facilitates the delivery of bone marrow mesenchymal stem cells (BMSCs) to the brain tissue. Additionally, it plays a significant role in promoting functional neuronal differentiation of BMSCs and in the stroke repair process. Dinescu et al. (2013) analyzed a 3D scaffold made of collagen-sericin that had been infused with 10% hyaluronic acid and 5% chondroitin sulfate. This resulted in the formation of a porous and uniform structure that closely imitates the extracellular matrix found in cartilage. The implementation of scaffolds enabled the rapid expansion and mobility of stem cells derived from human fat, making it a highly promising biomaterial for engineering cartilage tissue.

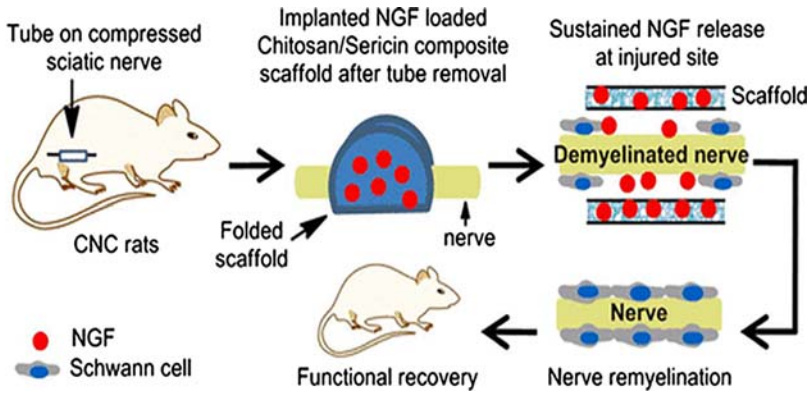


Figure 9.8 The NGF-loaded chitosan/sericin scaffold. The NGF-loaded chitosan/sericin scaffold is depicted schematically to illustrate its enhancement of nerve regeneration in cases of chronic nerve compression.
Reprinted (adapted) with permission from Zhang, L., Wen, Y., Tao, K., Song, Y., Xie, H., Wang, J., Li, X., Shuai, X., Gao, J., Chang, P., Wang, G., Wang, Z., & Wang, L. (2017). Sustained local release of NGF from a chitosan−sericin composite scaffold for treating chronic nerve compression. *ACS Applied Materials and Interfaces, 9*(4), 3432−3444. https://doi.org/10.1021/acsami.6b14691. Copyright (2017) American Chemical Society.

2.5 Sericin-based fibers

The process of electrospinning uses a powerful electric field to transform a solution of polymer material into a stream of continuous fibers at the nano-scale. This results in the creation of nanofibers (Agrahari et al., 2017, pp. 189–215). Nanofibers have diameters of less than 1 μm (1000 nm) and are characterized by their low density, high surface area to volume ratio, significant pore volume, and small pore size. These unique properties make them suitable for a wide range of applications such as air and liquid filtration, tissue engineering, drug delivery, energy storage, sensors, catalysts, and smart textiles (Li et al., 2019).

Electrospinning of sericin into nanofiber solutions, through the application of trifluoroacetic acid as the solvent, was achieved by Zhang et al. (2012). However, the mechanical properties of the resulting sericin nanofibers were found to be considerably weak, presenting a drawback for their potential utilization in diverse industrial applications. Thus, to address the weak mechanical properties and enable diverse industrial applications, sericin has been effectively combined with other natural and synthetic polymers (such as chitosan, silk fibroin, PVA, and poly (L-lactic acid) [PLA]) to improve the performance of the nanofiber mats (Carissimi et al., 2019). Yang et al. (2014) devised a method to create microparticles and nanofibers of sericin using both low-molecular-weight sericin and high-molecular-weight sericin (HS). This was achieved through two distinct extraction conditions, involving dissolution in trifluoroacetic acid (TFA) followed by electrospinning for each type of sericin, resulting in the formation of unique materials.

In a recent study, sericin from degumming effluent was successfully extracted and precipitated. They then blended the sericin with PVA in formic acid and utilized a wire electro-spinneret unit for electrospinning. The resulting SS/PVA nanofibers exhibited remarkable efficiency in capturing both acidic and basic colorants, as well as metal ions. This effectiveness can be attributed to the presence of polar groups in sericin, such as −OH, −COOH, and −NH2 groups (Mowafi et al., 2018).

A study conducted by Chao et al. (2018) aimed to create a wound dressing material using tigecycline-loaded sericin/PVA composite fibers (TCSS/PVA). The electrospun fibers displayed a smooth texture, appropriate porosity, and effective water vapor transmission rate. The release of tigecycline from TCSS/PVA took 100 min, and the encapsulation efficiency was high. The composite fibers exhibited strong antibacterial properties against *E. coli* and *Bacillus subtilis*. In vivo tests showed that TCSS/PVA helped to speed up wound healing compared to other materials, indicating their potential as advanced antibacterial wound dressings.

Recently, a remarkable breakthrough has emerged with the introduction of a novel multifunctional core–shell nanofiber (CSF). This pioneering CSF features an innovative combination of a hydrophilic core and a hydrophobic shell, setting a new standard in nanofiber design. The multifunctional core-shell nanofibers (CSFs) exhibit bactericidal activity and support cell adhesion and growth, making them promising for biomedical applications. They can incorporate bioactive materials and growth factors in the core, house antibacterial agents in the shell, and function as an extracellular

matrix within 3D scaffolds, enhancing tissue engineering possibilities (Tuancharoensri et al., 2022).

A group of researchers conducted a study on diabetic foot ulcers and developed nanofibrous mats using silk-sericin, polycaprolactone (PCL), cellulose acetate (CA), and ferulic acid (FA) through electrospinning. These mats had controlled drug release and low cytotoxicity. In wound-healing studies on diabetic rats, the nanofibers showed remarkable efficiency in healing wounds and restoring normal skin structure (Anand et al., 2022). The scientists conducted the development and characterization of poly(-vinyl alcohol) (PVA)/chitosan (CS)/silk sericin (SS)/tetracycline (TCN) porous nanofibers, intending to use them as wound dressings. These nanofibers display water uptake capacity and heightened hydrophilicity and promote enhanced fibroblast proliferation due to the incorporation of sericin. Additionally, they effectively inhibit bacterial growth and exhibit substantial advancements in wound healing and collagen deposition in vivo experiments (Bakhsheshi-Rad et al., 2020).

3. Potential applications

Sericin's use in food and cosmetics is due to its high hydrophobic amino acid content and antioxidant activity. The antioxidant activity of sericin is related to its low digestibility. Thanks to this feature, in addition to having antitumor, antimicrobial, and anticoagulant activities, sericin is a protein with unique physical, chemical, and biological properties. It is preferred in many application areas, thanks to its various characteristics such as antioxidant activity, pH response, biocompatibility, biodegradability, low immunogenicity, supporting cell proliferation, antibacterial activity, and photoprotective activity. The main reason why sericin is preferred in various fields is that it can be modified into biomaterials through copolymerization, cross-linking, and combination with other alternative polymers (Yang et al., 2023). These application areas include many fields such as biomedical, regenerative medicine, cosmetics, food industry, tissue engineering, pharmaceuticals, drug delivery, and textile engineering (Liu et al., 2022) (Fig. 9.9).

Sericin gains qualities such as being an anti-inflammatory agent and protecting the body from obesity. It also finds use as a biomaterial in areas such as drug delivery and tissue engineering. Sericin's moisturizing potential makes it preferred as a therapeutic agent for wound healing, protection against UV rays, inducing cell proliferation, and in the formulation of products such as creams/shampoos (Kunz et al., 2016).

3.1 Pharmaceuticals

Silk sericin is a protein extracted from dried silk cocoons and composed of a polar amino acid chain with functional hydroxyl, carboxyl, and amino groups. The functionality inherent in sericin is expected to give great assets such as stability, release-modifying capacity, and molecular interaction. It possesses numerous important qualities such as biocompatibility, biodegradability, nontoxicity, hydrophilicity,

Fields	Applications
Biomedical and Pharmaceutical	Drug delivery, Wound healing, Tissue engineering, Bone repair, Cartilage repair, Stem cell engineering, Neuro regeneration, Cell delivery, Implant matrix, Cell proliferation, Medium supplement, Metabolic effects on the immune system and lipid metabolism, Contact lens, Anti-bacterial/Anti-biofilm effect
Cosmetics	UV protection, Moisturizing, Anti-aging, Anti-wrinkle, Whitening, Skin elasticity,
Food industry	Use as a food additive Production of beverages rich in amino acids Use as an antioxidant in dairy products Fighting constipation and obesity In improving the taste of porridge In the prevention of browning reactions
Textile industry	In the development of nanofibers In the production of medical textile materials In the manufacture of UV-protected textile products In improving the moisture absorption property of fabrics
Additional fields	In the treatment of industrial wastewater In the production of air filter products In the development of anti-frosting agents for roads and roofs In the production of artificial leather products In the manufacture of roads and roofs

Figure 9.9 Sericin applications in various fields (Crivelli et al., 2018; Fatahian et al., 2021; Liu et al., 2022). The main areas where sericin is used are biomedical, pharmaceutical, cosmetics, food, and textile.
Adapted by the authors.

and so on. Furthermore, sericin can produce gels, NPs, microparticles, and sharp bioengineered materials. Sericin also provides stability due to its high affinity for medicinal substances/molecules. It is currently being researched for a range of pharmaceutical uses such as solubility enhancement, release adjustments, formulation stabilization, and drug carrier, among others. The purpose of this part is to give a general overview of sericin-based pharmaceutical applications, including stabilization of nanocrystals and NPs, inhibition of devitrification, improvement of solubility, formulation of controlled and extended-release drugs, targeted drug delivery, applications for wound healing, and suitable carrier. These features enable its interaction with polymers or other materials, whether at the bulk or nanoscale (Chirila et al., 2016).

Due to its potential to produce biocompatible and biodegradable materials with a variety of biomedical functions, such as antimicrobials and antioxidants, silk-based nanomaterials have recently attracted attention. They can also be employed as biomaterials due to their low immunogenicity, strong physicochemical stability, and long shelf life, which facilitate scale-up production (Chirila et al., 2016; Yalcin et al.,

2019). Fibroin and SER are two commonly utilized silkworm derivative proteins used for nanomaterial production that were licensed by the FDA in 2019 (Chouhan & Mandal, 2020), extending the possibilities for their medicinal use. Recent discoveries and advances have revealed pharmaceutical and cosmetics uses ranging from changes in isolation methods to reduce structural degradation to functionalization strategies and drug-delivery system design. The development of SER-based materials and formulations faces a challenge in maintaining SER structure because traditional degumming extraction processes use high temperature and/or alkaline conditions, which lead to protein chemical degradation. This can be avoided by using mild aqueous extraction (Chirila et al., 2016). Because methionine and cysteine amino acids are present in SER membranes, chemical degradation control promotes cell growth and attachment by preventing alterations in amino acid composition (Aramwit et al., 2009; Lamboni et al., 2015; Chouhan & Mandal, 2020). SER peptides with low molecular weight are generally used in hair care, skin care cosmetic formulations, and health-related products as formulation components, while SER peptides with high molecular weight are preferred for use in nanocarrier components, tissue scaffolds, functional biomembranes, and other applications (Suktham et al., 2018). Some studies emphasize SER as a component containing antibacterial compounds and by making it more functional with derivatives of natural polymers, especially chitosan, gelatin, alginate, collagen, and cellulose, and in various forms such as a sponge, nanofiber, adhesive, hydrogel, NP, and film (Chouhan & Mandal, 2020; Elahi et al., 2021).

There is a range of sericin-based nanomaterials, typically as composites, such as films and NPs, employed as drug carriers, which benefit from their biological activity (Salunkhe & Jadhav, 2018). SER-based nanoformulations (e.g., nanoparticulate systems, hydrogels, films, and different nanocarriers [hybrid systems]) highlight the structural and effective requirements for the development, as well as recent innovations and findings on their cellular and molecular mechanisms for various biological (anticancer, antimicrobial, antioxidant, wound healing processes, etc.) applications. Vitamin B12–conjugated sericin micelles are one of the additional active ingredients connected to sericin nanoformulations (Guo et al., 2019). SER-Pluronic F-127-loaded micellar NPs showed fast internalization by breast cancer cells, followed by Bax up-regulation and Bcl-2 down-regulation, both of which are proapoptotic and antiapoptotic proteins. (Mandal & Kundu, 2009) also reported on the lethal effects of these particles. In general, SER-based NPs used for cancer chemotherapy have shown positive promising results due to integrated molecular mechanisms involving (i) drug-loaded SER-NP internalization via clathrin-modulated endocytosis; (ii) NP fragmentation and subsequent drug release into lysosomes with acid pH (observed in tumor environment); and (iii) induction of cell death pathways such as apoptosis, according to the following steps (Mandal & Kundu, 2009; Elahi et al., 2021; Pornanong Aramwit et al., 2010; Rocha et al., 2017; Rupesh Dash et al., 2006; Salunkhe & Jadhav, 2018; Suktham et al., 2018; Weihong Guo et al., 2019).

Isolated SER has previously been found to have antitumoral effects due to its integrated proapoptotic activities such as caspase-3 expression reduction, Bcl-2 downregulation, and human colorectal cancer cell cycle arrest (Kaewkorn et al., 2012). All of these characteristics underline the advantages of employing SER-based nanocarriers

for cancer therapy. Hu et al. (2017) described another approach for doxorubicin release that used SER as an NP dispersion stabilizer and cryoprotectant due to its ability to reduce plasma protein adsorption. Because doxorubicin (DOX) treatment is usually associated with cardiotoxicity due to its affinity with cardiolipin, the NPs' physicochemical stability, and the reduction of pharmacological side effects were major advantages mentioned for the systems. Another study noted that SER NPs that caused significant tumor cell necrosis in vivo anticancer efficacy studies were biocompatible due to their hydrophilicity and negative surface and were sufficiently self-stabilized to be injected intravenously. Furthermore, in vitro, experiments revealed no effects on the coagulation cascade or hemolysis.

3.2 Cosmetic

Obtaining high-purity silk peptide powder starts with boiling the silk, decolorizing the boiled silk, dissolving it enzymatically, purifying it by ion exchange, then concentrating it, and finally drying it by atomized drying. It can be used as a natural cosmetic ingredient in high-end cosmetics. The amino acid components of sericin are known to promote good moisture absorption and retention in the skin. Furthermore, the molecular weight of sericin has a direct impact on the types of cosmetic applications. Research results show that sericin can effectively suppress tyrosine activity and melanochrome production. In another study, it was observed by experiment and SEM images that the sericin on hair provides excellent hair care and repair. As a result of these applications and observations, the use of sericin in cosmetics will provide experimental opportunities for the production and development of new sericin species in cosmetics. The skin, a complicated structure formed of the epidermis and the dermis (collagen-rich layer), serves as a barrier between the body and its surroundings (Leal-Egaña & Scheibel, 2010).

Adult mammals, including humans, have a difficult time achieving skin renewal and protection. Wound healing often results in scar tissue devoid of skin appendages, and due to their unique properties such as biocompatibility and degradability, SF and sericin, the most intensively investigated materials in recent years, have been widely studied as biomaterials (Bouwstra & Honeywell-Nguyen, 2002; Cao et al., 2009). Furthermore, an increasing number of studies on silk-based materials focus on skin restoration capabilities in tissue engineering. Chlapanidas et al. (2013) discovered that sericin has ROS scavenging, antityrosinase, and antielastase activity, implying that sericin is an appropriate cosmetic ingredient. Sericin is a biopolymer that can be used in toothpaste and shaving creams to stop the spread of HIV, as well as sunscreens because it absorbs UV radiation (Fatahian et al., 2021).

Sericin has been shown by Fan et al. (2009) to have strong antioxidant activity against linoleic acid peroxidation as well as significant radical scavenging activity for hydroxyl, superoxide, and 2-diphenyl-2-picrylhydrazyl hydrate (DPPH) radicals. In addition, according to some studies, SF can support human keratinocytes and fibroblasts (Min et al., 2004), and vitamin E or vitamin C-loaded SF nanofibrous mats have a promising future in the treatment of rashes and other skin conditions (Fan et al., 2012; Sheng et al., 2013). 3D SF nanofiber scaffolds were created by Sheikh et al.

(2015) as an intriguing possibility for synthetic skin reconstruction. The largest obstacle to the widespread usage of SF materials is that SF produced in the lab employing a powerful solvent−dialysis technique would inexorably move to a denaturized solid state within a week at room temperature with the change from random coil to sheet (Su et al., 2017). Many scientists have put a lot of effort into developing a range of silk-based materials that are appropriate for commercial production, shipping, preservation, and potential general use.

3.3 Regenerative medicine

Sericin has been discovered to have no immunogenicity on its own and is presently used in biomedical applications (Zhang, Ma, et al., 2006; Zhang, Tao, et al., 2006). A growing number of research have been conducted to investigate the utility of sericin in biological applications. Sericin has been shown to exhibit a variety of biological functions, including antioxidation, antibacteria, anticoagulation, and cell proliferation and differentiation (Baba et al., 1996; Kato et al., 1998; Miyazaki et al., 2004; Sasaki et al., 2000; Takeuchi et al., 2005). Due to its biodegradability, accessibility, and hydrophilicity with many polar side groups, sericin is typically copolymerized, crosslinked, or combined with other polymers to form various scaffolds in the field of regenerative medicine. This helps obtain improved properties for pertinent biomedical applications (Ahn et al., 2001; Cho et al., 2003; Kundu & Kundu, 2012; Lim et al., 2012; Nagura et al., 2001; Nayak et al., 2012; Agrawal et al., 2013), such as skin regeneration (Kundu & Kundu, 2012). Aside from being co-fabricated with other biomaterials, the idea of producing scaffolds entirely from pure sericin has just recently been investigated. Pure sericin 2D films (Teramoto et al., 2008), brittle gels (Nishida et al., 2011), and 3D sponge-like matrices (Nishida et al., 2011; Sunita Nayak et al., 2013) have all been observed. Although sericin is known to degrade when exposed to high heat and alkali (Takasu et al., 2002; Terada et al., 2002), the sericin used in these studies was extracted using this traditional harsh method. As a result, the polypeptides produced have low molecular weights and are physically fragile (Terada et al., 2002) and highly soluble, which makes effective crosslinking challenging. Unknown physical and chemical characteristics that might be advantageous for tissue engineering applications may exist in sericin-created scaffolds with an intact protein profile.

3.4 Drug delivery

The enhanced content of sericin is critical to the improved hydrophilicity of the materials. Other factors, including swelling and water absorption qualities, may be more favorable to the wound environment due to intrapolymer chain reactions of the nanofibers. Silk fibroins and other silk fiber−inspired proteins have been demonstrated to be biocompatible and easily digested by immune cells and proteolytic enzymes into molecules that can reenter native metabolic processes on a customizable time scale (Jameson et al., 2021; Guo et al., 2020).

Silk proteins, in addition to their biocompatibility and tunable biodegradability, are excellent polymers for the creation of drug delivery systems (DDSs) due to the

numerous options for increasing crystalline content. This translates into multiple ways for engineering nanomaterials of various sizes that do not require the use of harsh solvents, depending on the end-state application (Pham et al., 2020). Increased crystalline content inhibits burst release behavior (Pham et al., 2020; Wongpinyochit et al., 2019). Silk fibroins from the *Bombyx mori* silkworm are the major silk proteins that have been investigated for use in several NP DDS. The most well-characterized silk protein source is *Bombyx mori* silk fibroin, which contains a variety of reactive amino acids that allow for functionalization (Asakura et al., 2015; Bittencourt et al., 2022; Heichel & Burke, 2020; Murphy et al., 2008; Murphy & Kaplan, 2009). Other silk proteins, such as *Bombyx mori* sericin, genetically engineered silk fibroin proteins, silk fibers from other *Antheraea* species, and bioengineered spider fibroin silks (Bittencourt et al., 2022), are being investigated due to their improved functionalization ability, potential for a broader range of material and mechanical properties, and increased homogeneity of the starting polymer.

Researchers have developed a hydrogel microneedle for itching due to chronic kidney disease and used sericin in this hydrogel (**Patent: CN118319838A**). In the study, a hydrogel was used as a microneedle matrix to simultaneously deliver the drugs methacryloylated sericin, capsaicin, and DIFELIKEFALIN. These two drugs cause a desensitization reaction that inhibits itching, and they cooperate to prevent itching associated with chronic kidney disease. In another invention, researchers worked on photothermal antibacterial hydrogel wound dressing and preparation method. The dressing contains methacrylic acid—modified sericin and copper sulfide NPs. In the dressing preparation method, they aimed to obtain a better porous, photo-thermal, biocompatible antibacterial hydrogel wound dressing that sterilizes wound healing (**Patent: CN118304464A**).

4. Lab to industry and cost/benefit analysis

Previously, silk sericin was disposed of in textile silk processing processes. However, today, as the beneficial properties of the sericin are discovered, the recovery of this biopolymer has gained value both in terms of the environment and various industries. In recent studies, various protocols have been developed in which sericin is used to obtain biocompatible proteins in the synthesis of new biomaterials. The fact that silk sericin is a versatile polymer enables research such as carrying out certain therapeutic studies and optimizing its various properties and drug-carrying capacity. In this context, following laboratory research, the necessary protocols must be carefully implemented on the way to clinical studies and industrial-scale production. It is of great importance to confirm the reliability of the sericin by conducting extensive in vivo studies and thus pave the way for its industrialization/commercialization.

It is important to include low-cost and environmentally friendly practices to ensure continuity in industrial production. In this context, recovering valuable raw materials such as sericin from waste and incorporating them into the production process after optimizing their properties and ensuring feasibility provides added value in terms of cost to various industrial areas (Capar & Pilevneli, 2024).

In the statistics of the International Sericulture Commission's data in 2022, it was reported that global silk production was 91,319 metric tons (MT) (https://inserco.org/en/statistics). As can be understood from these data, the huge amounts of sericin waste generated in silk production are recycled in various ways and used in many industrial areas such as health and food, making sericin a significant biomaterial both economically and environmentally as a high-value-added protein polymer (Seo et al., 2023).

Sericin polymer, which is released in large quantities during the degumming phase of the silk production process in the textile industry and is removed as waste, can actually be used as a functional food ingredient in the food industry or in food packaging/coating. The use of plastic in food packaging is not good for health and causes increased environmental pollution as waste material. The production of alternative packaging materials made from environmentally friendly and natural materials is a positive option for the food industry. In this context, sericin, a natural and environmentally friendly protein, is a useful polymer that can be used both in food packaging as a low-cost edible coating and as food (Dhall, 2016, pp. 87−119). A wide variety of biomaterials such as proteins, resins, polysaccharides, and lipids can be used as edible coating materials. However, since these materials are generally expensive, they are not commercially and economically suitable. To make food packaging commercially feasible, safe, and cost-effective, they turned to sericin polymer, which is sustainable, available in large quantities, and industrial waste (Tarangini et al., 2022). This is an example that reveals the cost/benefit balance of the sericin from an industrial perspective. The reuse of this polymer, which is also a textile waste, is an alternative that both reduces the environmental waste burden and contributes to reducing economic costs.

To give another example, sericin's hydrophilic nature, biocompatibility, and cost-effectiveness make it a valuable alternative in developing conventional bone graft materials. Traditionally used bone graphite materials are autografts (from the patient's own body), allografts (from a human donor), xenografts (from a nonhuman species), and synthetic substitutes. These materials may cause morbidity in the donor because they have to be taken from various donors. Additionally, they can be supplied in limited volume quantities. There may be risks of immunogenicity and disease transmission (Kim et al., 2023). It has been reported that the addition of sericin to traditional bone graft materials increases the biocompatibility of graphite and promotes the development of bone cells. While the hydrophilic composition of the sericin ensures cell adhesion and proliferation, its anti-inflammatory, UV-resistant, and antioxidant properties contribute to healthier ossification. There is also research that it can accelerate bone healing by increasing calcium deposition and collagen formation (Kim et al., 2023; Veiga et al., 2020). Both these properties and its naturally abundant availability make sericin a beneficial polymer that is both sustainable and cost-effective.

5. Challenges

There are various challenges that researchers must overcome for biopolymers used in pharmaceutical, textile, biomedical, food, etc. fields. Although they have desirable

properties such as biocompatibility and biodegradability, there are some limitations in the use of biopolymers (Bejenaru et al., 2024).

To increase the functionality and pharmaceutical applicability of biopolymers, the properties of the materials need to be improved. The sustainable use of biomass and polymer-based medical materials depends on the in vivo evaluation of the material's biocompatibility and functionality. The properties of materials examined in the laboratory and clinically will be better investigated. At the same time, polymer formulations developed multidisciplinary will be produced in a scalable manner, their economic feasibility will be established, and their accessibility will be ensured in fields such as biomedical and pharmaceutical (Bejenaru et al., 2024).

Since the natural source of silk proteins is limited, there are various difficulties in the industrial application of silk-based materials. In this context, the suitability of silk materials for these applications should be evaluated first (Bernardes et al., 2024). However, sericin was known as a by-product of the textile industry in silk production, and this protein, which was mixed into aquatic ecosystems from textile wastewater, caused water pollution (Bernardes et al., 2024; Hossain et al., 2021, pp. 447−463). On an industrial scale, obtaining sericin protein without denaturation is challenging. However, the synthesis of sericin-based biomaterial should be carried out after the properties of sericin are well determined in the stages of obtaining sericin from the cocoon by dissolving it using mild extraction methods (Liu et al., 2022). Large-scale production is required for its use in healthcare, but this production must be cost-effective. Although silk sericin protein has been frequently researched in recent years and used in various fields such as bioengineering, it is still in development (Bernardes et al., 2024). The first and most important condition for the use of this protein in health-related areas is that it does not cause immunological response and cytotoxicity (Veiga et al., 2020). Studies have shown that these problems can be overcome when appropriate extraction and purification methods are applied.

Proteins, frequently preferred biopolymers in various fields, can trigger immune responses in the body and may cause allergic reactions when used in biomedical applications or drug delivery systems (Kuten Pella et al., 2022). Many studies on the immunogenicity, allergenicity, and biocompatibility of sericins have reported that this biopolymer is a safe biomaterial for health. It has been stated that this study, which was conducted with mulberry silkworm cocoons and mice, should also be carried out with different silkworm cocoons, other animals, and humans (Liu et al., 2022). Since sericin is among the most used proteins in biomedical applications, DDSs, regenerative medicine, and cosmetics, these difficulties must be overcome and prevented in the areas where this protein will be used. Various purification methods, surface modification techniques, and sterilization practices (heat, irritation, etc.) should be applied to reduce the immunogenic response. However, it should not be ignored that these methods may affect protein structure and properties. To maintain the safety and quality of the product, microbial contamination must be prevented, and at the same time, the functionality of the protein structure must be preserved (Bejenaru et al., 2024). Polymer stability of sericin-based biomaterials is one of the primary features of the material for use in pharmaceutical applications (Feier et al., 2022). Using stabilization techniques such as cross-linking and encapsulation is important in this respect.

The fact that silk sericin was considered textile waste for many years shows that sericin was valued less than silk fibroin. However, the lack of research on the immunogenic properties of sericin has been an obstacle to developing sericin-based biomaterials. Therefore, studies on the structural characterization of sericin, determination of its biological activity, and development processes of sericin-based products are less than those of silk fibroin (Liu et al., 2022).

There is a large amount of random coils in the structure of the sericin, which causes the brittleness of the sericin-based material to increase. In addition, chemical and harsh physical extraction methods can reduce the molecular weight of the peptide and cause damage to the structure of the protein. Sericin-based biomaterials obtained with these methods may also have poor mechanical properties (Lamboni et al., 2015).

Despite its health-beneficial properties, sericin also poses many challenges for the food industry. It may pose a problem for food packaging as it may have poor mechanical properties due to its self-aggregation feature. Additionally, the hydrophilic structure of sericin limits its for use in aqueous environments (Seo et al., 2023). The limited solubility of the powder sericin in solvents and the unpleasant odor of silkworm chrysalises also limit the use of the sericin as a food additive. To avoid these limitations and facilitate its use in foods, some researchers have aimed to increase the emulsifying and antioxidant properties of the sericin by applying Maillard reaction techniques. In addition, there are studies using glycation methods (Seo et al., 2023; Wang & Zhang, 2023).

To overcome the difficulties of mechanical properties, effectiveness, and biosafety in the development of sericin-based biomedical products, it is necessary to first develop extraction methods that will enable sericin to be obtained from silkworm cocoons with minimum degradation and denaturation. Then, the peptide sequences of the sericin must be identified and the conformation of this protein determined. Subsequently, various clinical tests of sericin-based formulations should be performed. The mechanical properties of sericin-based materials should also be thoroughly investigated (Hossain et al., 2021, pp. 447−463; Liu et al., 2022). The biological activity of the sericin should be stabilized and its metabolic pathway and effects on living things should be determined. However, it has been reported that sericin, a natural polymer, is a safe protein with low immunogenicity for biological systems and does not cause an allergic response (Jiao et al., 2017). In this way, the use of sericin biopolymers, whose in vivo safety has been confirmed, will increase in tissue engineering, regenerative medicine, bioengineering, food, and many other fields (Yang et al., 2023).

6. Conclusions and perspectives

In recent years, research on sericin, which is released as a by-product of the silk production process, has increased and obtained great consideration. Several biological, chemical, and physical properties such as antioxidant activity, low immunogenicity, biocompatibility, pH responsiveness, mechanical strength, and the ability to promote cell proliferation enable sericin to take place in various fields such as biomedical, pharmaceutical, and food.

The structural composition of polar hydroxyl, carboxyl, and amino groups of sericin determines its biological properties and increases the mechanical strength of sericin-based biomaterials by enabling its copolymerization, crosslinking, and blending with other polymers. When sericin is combined with different polymers, it is used in various biomedical applications, such as tissue engineering, drug delivery, and wound dressing, in hydrogels, films, sponges, particles, and fibers and in the field of pharmaceuticals. Self-assembling stimuli-responsive polymeric systems are novel approaches in numerous fields such as DDSs regenerative medicine, tissue engineering, disease-specific studies, biosensors, etc., and have shown promising results.

As the components and biological activities of sericin, which is seen as a by-product of the silk production process, were discovered, it became clear that it could have various contributions, especially in the field of health. Sericin, consisting of 18 essential amino acids, is a sustainable protein that can trigger cell adhesion and rapid proliferation of cells. It can be used in the food field as a food additive and packaging material that can be digested/absorbed by the living body and as an advanced biopolymer in the biomedical field as it exhibits biological properties such as biocompatibility, water solubility, and biodegradability. The production of sericin-based materials is a newly developing field, and a lot of research has been done. Its production to overcome the challenges of supplying sericin material as a sustainable biomass source will ensure the accessibility and economic value of this polymer. Ensuring scientific and commercial collaboration will promote the use of biopolymers such as sericin in different biomasses designed for medical applications. In this way, the development and maintenance of promising technologies in the pharmaceutical and biomedical fields will open new horizons, especially in the field of healthcare.

Self-assembling stimuli-responsive polymeric nanosystems are interesting approaches that are frequently used in the therapeutic field, regenerative drugs, DDSs, biosensors, tissue engineering, etc. Features of these systems such as biodegradability, biocompatibility, delivery to the targeted location, and chemical diversity make them preferred in many areas. The self-assembling polymeric systems provide satisfactory results in processes such as regenerative and restorative drugs, wound healing, and anticancer treatment. It can be seen in the literature that studies on these materials continue at an increasing pace.

In conclusion, the recovery of sericin from industrial wastes will not only reduce its impact on environmental pollution but also make valuable contributions to biomaterial research and various medical applications. Increasing research on sericin polymer, which has environmental, health, economic, and social importance, will contribute to more benefits from this sustainable natural protein, which has excellent properties.

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Further reading

Jia, L., Lin, S., Deng, Y., Zou, M., Cai, B., Song, Y., Wang, Z., & Wang, L. (2022). Silk sericin-based materials for biomedical applications. *Biomaterials, 287*, Article 121638. https://doi.org/10.1016/j.biomaterials.2022.121638

Novel developments and scope of nano- and microstructured sericin materials for drug delivery system

10

Ayse Demirbas[1], *Nihan Arabaci*[2], *Nimet Temur*[3], *Cemile Yilmaz*[3] *and Ismail Ocsoy*[3]

[1]Department of Seafood Processing and Technology, Faculty of Fisheries, Recep Tayyip Erdogan University, Rize, Turkey; [2]Department of Biology, Faculty of Arts and Sciences, Cukurova University, Adana, Turkey; [3]Department of Analytical Chemistry, Faculty of Pharmacy, Erciyes University, Kayseri, Turkey

1. Role of nano- and micro-structured materials in drug delivery system

Until recently, simple tablets, pills, capsules, creams, liquids, aerosols, suppositories, injectables, and ointments were frequently used to treat many diseases with traditional and simple spraying methods (Laffleur & Keckeis, 2020). Despite their toxic properties and unwanted side effects, most drugs have been approved and used because they are more beneficial than the potential risk they pose to the organism (Lasala et al., 2020). The undesirable reaction of the organism often increases due to the circulation time of the drug used in the blood and the possibility of penetrating various organs until it reaches the target organ. The biggest disadvantage of traditional spraying methods is the uncertain biodistribution and the inability to control the drug release. At the same time, it should not be ignored that a patient will die as a result of a side effect of cancer treatment (O'Brien et al., 2006). However, another disadvantage of conventional drug delivery methods is the use of higher dosages due to insufficient absorption time of the drugs used. For this reason, the demand for research and applications to increase the safety of pharmacological treatment has increased in recent years. In particular, this area has focused on DDSs, defined as devices or preparations that provide controlled delivery and delivery of drugs to the body (Jain, 2008).

The steps followed in the design and implementation of DDSs can be listed as follows; (1) synthesizing the carrier, (2) immobilizing the drug in the carrier, (3) injecting the drug carrier products into the bloodstream, and (4) providing the release of the active substance at the targeted place, time, and at a certain rate. The biggest advantage of DDSs is directly to the target, to reduce the negative effects on healthy cells and the emergence of side effects. DDSs can generally eliminate or reduce not only toxicity to healthy cells or damage to other organs but also deficiencies such as low drug

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solubility and biocompatibility (Boverhof et al., 2015). The most used area of DDSs is cancer treatments. However, there are studies in the literature that DDSs are also used in the treatment of other diseases.

Recently, micro- and nano-delivery systems designed for anticancer drugs have gained popularity in terms of application. Most synthesized NPs are designed in organic or inorganic structures such as magnetic and metallic particles, hybrid nanoparticles (NPs), quantum dots and micelles, dendrimers and polymers, and liposomes (Hossen et al., 2019). Hydrogels have been shown to be more attractive materials in DDSs compared to other structures due to their ability to be made of polymers and to form three-dimensional networks filled with aqueous media. The most important advantage of hydrogels is their water absorption capacity due to the presence of hydrophilic groups in monomers and crosslinkers used in the synthesis of polymer chains (Hamidi et al., 2008; Peppas & Khare, 1993). Another interesting feature of hydrogels is their extensive change in volumes during phase transformation that occurs in response to a change in environmental factors such as temperature, pH, ionic strength, and concentration of specific ions (Constantin et al., 2020; Karbarz et al., 2017). A small amount of nano hydrogel allows the drug to be easily injected and distributed throughout the body through the bloodstream and enter cells by endocytosis. Until now, a wide variety of polymers have been used to design DDSs. Chief among these are chitosan (Mahmoodzadeh et al., 2019; Rosso & Martinelli, 2020), gelatin (Suraiya et al., 2020), collagen (Ghorbani et al., 2020; Lazurko et al., 2020), polylactic acid (Lu et al., 2020; Pandey & Saha, 2020), polysiloxane (Zhao et al., 2019; Wei et al., 2019), and alginate (Manuja et al., 2020; Singh et al., 2020). Besides these natural polymers, poly (N-isopropyl acrylamide) (Wang et al., 2020; Waleka et al., 2020), poly (acrylic acid) (Kalasin et al., 2020; Mackiewicz et al., 2019), poly (N-vinyl caprolactam) (Cerda-Sumbarda et al., 2020; Xu et al., 2020), polyethylene glycol (Fang et al., 2021; Kaldybekov et al., 2019), polyurethane (Zhang et al., 2019/2019; Quérette et al., 2019) are also used. Despite these studies, the structures designed for micro and nano DDSs are still insufficient to reveal the unique properties of these materials.

Nerve regeneration and functional reconstruction is a multifaceted process that must be understood at the molecular, cellular, and tissue levels. Nanomaterials developed to heal nerve damage speed up neuron regeneration by controlling the ECM environment and cell activity. It is conceivable to construct a physiological environment that can support neurite formation by combining standard microfabrication techniques with nanotechnological tools, building implantable scaffolds, and regulating their surface chemistry (Zhang et al., 2018). A neural scaffold directs axonal growth and increases Schwann cell migration after implantation, allowing healing of peripheral nerve injury. For neural tissue engineering, several polymers are used, and experimental results including human neural stem cell differentiation and neurite outgrowth have been highly successful. Not only do the polymeric structures provide mechanical support for neurite growth and scar tissue inhibition, but they also direct axonal growth, facilitating integration into existing healthy tissue (Willerth & Sakiyama-Elbert, 2007). Polymer scaffolds, hydrogels, NPs, and nerve channels are some of the structures created for nervous tissue engineering. Materials should have

permeability or porosity, infection resistance, high mechanical qualities, and electrical conductivity.

Natural polymers employed in neural tissue engineering include collagen, alginate, chitosan, silk, elastin, and keratin (Boni et al., 2018). Natural polymers are the most studied type of polymer in neural tissue engineering and have been thoroughly explored in a variety of animal models, including primates. Furthermore, collagen is the only biopolymer that has been approved for clinical trials aimed at peripheral nerve regeneration. However, natural polymers' usefulness is hampered by weak mechanical qualities, temperature sensitivity, and processing challenges that frequently need the use of solvents, prompting researchers to combine them with synthetic or electroconductive polymers.

2. Preparation of sericin-based nano and microstructured materials

Several strategies for generating SER-based nano-carriers are reported, most of them are focused on increasing protein unfolding and minimizing hydrophobic interactions between chemical groups in the protein structure. To date, many simplified approaches including desolvation, self-assembly, and salting-out are commonly used for the production of silk-based NPs because they use light processing conditions and are simple to implement (Zhao et al., 2015). In addition, capillary microdot printing, electrospraying, microemulsion, supercritical fluid procedures, and electric fled applications are used in the production of silk-mediated NPs. The most often utilized strategies for SER-based NP production are desolvation, self-assembly, and cross-linking, which are reviewed in the following areas (Zhao et al., 2015; Jain et al., 2018). Because mild conditions are employed, desolvation is the most commonly used approach for creating protein-based NPs. This approach applies a desolvating chemical, such as acetone or ethanol, to a water-based section containing the protein, resulting in protein dehydration and protein coil conformation. Some research employs the double desolvation process to obtain NPs of decreased and thin size (Jahanban-Esfahlan et al., 2016). Furthermore, the amino groups of proteins can be cross-linked, resulting in denser and more stable NPs. The primary disadvantages of this extensively used approach include the use of organic solvent, the use of hazardous cross-linkers such as glutaraldehyde, and the low encapsulation efficiency. (Zhao et al., 2015; Jain et al., 2018; Suktham et al., 2018) employed the desolvation process to create sericin NPs stabilized with pluronic loading resveratrol. The NPs containing resveratrol were not hazardous to normal skin fibroblasts (CRL-2522), but they did impede the development of colorectal adenocarcinoma cells (Caco-2). The internalization of NPs by Caco-2 cells was time-dependent; after 6 h, less than 10% of NPs were uptaken by cells; however, after 24 h, the internalization rate increased to 97%.

The formation of functional complexes by spontaneous organization via self-assembly is mediated by numerous weak noncovalent interactions of tiny building blocks (Mandal & Kundu, 2009). Proteins can form nano-sized masses when dissolved

in an aqueous solution above the critical micelle concentration and critical solution temperature (Tarhini et al., 2017). This approach is widely used in the use of various polymers to harden and stabilize self-assembled micellar NPs by cross-linking the polymer chains (Elzoghby et al., 2015). Mandal and Kundu (Mandal & Kundu, 2009) employed the self-assembly approach to creating sericin NPs mixed with Pluronic (F-127 and F-87) to load either hydrophobic (paclitaxel) or hydrophilic (FITC-inulin) medicines. Furthermore, NPs containing paclitaxel demonstrated increased cytotoxicity to MCF-7 (breast cancer) malignant cells than nonencapsulated medicines while being nontoxic to normal cells. Cell toxicity was caused by the up-regulation of proapoptotic proteins (Bcl-2-associated X-protei-Bax), the down-regulation of antiapoptotic proteins (B-cell lymphoma 2-Bcl-2), and the degradation of the regulatory protein poly (ADP-ribose) polymerase (PARP). Crosslinking methods are another straightforward method for creating protein-based NPs.

Crosslinkers of various types, including chemical, ionic, enzymatic, and thermal, are employed to create protein-based NPs. Glutaraldehyde is the most often utilized crosslinker chemical, and it promotes multifunctional crosslinking into protein networks by joining free amino groups (Elzoghby et al., 2015). However, due to safety concerns, the use of natural crosslinkers has been intensively researched. (Zhao et al., 2015; Jain et al., 2018; Hu et al., 2017) created charge-reversal SER-based NPs using a two-step cross-linking method that involves a physical reaction between sericin and chitosan followed by a chemical EDC crosslinking, with the goal of increasing the cellular uptake of NPs containing the anticancer drug doxorubicin. NPs exhibited pH-responsive charge-reversal properties, for example, becoming negatively charged at neutral pH and positively charged in acidic conditions (pH 6), which subsequently becomes a distinguishing trait for differentiating malignancies and their surroundings. Cellular absorption was sixfold higher in HeLa cells treated at pH 6 compared to those incubated at pH 7.4, and uptake NPs were accumulated into lysosomes and the drug was released into malignant cells' nuclei.

2.1 Sericin-based polymeric materials in drug delivery

With the studies carried out in recent years, new drug forms that can be released in specific regions are being developed. Thanks to the modification of drug release, drugs that can show the desired effects, have reduced side effects, have a longer duration of action, and have a lower cost can be developed (Freitas et al., 2021; Tiwari et al., 2012). In this regard, the use of natural and synthetic polymers is very important in obtaining new drug delivery methods in drug therapy. Polymers can be used in controlled drug release by being modified, thanks to their flexibility feature (Freitas et al., 2021).

Drug delivery systems prepared using polymer matrices have been frequently preferred recently due to the various properties of the macromolecules they contain, such as biodegradability, biocompatibility, and abundance in nature (Vieira et al., 2023). Among the most widely used natural polymers in the field of drug delivery, there are various polysaccharides, especially proteins, gelatin, chitosan, alginate, collagen, cellulose, and its derivatives (Das et al., 2021/2021; Freitas et al., 2021).

Bioconjugation of drugs such as enzymes, peptides, and oligonucleotides with polymers aids the transport of these drugs and decreases the immunological response and stability. These drug−polymer associations, which offer various advantages, also have an important role in the targeting of tumors (Kundu et al., 2008; Vicent & Duncan, 2006). In the DDS sensitive to natural proteins, the processes of delivering the drug directly to the tumor site, providing continuous drug release, and suppressing tumor growth with reduced systemic toxicity are performed (Liu et al., 2021).

Sericin is a natural polymer of choice for bioconjugation with therapeutic proteins, enzymes, and various polysaccharides. It can be conjugated with polymers with the active groups −OH, −COOH, and $-NH_2$ on its surface (Kundu et al., 2008). In addition, its amino acid composition contributes to the amphipathic and acid−base responsiveness of the series, making it valuable for drug delivery (Hu et al., 2017). Due to its biocompatibility, low immunogenicity, oxidation resistance, ability to adhere to cells, and biodegradability, sericin has been used to form hybrid films, scaffolds, nanofibers, sponges, and hydrogels with various polymers (Das et al., 2021; Liu et al., 2016). Sericin is preferred in drug delivery because of its chemical activity, pH sensitivity, bioactivity, convenience in the production of conjugated molecules, hydrogels, nano and microparticles, and increasing the activity of drugs (Lamboni et al., 2015). Conjugates consisting of sericin and polymers, which increase the stability of drugs and decrease the immunogenicity, are very important DDSs (Mandal & Kundu, 2009).

Pure sericin can be crosslinked, copolymerized, or mixed with other macromolecules to become a membrane (Wu & Wang, 2010). To form stable sericin structures, hydrogels are formed by combining sericin, usually with some polymers such as alginate, chitosan, collagen, gelatin, and poly (vinyl alcohol) (PVA), polyethylene glycol (PEG), polyethylene oxide (PEO), and hydroxymethyl propyl cellulose (HPMC) (Freitas et al., 2021; Mandal & Kundu, 2009). Injectable sericin-based hydrogels are localized drug delivery tools that can reach higher therapeutic drug concentrations by controlling drug release at cancer sites, controlling the drug release rate, and minimizing the risk of infection (Liu et al., 2016; Li et al., 2012). As reported by Freitas et al. (2021), release forms were produced by incorporating naproxen molecules into a mixture of sericin and alginate as the polymer matrix. BSA was used as a model drug added to sericin-poly (methacrylic acid) hydrogel, which is porous and flexible and has the ability to swell and decrease swelling due to its sensitivity to pH changes (Freitas et al., 2021). It has been observed that the permeability rate of BSA in this form varies under gastric and intestinal pH conditions (Lamboni et al., 2015).

Alginate, a natural polysaccharide polymer produced by brown algae, is preferred in many biomedical applications, especially drug delivery, due to its biocompatibility and biodegradability properties (Zhang et al., 2015; Kanpipit et al., 2022) designed a hydrogel consisting of sericin-alginate containing anthocyanin. They loaded anthocyanin into the hydrogel with ionic interactions and evaluated anthocyanin in terms of its antiinflammatory properties. As a result of the study, they determined that anthocyanin could be released continuously for 8−12 h. In addition, in various studies, a sericin−alginate mixture was prepared for drugs such as naproxen, ibuprofen, diclofenac sodium, aceclofenac, ketoprofen, and furosemide (Santinon et al., 2021). In another study, significant tumor cell death and apoptotic cells in tumor tissues were obtained

as a result of treatment with tumor growth suppressor doxorubicin (DOX) loaded on sericin-dextran hydrogels. This result was thought to be due to the continued release of DOX loaded into the sericin-dextran hydrogel. This injectable hydrogel provides an effective drug delivery for site-specific cancer therapy (Liu et al., 2016).

Research by Santinon et al. (2021) included the drug valsartan in the sericin-alginate-based matrix to maintain the concentration of the drug and reduce the possibility of side effects when given to the patient. In this study, in which they aimed to prolong the in vitro release time of the drug, they obtained very efficient results even 90 and 180 days after the stability of the drug. The half-life of the drug is 6 h, indicating that the drug is suitable for the modified release form (Santinon et al., 2021; Sokar et al., 2015). Vieira et al. (2023) developed a natural and multiparticle polymer, kappa-carrageenan (k-Car), and sericin carrier for the encapsulation of indomethacin (IND), a nonsteroidal antiinflammatory drug. In this way, they aimed to minimize the gastrointestinal effects caused by the immediate release of the drug (Vieira et al., 2023). Kappa-carrageenan is a highly suitable polymer for enteral administration, as it is degraded to a limited extent in simulated gastric juice (Capron et al., 1996). In addition, when mixed with a polymer such as sericin, its mechanical strength increases. According to the findings, Vieira et al. (2023) obtained from the study, it was seen that k-carrageenan/sericin provides a long-term release for the drug they carry and has the potential to carry antiinflammatory due to its gastro-resistant nature (Vieira et al., 2023).

2.2 Sericin-based metallic materials in drug delivery

Nanostructures are widely used for controlled drug release because they provide materials with physical and chemical properties such as high surface area, permeability, dispersion, and retention. Since NPs can cause inflammation and toxicity due to their stability and dispersibility in the physiological environment, they must be modified and coated with substances that will ensure their stability (Di Zhang et al., 2020; Liu et al., 2022). For this purpose, sericin is preferred in the production of nanomaterials due to its properties such as amphiphilicity, pH sensitivity, biodegradability, and good biocompatibility (Liu et al., 2022).

Since most anticancer drugs are not tumor-targeted, they cause nonspecific cell death. However, multifunctional metallic NPs have taken their place in drug delivery as therapeutic DDSs (Desai et al., 2021). Metallic NPs can detect tumor sites through active or passive targeting and deliver drugs to the target tumor mass. In this way, drug accumulation in healthy tissues is reduced (Ahmad et al., 2010; Desai et al., 2021). The accumulation of NPs in the desired region is very valuable in diagnosis, drug delivery, and treatment (Tran et al., 2020).

Bio-based NP synthesis using microorganisms, plant structures, various extracts, etc., has an important place in biomedical applications because it is environmentally friendly and economical compared to physical and chemical synthesis (Das et al., 2023). Especially, metallic NPs such as gold, silver, and iron oxide are frequently used for biomedical applications (e.g., drug delivery) (Tran et al., 2020). Gold NPs (AuNPs) are bioconjugated with proteins, drugs, antibodies, and fluorescent dyes

without the use of thiol-based stabilizers and can be used in a variety of biological applications (Alex & Tiwari, 2015; Shin et al., 2022). AuNPs synthesized through green synthesis, in which natural polymers are used as reducing and capping agents, are used in various fields such as cancer therapy, drug delivery, tissue engineering, and antibacterial applications (Das et al., 2023).

Chemotherapy in metastatic lung cancer is an important application to control symptoms and prolong patient survival (Waqar & Morgensztern, 2017). However, the lack of targeting and nonspecificity of anticancer drugs used in chemotherapy cause ineffective drug accumulation in the tumor region and distribution of drugs in normal organs, resulting in toxic side effects (Burris, 2009; Liu et al., 2021). In the study of Liu et al. (2021), TA-Fe^{3+}-based metal-organic networks (MONs) and sericin microparticles were prepared for the treatment of lung metastatic cancer (Liu et al., 2021). They obtained DOX@SMPs-MON structures by loading the doxorubicin (DOX) drug into these structures, and when administered to tumor-bearing mice, they found that the lung metastasis nodule size was reduced on the fifth day and the functions of other organs of the animal model were not damaged. Oh et al. (2007) prepared sericin beads after dissolving the sericin in the LiCl/DMSO solvent system and used these structures as drug carriers (Oh et al., 2007). They applied the diclofenac drug to the sericin-based beads they prepared and investigated the release profile. Diclofenac is a nonsteroidal and antiinflammatory drug that causes gastrointestinal complaints. Therefore, the release of this drug in the stomach should be suppressed.

2.3 Sericin-based metal oxide materials in drug delivery

Sericin, one of the silk proteins, is known to contain various amino acids and functional groups. It can be used in areas such as food packaging and cosmetics with its nature, cheap, and strong mechanical properties. Sericin, which is released as an unused product in the textile industry, is used in these applications and provides transformation. For instance, they can be preferred in cosmetics as they have UV and oxidation resistance and antibacterial properties (Aramwit et al., 2012). In addition, they are also widely used in biomedical applications due to their unique biocompatibility and different chemical and biological properties. It can be easily used in drug targeting by binding with molecules with the amphiphilic groups it contains. The effects of active compounds used to provide bioactivity and release control in DDSs are very important (Jia et al., 2013). Here, sericin with polar and nonpolar side chains is abundantly efficient in binding to drug molecules (Nishida et al., 2011). Sericin used in DDSs can be loaded into hydrogels, fibers, metals, and particles depending on the treatment and method (Mandal & Kundu, 2009; Nayak et al., 2014; Wu & Wang, 2010).

Especially, sericin is implanted in metal NPs, which have an important place in drug delivery (Florczak et al., 2020). NPs are unstable in the biological environment and tend to aggregate. Fortunately, they are very suitable for surface modification and the stabilization of NPs increases with the groups such as dihydroxy and amine contained in the series. Thus, the metallic properties of NPs combined with the biological and chemical properties of sericin are widely used as a biomaterial in tissue

engineering and drug release (Yang et al., 2023). As an example of the work done by Zhang et al., in order to minimize toxicity due to doxorubicin (DOX) in cardiomyocytes, biocompatible silk sericin nanobiocomposites were developed with iron NPs. The cardiocyte of the synthesized new-generation iron NP-sericin structures was less toxic than the free DOX structure. Here, the toxicity rate has been reduced by taking advantage of the biocompatibility of the series. They also examined the acoustic properties of the magnetic−serine hybrids obtained and explained that they can be used as ultrasound contrast agents in further studies of their activity. In addition, due to their biocompatibility and targeted properties, inexpensive agents that can be synthesized easily and quickly, which are also used in methods such as optical imaging and MRI, have been obtained (Zhang et al., 2021).

Another metal oxide modified with sericin study was done by Kara et al. They aimed to develop siRNA delivery systems based on superparamagnetic iron oxide NPs. In order to overcome the undesirable properties of magnetic NPs, which have toxicological effects, biocompatible sericin coatings have been preferred. In addition, negatively charged magnetic NPs coated with sericin gained function by being coated with a positive charge, and loading of negatively charged siRNAs was ensured. Using the biocompatibility and amphiphilic properties of sericin, Kara et al. demonstrated the use of sericin-coated superparamagnetic iron oxide NPs as siRNA carriers (Kara et al., 2021). Different studies of metal oxide sericin for the target of siRNAs were done by Shirangi et al. In this study, surface functionalization was performed with sericin by synthesizing superparamagnetic NPs, which are of great importance in nanomedicine. The synthesized NPs were targeted to cause cancer cells to undergo apoptosis by removing the ROR1 gene in breast cancer. Sericin magnetic NPs were loaded with siRNA to eliminate the ROR1 gene. To eliminate the ROR1 gene, sericin magnetic NPs were loaded with siRNA. After the obtained functional NPs were treated with cancer cells, a decrease in cancer cells was observed. Cancer cells were monitored by magnetic NPs, and it was determined that the tumor decreased. As a result, the suitability of sericin, which are biocompatible and suitable for modification with their functional groups, and magnetic NPs, for use as therapeutic agents have been explained, and it has been reported that they can be used in biomedical applications in the future (Shirangi et al., 2022).

A contrast material study with sericin-based metal oxide NPs was done by Huang et al. In this study, tumor targeting was carried out with the pH sensitivity of sericin-gadolinium NPs. The obtained NPs showed that they have cell compatibility and prevent hemolysis and inflammation (Huang et al., 2021). Ai et al. reported a remarkable study in which they developed sericin-based wound dressing agents. By reinforcing the sericin structure with PVA, they pushed cotreatment to impart antimicrobial properties to ZnO NPs. The obtained sericin-modified ZnO NPs were determined to have high stability, which was characterized by various characterization methods. Mechanical tests of the NPs confirmed their improved performance characteristics. Antimicrobial activities of the obtained NPs against *S. aureus* and *E. coli* have been proven (Ai et al., 2019).

In studies, sericin-based metal oxide NPs exhibited unique biocompatibility properties, and sericin-functionalized materials have been used efficiently in drug delivery

and contrast agents. Sericin, which is released as a by-product, provides an appropriate cost advantage. It is very suitable for use in nanomaterials with 18 kinds of amino acids it contains. It is promising in biomedical applications with its biocompatibility, biodegradability, and water solubility.

2.4 Sericin-based carbon materials in drug delivery

Silk, with its exceptional mechanical properties and suitability for biomedical applications, has long attracted the interest of researchers in textile and biomedical fields. Regenerated silk fibroin (SF) fibers are commonly used in biomaterials such as tissue scaffolds and DDSs. However, due to their lower β-sheet content, they have lower mechanical properties and thus lower mechanical strength. To improve the mechanical properties, researchers have explored the use of reinforcing agents such as carbon nanotubes (CNTs). In a study conducted by Wei et al., silk fibers containing multiwalled CNTs (MWNTs) were produced using the electrospinning method, and it was demonstrated that the mechanical properties of the resulting nanofibers varied depending on the number of MWNTs incorporated (Wei et al., 2011). Similarly, SF is a natural protein polymer used in biomedical applications such as drug delivery, and its properties are enhanced by blending with hydrophilic polymers. Cheerarot and colleagues prepared biodegradable microparticles from the first SF/CS (SF /chitosan) blend using the water-in-oil emulsion solvent diffusion method and examined the morphological and physicochemical properties of these particles (Cheerarot & Baimark, 2015).

Sericin is a natural protein obtained from silkworm cocoons and has been extensively studied and utilized in the biomedical field. Sericin exhibits biologically compatible and naturally adhesive properties to cells, which enhance cell attachment, proliferation, and differentiation in sericin-based materials. Additionally, the diverse amino acid composition of sericin allows it to form a cross-linkable and chemically modifiable protein matrix, making it a versatile material for biomedical applications. Recently, sericin has been transformed into various biocompatible materials for tissue engineering and regenerative medicine (Liu et al., 2022). The obtained biomaterials have the ability to modify the drug release model and can be used in the formulation of sustained, controlled, pH-triggered, and targeted DDSs. Thanks to these features, degradation and release of the drug during the transit process can be prevented before reaching a specific region (Parashar & Pathak, 2023). Sericin-based nanomaterials have attracted attention due to their biological properties, including antibacterial, antiinflammatory, and antioxidant effects. The physicochemical characterization, biological properties, and therapeutic potential of sericin-based nanomaterials support their effective use in medical applications (Dhilip Kumar & Abrahamse, 2022). Sericin NPs are also successfully used in the delivery of various drugs. One of the studies showed that these NPs inhibit the formation of colorectal adenocarcinoma while exhibiting a nontoxic effect on skin fibroblast cells. These findings highlight the significant potential of sericin NPs as a biologically suitable carrier (Parashar & Pathak, 2023).

Biomass-derived carbon materials have attracted significant attention due to their low cost, lightweight nature, and moderate electrical conductivity. Furthermore, the porous nature of biomass-derived carbon promotes multiple reflections of microwaves, increasing microwave absorption. These properties have been found to contribute to impedance-matching performance and improvement of electron transport capabilities in biomass-derived carbon/reduced graphene oxide (rGO) hybrids (Deng et al., 2022).

Sericin, with its content of C, O, and N elements, enables the preparation of N and O-doped carbon materials using it as a clean precursor free from other additives (Li et al., 2021). The sericin-based carbon material is a carbon material obtained through the carbonization of sericin protein. These materials can enhance drug efficacy and reduce side effects by delivering drugs to targeted areas. The high surface area and porosity of sericin-based carbon materials can increase drug-loading capacity (Dhilip Kumar & Abrahamse, 2022; Hong et al., 2020). Sericin-based carbon materials maintain their biodegradable and biocompatible properties while showcasing the unique characteristics of carbon. They have the ability to enhance drug efficacy and reduce side effects by delivering drugs to targeted regions. As a result, sericin-based carbon materials hold great potential for future applications in drug delivery (Parashar & Pathak, 2023). Sericin is a preferred material for nerve repair due to its biological compatibility and biodegradability. In studies, by combining sericin with silicone and using drug-loading methods, a clobetasol-loaded sericin tube successfully repaired nerve defects in rats. Additionally, CNTs were added to the tube to provide electrical conductivity, resulting in more effective recovery of nerve structure and functions (Lin et al., 2022).

Lin et al. have created a flexible network by combining sericin-modified CNTs with carboxylated styrene-butadiene rubber (XSBR). This flexible structure can be utilized as a versatile sensor capable of detecting subtle deformations and temperature variations. These wearable devices offer an easy approach to monitoring human health and motion (Lin et al., 2022). In the study conducted by Li et al., silkworm hemolymph was exposed to high doses of cadmium telluride quantum dots (CdTeQDs), citric acid-nitrogen doped dots (C-NCDs), and silicon NPs (SiNPs). The immune responses and programmed cell death induced in hemocytes by different nanomaterials were compared. The results showed that hemocytes in the hemolymph took up these three different nanomaterials through endocytosis, and their toxicities differed significantly. Specifically, C-NCDs induced autophagy in the hemocytes (Li et al., 2017).

Chuang et al. utilized industrial wastewater as a precursor to produce silk-based carbon nanolayers (SCN) through the hydrothermal carbonization method. The study demonstrates the suitability of nano-sized fluorescent carbon NPs based on the silk series, which consists of water-soluble proteins, for cage imaging and especially stem cell imaging. These NPs are obtained through the process of carbonization and dehydration of the protein, resulting in a strong fluorescent property and a unique carbon framework. Additionally, it has been observed that these carbon-based NPs exhibit low toxicity and are applicable for effective stem cell labeling and stem cell imaging for tissue regeneration (Chuang et al., 2018). Wang et al. revealed that converting silk spreaders to carbon aerogels offers an economical and environmentally friendly solution to environmental pollution problems. Carbon aerogels with high surface area have

the potential to be used as carriers for drugs and play an active role in drug release. In addition, sericin-derived carbon aerogels are an effective solution for the removal of pollutants such as antibiotics, organic dyes, and heavy metal ions, demonstrating that they are a versatile material not only for environmental problems but also for drug development (Wang et al., 2022).

3. Conclusion

Sericin known as a natural protein obtained from silkworm cocoons has been extensively and actively used in the development of nano- and micro-structures especially for DDSs. Sericin-based NPs or sericin-conjugated NPs have been designed as drug delivery tools with various stimuli-responsive systems like pH, temperature, and light stimuli. Recently, sericin has been also integrated into various biocompatible materials for tissue engineering and regenerative medicine. Sericin-based NPs have shown unique biological properties including antibacterial, antiinflammatory, and antioxidant effects, which make them used in a variety of biomedical applications.

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Applications of sericin hybrid materials in wound healing

11

Tejas Nikam, Sakshi Y. Mastoli, Vijay Kumar Boga, Bhargavi Sreepathi, Shashi Kashyap and Shubhini A. Saraf
Department of Pharmaceutics, National Institute of Pharmaceutical Education and Research, Lucknow, Uttar Pradesh, India

1. Introduction

Sericulture is the oldest form of cottage industry. Silk obtained from the silkworm *Bombyx mori* belonging to the Bombycidae family is used commercially (Parashar et al., 2020). Silk fibers belonging to the silkworms of Lasiocampidae and Saturniidae families are limited due to their extraction conditions (Das et al., 2021; The International Sericulture Commission released data, 2022) that revealed 91,221 MT of global silk production. India is the second highest producer of silk worldwide, producing 36,582 MT of silk in 2022, followed by China, which produced 50,000 MT of silk in 2022 (International Sericulture Commission, 2022).

The silk fiber comprises two principal proteins—hydrophobic fibroin and hydrophilic sericin (Seo et al., 2023). The silk fiber is a double-stranded fibroin bond by the adhesive sericin protein (Padamwar & Pawar, 2004). The percentage of fibroin present is about 70%−80% and that of sericin is 20%−30%, including inorganic matter, waxes, pigments, and other materials (Silva et al., 2022). Since sericin is a macromolecular, hydrophilic protein, it is chemically made of polar hydroxyl, carboxyl, and many amino acid groups (Arango et al., 2021; Das et al., 2021). Serine (32%), aspartic acid (16.8%), glycine (8.8%), and 16 other essential amino acids are seen in high concentration in sericin (Ahsan et al., 2018; Arango et al., 2021; Das, 2022). Of all the amino acids present, 70% are hydrophilic, making them partially water soluble and thus absorbing water in large quantities. Sericin, being hydrophilic, requires a substrate to make it rigid; it is incorporated with various natural or synthetic polymers. These amino acids are helpful in various sericin applications (Arango et al., 2021; Seo et al., 2023).

The total weight of serine in the cocoon is about 20%−30%. Sericin is amorphous and randomly coiled, which quickly modifies to β-sheet structures due to continuous moisture uptake. As the temperature lowers, the random coils of sericin in the solution are modified into β-sheets, reducing aqueous solubility. These modifications give gel formation without changing its chemical properties; a reversible sol-to-gel transition can be seen (Arango et al., 2021). The molecular weight of sericin depends on its extraction process and ranges from 20 to 400 kDa (Padamwar & Pawar, 2004; Silva et al., 2022). Depending on the molecular weight and aqueous solubility, sericin is

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categorized into three classes: Sericin A is the outermost layer with a random coil structure and is water soluble at 60°C. Sericin B is the mid-layer, having its filaments in a cross-direction to fiber, and is water soluble at 60°C. Neighboring the fibroin filament, the innermost layer, sericin C is unable to solubilize in water at high temperatures (Ahsan et al., 2018; Arango et al., 2021; Kunz et al., 2016).

Sericin is a protein-based byproduct that is obtained during the production of silk textiles. It is usually discarded, leading to resource waste and environmental pollution. To overcome this problem, researchers are interested in recovering sericin from the waste, as sericin, when hybridized with different polymers, can be consolidated in various nanoparticles, hydrogels, films, scaffolds, and microneedles. Sericin is a versatile protein with antibacterial, anticancer, and anticoagulant properties, antioxidant activity, moisturizing and healing properties, and antimicrobial protection against ultraviolet radiations and antiapoptotic activity (Mathew et al., 2024). Sericin is helpful in wound healing as it is biodegradable and biocompatible (Suryawanshi et al., 2020; Tao, Cai, et al., 2019). Because of these properties, they are preferred in biomedical applications, like in drug delivery systems, wound dressing, tissue engineering, and the cosmetic industry (Ahsan et al., 2018; Kunz et al., 2016; Seo et al., 2023; Silva et al., 2022). In order to obtain sericin from cocoons, the cocoons were initially cut into smaller sections measuring approximately 5 mm^2 (Hossain et al., 2023). Degumming is performed to extract the sericin from *B. mori* cocoons. There are different ways of degumming processes. They are conventional, chemical, enzymatic, and heat treatment methods (Manjubala et al., 2020), as shown in Fig. 11.1.

From Fig. 11.2, it is evident that researchers are increasingly interested in using sericin as a therapeutic material, particularly in wound healing. The number of publications and patents has substantially increased in the past 5 years.

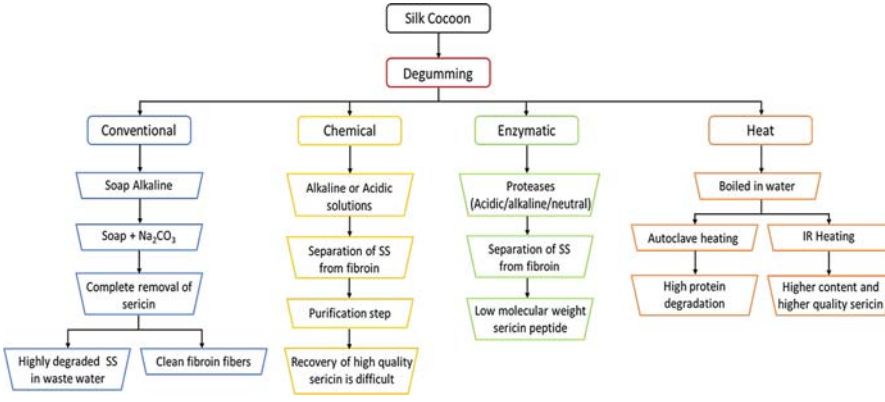


Figure 11.1 Degumming processes of silk sericin from silk cocoon.

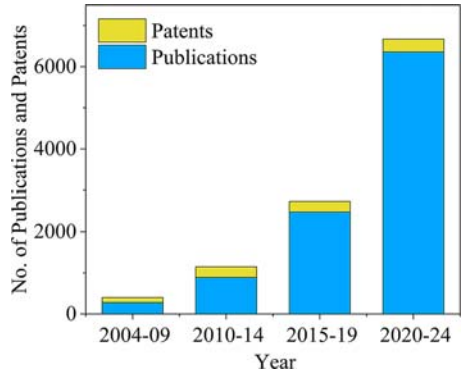


Figure 11.2 Graphical representation of publications and patents relating to sericin-based hybrid materials from the last 20 years.

2. Biological properties of sericin

Silk, a natural protein, is essential in developing various biomedical materials because of its biocompatibility and mechanical and chemical properties. The silk sericin, a byproduct of silk, has many biological properties (Jung et al., 2021).

2.1 Antioxidant and antityrosinase activity

Low levels of reactive oxygen species (ROS) and oxidative stress regulate the process of normal wound healing. In contrast, an elevated level of ROS can lead to oxidative stress, hindering the wound healing. Sericin's antioxidant property is beneficial in regulating oxidative stress, thereby enhancing wound healing. The antioxidant and antityrosinase activity of sericin was first reported by Kato et al. to estimate its antioxidant activity; lipid peroxidation was evaluated by assessing the thiobarbituric acid reactive substances (TBARSs). In experimentation by Kato et al., it was found that 40% hydroxyl amino acids (serine and threonine) can trace elements like iron and copper, and free electrons lead to a reaction with free radicals. Apart from that, whether the sulfur-containing amino acid is deficient in sericin, sulfhydryl of sericin can also show antioxidant activity. It was also found that sericin inhibits tyrosinase activity. It was reported that 0.5%−1.0% sericin could inhibit tyrosinase activity (Kato et al., 1998). Kurioka et al. reported that sericin layers of cocoons of *B. mori* contain flavonoids and carotenoid pigments, which show antioxidant and antityrosinase properties (Kurioka & Yamazaki, 2002). Manosroi et al. conducted a study on sericin and found that mild extraction processes such as basic hydrolysis and cold process result in a sericin extract that exhibits significant free radical scavenging activity and the highest tyrosinase inhibition activity (Manosroi et al., 2010). Meanwhile, Dash et al. reported that the non-mulberry tropical tasar silkworm, *A. mylitta*, has more antioxidant activity than the mulberry silkworm, *B. mori*, against hydrogen peroxide−induced oxidative-

stressed skin fibroblast cell line (Dash, Acharya, et al., 2008a, Dash, Mandal, et al., 2008b). Finally, Takechi et al. experimented with different methods, such as DPPH, ORAC, chemiluminescence, and ESR to study the antioxidant properties of sericin. They found that silk sericin protein obtained from mulberry silkworms exhibits suitable antioxidant activity (Tayori et al., 2014). Mumtaz S et al. investigated the D-galactose-induced mice model where sericin is capable of reducing the oxidative stress level in aged mice as well as restoring the immune system and promoting the antioxidant potential (Mumtaz et al., 2023).

2.2 Antibacterial

The antibacterial property of sericin is dependent on the functionality of proteins found in sericin like-protease inhibitors, and seroins, where seroins showed antimicrobial properties, and this protein shows greater abundance in the sericin layer than the fibroin layer (Dong et al., 2023). Studies found that bacterial biofilm formed on acute wounds, so biofilm targeting is required to inhibit the morbidity and mortality related to wound infection (Patenall et al., 2023). Sericin-based nanoparticles (SNPs), obtained from different molar masses (10−300 kDa), show antimicrobial properties against Gram-positive and Gram-negative bacteria. However, the antibacterial property of the SNPs with a positive surface charge by coating the SNPs with poly-L-lysine shows more antibacterial activity against Gram-positive bacterial owing to the electrostatic interaction of SNPs with negatively charged bacterial cells leads to disruption of the bacterial cell wall and enhances the ROS production inside the bacterial cell. It was evaluated that the antibacterial property also depended upon the degumming methods, which showed a higher density of sericin protein and higher antibacterial activity (Dutta et al., 2020). Senakoon et al. demonstrated in a study that *Samia ricini* sericin showed a higher antibacterial capacity than *B. mori* sericin, and only *Samia ricini* showed inhibitory activity against *S. aureus* (Senakoon et al., 2009).

2.3 Immunological response and biocompatibility

Gil et al. found that sericin shows inertness or does not lead to the activation of macrophages (Gil et al., 2013). Interestingly, in vitro and in vivo studies show the biocompatibility of silk sericin in comparison to silk fibroin. The immunological inertness makes silk sericin applicable to biomedical devices. Researchers have found the immunological inertness of sericin in the culture of murine macrophage cells. On the other hand, it was also found that fibroin protein can be involved in the release of TNF-α. So, if sericin covers the fibroin fibers, it is sufficient to show minimal immune response (Fu et al., 2022; Panilaitis et al., 2003). Chlapanidas et al. reported that sericin protein obtained from different silkworm strains shows some beneficial biological activity compared to other strains. In vitro studies revealed that few strains of silkworms release sericin, which has antiinflammatory properties, and some do not have antiinflammatory properties (Chlapanidas

et al., 2013). Yong et al. used sericin for increasing bone function. Sericin is a naturally found protein, which is not only safe but also has less denaturation and is biocompatible, which can be used in bone dysfunction. This drink can be a health supplement with sericin as its active ingredient, which improves the bone function by eliminating the invasive methods of administering therapeutic agents to the patients (Composition for Improving Bone Function Comprising Sericin and Use Thereof, 2024).

2.4 Photoprotective activity

The antiapoptotic effect of sericin was evaluated by Dash et al., and they reported that induction of intracellular hydrogen peroxide on UVB-treated keratinocytes was suppressed in the pretreatment of the mouse skin model with sericin (Dash, Acharya, et al., 2008a, Dash, Mandal, et al., 2008b). Kumar et al. reported that *Philosamia ricini* sericin and *Antheraea assamensis* sericin treatment promotes the cell viability of keratinocytes before exposure to UVA and UVB radiation to the skin via suppressing the IL-6 and IL-8 (Kumar et al., 2018).

2.5 Wound healing

Native sericin shows excellent stability, mechanical properties, and biological properties that are not compromised due to harsh processing. Li et al. demonstrated that fibroin-deficient mutant silkworm produces the native sericin by controlling the spinning behavior, showing good wound healing properties due to good biocompatibility and cell viability because no toxic solvent is involved during the extraction process (Li, Wu, et al., 2023). In wound healing, sericin-based hydrogel has shown greater efficacy; the antibacterial activity of sericin against *E. coli*, a Gram-negative bacterium, depends on the concentration of sericin and the elevation of the fibroblast cell proliferation and migration and formation of granulocyte tissue (Xue et al., 2016). Silk sericin−based hydrogel shows an essential role in wound healing because degummed sericin contains about 30% serine, and the presence of amino acid−containing hydroxyl groups leads to the absorption of water molecules, which will provide natural moisturization properties to the skin. On studies, it was also found that silk sericin elevates the fibroblast proliferation and collagen production (Bhowmick et al., 2016). Studies demonstrated that silk sericin−based hydrogel shows significant wound contraction, and wound healing takes about 11 days. On the other hand, when sericin-based hydrogel combined with the beneficial plant extracts and silver nanoparticles will further expedite acute wound healing by reducing the serum level of proinflammatory cytokines (IL-6) and promoting the IL-10, antiinflammatory cytokines, and antioxidant activity (Munir et al., 2023). Aramwit et al. estimated the significant curative or wound repair role of sericin-coated thin polymeric films fabricated from silk fibroin on psoriatic skin, lessening keratinocyte proliferation via downregulating the IL-17 (Aramwit et al., 2023).

3. Method of preparation for sericin-based hybrid materials

Various methods are investigated for describing the preparation of sericin-based hybrid materials, such as self-assembly, desolvation, crosslinking, and salting out have been summarized in Table 11.1. This sericin-based hybrid material predominantly involves nanocarriers, gels, films, scaffolds, and microneedles (Yang et al., 2023).

3.1 Sericin–nanocarriers hybrid formulations

The sericin-based nanocarrier is principally based on improving the protein unfolding by reducing the hydrophobic nature of the protein. Many technologies are also used to synthesize sericin-mediated nanoparticles, like electrospraying, supercritical fluid technologies, capillary microdot technique, etc., (Das et al., 2021; Yang et al., 2023). The desolvation method is commonly used to develop protein-based nanoparticles. This method involves the developed dehydration of protein when stirring the aqueous solution of protein by introducing acetone or alcohol as a desolvating agent that further leads to a modification in the conformation of protein structure from stretched to twisted (Elzoghby et al., 2015). Besides this, to stabilize sericin-based nanoparticles, they get crosslinked by adding cross-linking agents such as 2% v/v glutaraldehyde. Sericin contains an amino group that helps to increase density and stability by undergoing cross-linking (Das et al., 2014). As a crosslinker, glutaraldehyde possesses disadvantages like toxicity and low entrapment efficacy. So, it can be reduced by using a nontoxic crosslinker. For example, Kanoujia et al. developed novel genipin–sericin hybrid nanoparticles by desolvation method followed by crosslinking that can carry atorvastatin. This sericin-based nanoparticle has reduced particle size and increased the entrapment efficacy of atorvastatin with sustained release. Due to this, atorvastatin in nanoparticles significantly increased therapeutic efficacy. Also, cellular uptake studies of nanoparticles propose an interaction between the anionic charge of nanoparticles and cell surface, suggesting a reduction in systemic toxicity (Kanoujia et al., 2016). Furthermore, Hu et al. prepared sericin-based nanoparticles for doxorubicin delivery by reversing the surface charge with pH interference. This is achieved by crosslinking with chitosan, which enhances the cellular uptake (Hu et al., 2017). Recently, Das et al. utilized a waste sericin solution to develop biosynthesize gold nanoparticles. This sericin was used as a reducing and capping agent (Das et al., 2023).

3.2 Sericin nanocarrier–based hydrogels

Nowadays, several natural, semisynthetic, and synthetic polymers enhance wound healing performance by fabricating the wound dressing. Among them, hydrogel is primarily used for wound dressing (Punyamoonwongsa et al., 2019). Hydrogel is a three-dimensional structure due to polymer cross-linking in an aqueous environment. It can

Table 11.1 A summary of the investigation on a sericin-based hybrid system.

Hybrid material	Therapeutic agent	Method of preparation	Model	Findings and outcome
Nanocarrier				
Sericin−chitosan	Doxorubicin	Double crosslinking method	In vitro cytotoxicity	Double crosslinking provides stable nanoparticles with pH-triggered doxorubicin release, enhancing cellular uptake.(Hu et al., 2017)
Sericin−silver nanoparticles	−	In situ green synthesis	In vitro cytotoxicity	An antibacterial activity assay revealed inhibition of growth of *S. aureus*, the minimum concentration is 25 mg/L, and 100 mg/L for complete inhibition (He et al., 2017).
Sericin−propolis	Amoxicillin	−	In vivo study	In the initial 2 h, the study showed a decrease in bacterial growth, and complete inhibition was observed after 4 h incubation (Diab et al., 2022).
Sericin−poly(ethyl cyanoacrylate)	Fenofibrate	Interfacial polymerization	In vivo	Prepared sericin/ poly(ethylcyanoacrylate) nanospheres helps to enhance therapeutic efficacy which reduces the cholesterol and harmful lipoprotein levels (Parisi et al., 2015).

Continued

Table 11.1 A summary of the investigation on a sericin-based hybrid system.—cont'd

Hybrid material	Therapeutic agent	Method of preparation	Model	Findings and outcome
Sericin−keratin in gelatin	−	Chemical crosslinking method	In vitro	Human mesenchymal stem cells are used for in vitro study. It shows an increase in cell proliferation, suggesting synergistic effect combined with sericin and keratin (Vineis et al., 2021).
Sericin poly(γ-benzyl-L-glutamate)	Doxorubicin	Self-assembly method	In vivo study	Prepared hybrid micelles show efficient drug loading and pH-dependent controlled release of doxorubicin (Guo et al., 2018).
Sericin coating of poly-L-lysine	Fluorescent silk protein	Desolvation method	In vitro cytotoxicity study	DNA possesses an anionic charge. So, modification to cation due to the coating of poly-L-lysine leads to improved DNA binding with a dense arrangement of plasmid DNA (Das et al., 2014).

Sericin-gellan gum-rice bran albumin	Doxorubicin	Self-assembly method	In vitro	The clonogenic assay showed doxorubicin ability, which reduced tumor cell survival rate from 56% to 42% after encapsulation into a hybrid nanocomposite (Arjama et al., 2018).
Hydrogel				
Sericin−poly (vinyl alcohol)	Azithromycin	Crosslinking and repetitive freezing-thawing method	In vivo experiment	An in vivo study revealed prepared hydrogel has a better effect than commercial Tegaderm™ by reducing systemic burn (Bakadia et al., 2023).
Gellen gum−sericin-containing halloysite@-polydopamine	–	Co-blending techniques	In vivo	PDA-encapsulated halloysite nanotubes enhanced mechanical strength of sericin hydrogel and also, have good impact on hemostatic effect (Yuan et al., 2023).
Sericin−poly (vinyl alcohol)−NaCMC	Curcumin, banana peel	Repetitive freezing-thawing method	In vivo	Hydrogel showed a remarkable increase in wound recovery percentage and antiinflammatory cytokinin (Munir et al., 2023).

Continued

Table 11.1 A summary of the investigation on a sericin-based hybrid system.—cont'd

Hybrid material	Therapeutic agent	Method of preparation	Model	Findings and outcome
Semi-IPN silk sericin and poly(NIPAm-LMSH)	–	Crosslinking method	In vivo	83% recovery from wounds in the first week and almost recovered in 13 days due to its antibacterial activity (Yang et al., 2017).
Chitosan-Ag^{+} nanoparticle–sericin	Lupeol	Self-assembled and ionic gelation method	In vivo	Prepared sericin-based hydrogel helps to accelerate epithelization restoration with antibacterial activity and increases collagen fiber deposition (Chu et al., 2023).
Copper sulfide nanoparticle (CuS)—a blend of xanthan gum and konjac glucomannan (KGM)—sericin	Sericin as bio-template	In situ green synthesis	In vivo wound healing assay	A blend of xanthan gum and konjac glucomannan (XK) provides good photothermal properties. The molecular interaction between XK and CuS increases its mechanical properties (Guo et al., 2023).
Sericin–horseradish peroxidase (HRP)	–	Enzymatic crosslinking method	In vivo assessment	Enzymatic degradation enhanced the antioxidant activity of Sericin-HRP hydrogel. In the in vivo mice model, it reduced cell damage and wound area compared to the marketed gel (Tegaderm™). It also shows rapid recovery of epithelial cells (Baptista-Silva et al., 2022).

Sericin−agarose	Lysozyme	Blending and lyophilization method and solution impregnation method	In vitro antibacterial assay	Antibacterial assay revealed the reduction of bacterial growth by 76% from 87% for *E. coli* and by 84% from 95% for *S. aureus* (Yang et al., 2018).
Sericin/chitosan/polyvinyl alcohol	Silver nanoparticle hybrid organic frameworks/ graphene oxide	Biomineralization	In vivo	The prepared hydrogel possesses a low hemolysis rate with a higher cell viability compared to others. It confirms enhanced biocompatibility with good hemostatic activity where rapid recovery of the wounds is proved through in vivo studies (Zhang et al., 2021).
Sericin/poly(vinyl alcohol)	Gentamicin	Repetitive freezing−thawing method	In vitro	Live/Dead staining assay indicates many cells were dead in bacterial culture. In the presence of gentamicin-loaded hybrid hydrogel maintained the cell viability (Tao, Cai, et al., 2019).
Sericin/poly(vinyl alcohol)	Silver nanoparticle	Repetitive freezing−thawing method	In vivo	This preparation avoids poor mechanical properties of sericin with PVA blending that enhances its tensile strength. Sericin-PVA dressing has a higher tensile strength compared to cellulose and chitosan dressing (Tao, Wang, et al., 2019).

Continued

Table 11.1 A summary of the investigation on a sericin-based hybrid system.—cont'd

Hybrid material	Therapeutic agent	Method of preparation	Model	Findings and outcome
Sodium alginate (SA)−silk sericin	Silver nanoparticle	Crosslinking method	In vivo wound healing assay	Presence of sodium alginate in sericin hydrogel showed excellent swelling index and retention properties by preventing dehydration and maintaining moisture. It also indicates high cytocompatibility in cell counting assay (Tao et al., 2021).
Film or membrane				
Sericin/hyaluronic acid−bacterial cellulose membrane	−	In situ and ex situ method	In vitro cell survival method	In studies such as tensile strength and water-holding tests, the composite film prepared by ex situ methods has been shown to have better mechanical stability and swelling ability than the composite prepared by in situ methods and controls (Wang et al., 2020).
Chitosan−silver−sericin	Moxifloxacin	In situ synthesis and solvent casting method	In vivo burn wound model	The prepared film revealed a better swelling index with sustained in vitro release at 24 h. It also displayed excellent skin restoration; no silver ion toxicity was detected within 7 days (Shah et al., 2019).

Sericin/agarose composite	Ag/ZnO	Layered-by-layered self-assembly	In vitro assay	In the inhibition zone assay, the film formed an apparent inhibition area in both *S. aureus* and *E. coli* bacteria. That confirms antibacterial action on gram negative or positive bacteria (Li et al., 2021).
Polyelectrolyte membrane (PEM) coated−sericin/agar	Silver nanoparticle	It is layered using the layered assembly technique and ultraviolet-assisted nanoparticle synthesis.	In vitro	PEM coating provides a better antibacterial effect for the film without an inhibition zone against *S. aureus* and *E.coli* (Liu, Cai, Wang, Tao, Ai, Wang, Yang, Zuo, Zhao, Shen, et al., 2018).
Polydopamine−sericin/polyvinyl alcohol (PDA-SS/PVA)	ZnO nanoparticles (ZnO NP)	Blending method	In vitro assay	Prepared ZnO NPs-PDA-SS/PVA film showed increase in tensile strength due to presence of PDA with ZnO. Also, Mass loss study confirms good stability of prepared hybrid film (Ai et al., 2019).
Scaffold				
Sericin−poly−hexamethylene−biguanide scaffold	Chlorhexidine	Blending and lyophilization method	In vivo safety test	SER dressing with 0.5% chlorhexidine showed immediate release and long-term antibacterial effects against gram-negative and positive bacteria (Ampawong & Aramwit, 2017).

Continued

Table 11.1 A summary of the investigation on a sericin-based hybrid system.—cont'd

Hybrid material	Therapeutic agent	Method of preparation	Model	Findings and outcome
PLA—sericin hybrid scaffolds	Gentamicin sulfate	Particulate leaching method	In vitro	NaCl has a significant impact on the porosity of developed nontoxic hybrid scaffolds, which can increase water retention and decrease compressive modulus with increasing NaCl content (Pankongadisak et al., 2019).
Cellulose/poly(vinyl alcohol)-based genipin—sericin	Azithromycin	Crosslinking method	In vivo model	Due to PVA, the porosity increased by approximately 30% and increased pore size and fiber diameter by 7 and 3.4 times, respectively. Also, the nontoxic nature of biofilm was confirmed in HaCaT and NIH3T3 cells (Bakadia, Boni, et al., 2022).

Trilayered nanofibrous scaffold-based sericin and fibroin	Silver(I) sulfadiazine	Triple-layered approach	In vivo wound contraction	Current scaffold made by triple-layered approach shows complete wound healing confirmed by in vivo wound study in male Balb/c mouse model (Kumar et al., 2022).
Microneedle				
Sericin−poly(vinyl alcohol)−poly(dimethyl siloxane)	ZnO	Template-based method	In vivo model	Developed antibacterial sericin microneedle has a bioinspired oriented shape that is arranged like lamprey teeth. This shape helps to provide the combined effect of penetration and guiding toward wound infection (Deng et al., 2022).

hold water, reduce the toxicity of hazardous materials, and help improve the healing process (Napavichayanun et al., 2019). In a recent investigation, Munir et al. developed a potent sericin-based hydrogel. The plant extract, curcumin, and banana peel were simultaneously loaded in silver nanoparticles to enhance acute wound healing. The in vivo and histological studies showed that sericin-based hydrogel significantly improved wound healing, which healed in 11 days. Besides this, the biochemical test confirms a decrease in proinflammatory cytokinin with increases in antiinflammatory cytokine levels in serum. These showed the potential contribution of sericin-based hydrogel in acute wound healing (Munir et al., 2023). Zhang et al. patented sericin/resveratrol repair gel in which the sericin fibroin will wrap the resveratrol nanospheres, easily gels in the range of 20−40°C under acidic conditions. It is used to promote tissue repair and oxidation resistance (Sericin/Resveratrol Repair Gel and Preparation Method and Application Thereof, 2024).

To promote wound healing, the dressing material is designed with properties like superabsorbency and biocompatibility in consideration. The superabsorbent property of wound dressing plays a crucial role in the rapid recovery of wounds. Yang et al. incorporated sericin and agarose composite to prepare interpenetrating crosslinked structured gel. This blended composite containing lysosomes was prepared by using the solution impregnation method. The result showed that high gel porosity, which enhances the water absorption property, gives potential alternative material for wound dressing (Yang et al., 2018). Wang et al. patented a preparation method of cross-linking sericin hydrogel in which the sericin is modified using methacrylic anhydride. This complex is then crosslinked by exciting it using ultraviolet light to make hydrogel. This hydrogel is useful in tissue engineering and skin injury repair and can be used in the preparation of biomedical materials (Photo-Crosslinked Sericin Hydrogel and Preparation Method and Application Thereof, 2024).

However, the self-assembly method is another way to develop hydrogel with sustained release of therapeutic agents. This can help prepare good biomedical material. Chu et al. used sericin to prepare self-assembled thermosensitive hydrogel that contains silver-conjugated chitosan nanoparticles loaded with lupeol. The silver-modified chitosan nanoparticles are synthesized by ionic gelation methods in a lupeol solution. These methods do not need any chemical crosslinking agent. The study revealed a 62.1% encapsulation efficacy of lupeol in nanoparticles that exhibited effective antibacterial properties against Gram-positive and Gram-negative bacteria, accompanied by a reduced hemolysis ratio of less than 5%. Also, sericin-based gel shows enhanced therapeutic efficacy by rapid re-epithelization and collagen fiber disposition, which reduces inflammation and accelerates wound healing (Chu et al., 2023). Feng et al. patented a hydrogel material for repairing alveolar processes in which they have repaired alveolar fissures by biologically producing TGF-beta 1 silk from the germplasm. TGF-beta 1 silk is used to develop TGF-beta 1 silk glue gel material, which can be additionally used to repair rabbit cleft lip and palate (Hydrogel Material for Repairing Alveolar Process and Application Thereof, 2024).

3.3 Sericin-based films or membranes

The film has shown eminent potential in topical applications like wound healing, tissue engineering, etc. Shah et al. prepared silver nanoparticles within a chitosan−sericin composite by in situ synthesis. This triple-component (silver-chitosan-sericin) composite was poured into the film using conventional solvent casting. The prepared film shows a sustained release profile with a good swelling index. Thus, the study suggests the prominent use of cinema in wound dressing (Shah et al., 2019).

Similarly, in a recent study, Liu and colleagues have developed a novel type of film by coating sericin agar with polyelectrolyte membrane using a layered-by-layered adsorption technique. The researchers then utilized an ultraviolet-assisted $AgNO_3$ synthesis method to further enhance the film's properties. This innovative approach has the potential to open up new avenues for the development of advanced materials with improved functionality and performance. The findings indicated that the prepared film exhibited remarkable mechanical strength, superior hydrophilicity and water absorption capacity, and long-lasting antibacterial effectiveness (Liu, Cai, Wang, Tao, Ai, Wang, Yang, Zuo, Zhao, Shen, et al., 2018).

3.4 Sericin-based scaffolds

Scaffolds are generally applied in tissue engineering for the delivery of bioactive substances. Here, the scaffold should possess appropriate porosity that facilitates cell migration by interconnectivity (Amini et al., 2012). There are different ways to create porous scaffolds, including foaming, 3D printing, electrospinning, particulate leaching, and phase separation. Among these methods, particulate leaching is commonly used because it is simple and allows the regulation of pore size by adjusting the salt/polymer ratio and particle size. Pankongadisak et al. developed a poly(L-lactic acid) (PLLA) scaffold through a particulate leaching technique using sodium chloride and prepared a PLLA-sericin hybrid scaffold by immersion of a PLLA scaffold in sericin solution. The scaffold shows high water retention followed by enhanced scaffold porosity with increasing NaCl content (Pankongadisak et al., 2019).

Kumar et al. investigated the hemocompatibility and biocompatibility of a trilayered nanofibrous scaffold based on a dual protein approach using silk fibroin and sericin. These triple-layered scaffolds showed complete wound healing, confirmed by histological, in vivo wound contraction, and micro-CT (Kumar et al., 2022).

3.5 Sericin-based microneedles

The wound dressing material, such as hydrogel and film, has a barrier to delivering the drugs into deeper tissue due to necrotic tissue in the wound. Here, microneedles have gained focus for great potential to penetrate the drug up to the epidermis. Deng et al. used sericin to fabricate the microneedle tip. During drying, sericin-based microneedles are fabricated in PDMS molds. However, these microneedles possess antibacterial properties, especially for wound healing, which emerge as promising wound dressing material to penetrate the drug into the stratum corneum (Deng et al., 2022).

3.6 Miscellaneous

The sericin hybrid metal oxide−based nanoparticles have a great impact on the delivery of drugs and genes. Kara et al. developed superparamagnetic iron oxide nanoparticles (SPIONs) for the delivery of siRNA. The SPIONs coat covalently with sericin and deliver anionic siRNA by using poly-L-lysine as a cationic polymer. The mechanism of this approach is to concentrate SPIONs at the site of action using an external magnetic field. Here, sericin is used as a coating material (Kara et al., 2021).

In some cases, like wet biological tissue surfaces, there is a major challenge for onset adhesion. Addressing this concern, Liu et al. reported advances in the preparation of self-hydrophobic adhesion. The co-assembly mechanism is based on the hydrolyzation of the disulfide bond of hydrophobic sericin and tannic acid. Self-aggregation of the hydrophobic chain was initiated in the presence of water, which helps in improving interfacial bond strength. These robust underwater adhesives enable leakage-sealing properties (Liu et al., 2022). With attention to the prolonged antibacterial activity in wound healing, Li et al. developed a sericin-based multifunctional composite sponge, which was able to give coherent antibacterial and hemostatic properties (Li, Jiang, et al., 2023).

4. Physiology of wound healing

The process of healing a wound is an intricate biological one that is initiated when the skin is damaged. This damage can be caused by either an unintentional accident or a deliberate procedure. Wound healing takes place in four distinct phases, which are known as hemostasis, proliferation, inflammation, and tissue remodeling, as shown in Fig. 11.3 (Mazurek et al., 2022; Wang et al., 2018). The hemostasis initiates wound healing. In the presence of collagen, platelets get activated, which helps produce clotting factors and cytokine (Almadani et al., 2021; Banerjee & Sen, 2015, pp. 631−651). Followed by hemostasis, inflammation at the site of the wound helps remove debris, which creates a defense mechanism (neutrophils and macrophages) for protection against infection by microbial content (Jones & Nelson, 2007). During proliferation, the epithelium forms granulation tissues to cover the wound (Alven et al., 2022). Re-epithelialization, granulation, angiogenesis, growth of tissue and development, and accumulation of collagen are the pivotal characteristics of this stage. Due to rapid progression in the proliferative phase, the provisional matrix of fibrin or fibronectin is substituted by the fresh granulation tissue. The wound epithelialization represents the last stage of the proliferative phase (Riwaldt et al., 2021). Its distinguishing features are fibroblast passage and newly produced extracellular matrix being deposited, which replaces the fibrin and fibronectin provisional network (Khanam, 2021). This procedure causes granulation tissue at the wound space and typically lasts 2−3 weeks after injury. At the remodeling tissue, the epidermis is durable from mechanical stress and safeguards the body from germs, UV rays, dehydration, and high temperatures (Rodrigues et al., 2019).

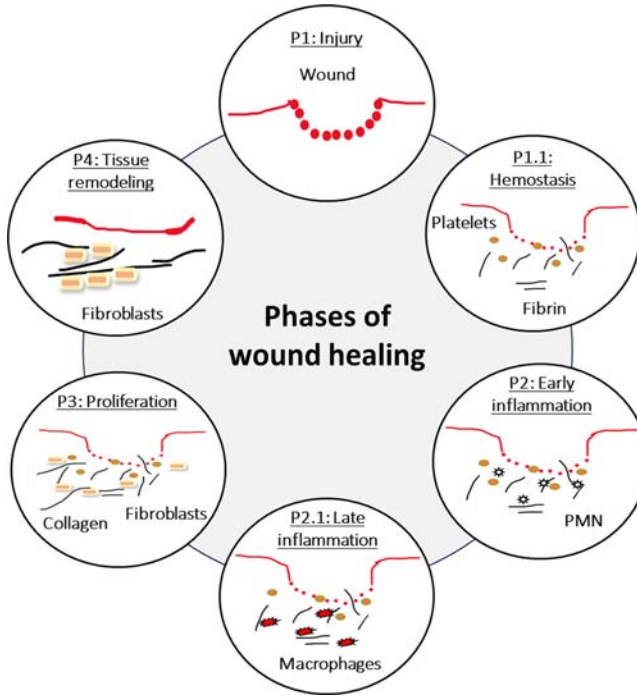


Figure 11.3 Phases of wound healing.

5. Applications of sericin-based hybrid materials in wound healing

Various properties and applications of sericin are shown in Fig. 11.4.

5.1 Antibacterial activity

Silver nanoparticles (AgNPs) have been remarkably utilized as an antimicrobial agent. It has potential applications in different fields for its antimicrobial activity. Several studies have been performed based on sericin hybrid nanoparticles. He et al. fabricated sericin AgNPs that effectively stun *S. aureus* and further kill the bacteria. Thus, hybridization provides a long-term antibacterial effect (He et al., 2017). Tahir et al. synthesized silver nanoparticles by using 0.2% sericin as a reducing agent of $AgNO_3$, and it was also used as a capping agent of AgNPs and found it to be an effective antimicrobial agent against *K. pneumonia*, *S. aureus*, and *E. coli* (Muhammad Tahir et al., 2020).

Ai et al. designed sericin/polyvinyl alcohol composite films with zinc oxide nanoparticles based on polydopamine. They reported that the composite films possess excellent hydrophilicity, swellability, antibacterial activity, mechanical properties, and stability, making them a promising candidate for antimicrobial biomaterials,

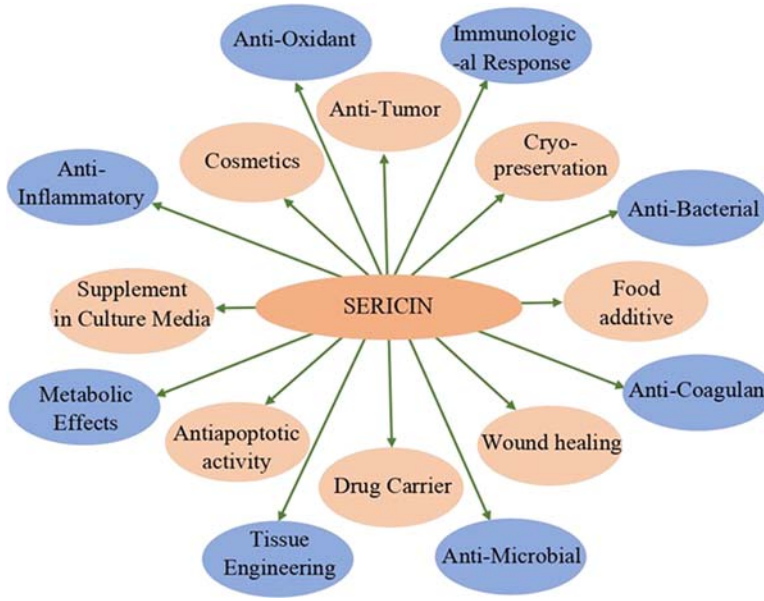


Figure 11.4 Properties and applications of sericin.

such as wound dressing (Lisha Ai et al., 2019). Akturk et al. fabricated sericin-based gold NPs in the presence of UV-C radiation in which sericin acts as a reducing and capping agent that enhanced the antibacterial activity of antibiotic streptomycin and thus acts as an effective antimicrobial agent (Akturk et al., 2019).

An approach for producing wound dressings is to incorporate active molecules or medicines. To promote faster wound healing and reduce the need for frequent dressing changes, wound dressings utilize sustained release of active substances. Aramwit et al. designed wound dressing materials that release chitosan and sericin from microspheres in a controlled manner. Thus, it prolonged the antimicrobial and wound healing efficacy (Aramwit et al., 2016). Yang et al. fabricated lysozyme-loaded sericin-agarose gel, which showed the sustained release of lysozyme and good antibacterial activity against *S. aureus* and *E. coli* and can be used as a potential wound dressing biomaterial that diminishes wound infection and enhances the wound healing (Yang et al., 2018).

Hydrogel has characteristics like hydrophilicity, water-holding ability, and porous structure, providing various applications. Bakadia et al. reported that azithromycin-loaded sericin-PVA hydrogel shows antifungal and antibacterial properties on *S. aureus*, *E. coli*, *C. albicans*, and *P. aeruginosa*. Hydrogel interacts with azithromycin and sericin, giving a synergistic antifungal effect (Bakadia et al., 2023). Similarly, combining antibacterials with healing agents has been an effective wound-healing strategy. Napavichayanun et al. developed sericin-based biocellulose wound dressing by fabricating sericin and polyhexamethylene biguanide. This combination performs the dual function of re-epithelization and antibacterial effect due to the interaction of sericin and polyhexamethylene biguanide (Napavichayanun et al., 2015).

Some studies, like photothermal performance tests, were used to track the antibacterial activity of hydrogel. Yuan et al. performed an antibacterial activity study of gellan gum/sericin-HNTs@PDA composite hydrogel compared with antibiotic or metal ion−based hybrid antibacterial activity. It revealed composite hydrogel shows an effective photothermal performance test that indicates rapid antibacterial action with biocompatibility (Yuan et al., 2023). Furthermore, photothermal therapy has been used by Guo et al. using CuS−sericin nanoparticles The formed composite hydrogel showed potent photothermal antibacterial activity (Guo et al., 2023).

Liu et al. developed polydopamine-assisted silver nanoparticles assembled on sericin−agar films that have strong and long-lasting antibacterial properties, as well as remarkable compatibility with fibroblast NIH/3T3 cells that make them exceptional qualities for applications like wound treatment, antibacterial packaging, and tissue engineering (Liu, Cai, Wang, Tao, Ai, Wang, Yang, Zuo, Zhao, & He, 2018).

However, sometimes, antimicrobial efficiency may be impacted due to stability problems. For chronic wounds, sericin hybridization improved antimicrobial activity with long-term stability. According to Ampawong et al., the addition of chlorhexidine to sericin scaffolds results in a longer-lasting antibacterial effect with a larger area of inhibition. Additionally, a unique technique called grafting copolymerization has been employed to enhance the microbial inhibition activity (Ampawong & Aramwit, 2017). Gok et al. have developed sericin-silver nanoparticles coated with modified PET fibers that exhibit antibacterial properties against both Gram-negative and Gram-positive bacteria. This antimicrobial surface has numerous applications in wound healing (Gün Gök et al., 2020).

Natural polymers can serve as a template to create inorganic-organic hybrids. Biomaterials related to proteins have gained attention in recent years due to their practical uses and unique properties. Antibacterial wound dressings are used to reduce infections, which accelerates the wound-healing process. Tao et al. designed a hydrogel with sericin-PVA loaded with gentamicin using repetitive freeze-thawing. This hydrogel restricts bacterial growth, maintains cell viability, and is expected to act as a drug carrier to promote wound healing, thus preventing wound infection (Tao, Cai, et al., 2019). Shah et al. developed nanocomposite films of silver-chitosan-sericin loaded with moxifloxacin and suggested they could be successfully used as wound dressing (Shah et al., 2019).

Silk sericin has been found to promote the formation of collagen and enhance the process of wound healing in both keratinocyte cells and fibroblasts (Cao & Zhang, 2016). Gilotra et al. developed sericin nanofibrous mats by electrospinning technique for wound dressing, indicating silk sericin as a fascinating substrate for treating chronic wounds such as diabetic foot ulcers (Gilotra et al., 2018). Bakhsheshi-Rad et al. developed poly(vinyl alcohol)/chitosan combined with sericin and incorporated tetracycline to form porous nanofibers through electrospinning technology, which revealed potential applications with better skin repair and wound covering applications (Bakhsheshi-Rad et al., 2020).

5.2 Tissue engineering

Sericin's excellent moisture-regulating capacity, oxygen permeability, ability to promote cell growth, UV radiation resistance, mitogenic effect, and biocompatibility make it a promising polymer for biomedical applications such as regenerative medicine, tissue engineering, and wound healing (Arango et al., 2021). Pankongadisak et al. developed sericin-chitosan hydrogels loaded with logan seeds, which are thermosensitive at body temperature, and reported that they can be efficiently used in the application of bone tissue engineering (Pankongadisak & Suwantong, 2018).

Wang et al. developed an injectable photoluminescent, three-dimensional sericin hydrogel that is crosslinked covalently. This hydrogel displayed remarkable success in promoting cell attachment, enhancing cell-adhesive capacity, and supporting the proliferation and long-term survival of various cell types. They reported the prolonged release of active material from the hydrogels and their utility in various tissue healing applications (Wang et al., 2014). Gang et al. developed a method of woven artificial blood vessels with anticoagulation/endothelialization function. The artificial blood vessel is made by isolating in a cavity through silk and polyester yarns, which are tightly combined by using silk fibroin and heparin on the blood vessel surface as a coating, which imparts anticoagulation/endothelization function. The silk fibroin and heparin layers are helpful in vascular endothelialization and also promote slow release of heparin molecules, which inhibits acute thrombosis (Preparation Method of Woven Artificial Blood Vessel with Anticoagulation/Endothelialization Promoting Function, 2024).

5.3 Corneal wound healing

Nagai et al. reported that the rise in the concentration of sericin showed an increased healing rate of the corneal wounds and mentioned a 12-fold increase in healing rate when using 10% sericin compared with 10% saline (Nagai, Murao, Ito, Okamoto, & Sasaki, 2009a, 2009b). Sericin was found effective in treating diabetic keratopathy–related corneal wounds in a type-II diabetic model (Nagai et al., 2009a, 2009b). In further studies, the instillation of sericin in rat eyes reported that corneal wound healing is by MAPK/ERK activation pathway resulting in enhancement of corneal wound healing (N Nagai et al., 2018).

Later studies developed a combination ophthalmic formulation of magnesium hydroxide nanoparticles and sericin and observed that using magnesium hydroxide nanoparticles promoted the therapeutic effect of sericin in the epithelial cornea wound healing. The instillation of the formulation initially expands the epithelial corneal intercellular space by magnesium hydroxide nanoparticles, which increases the levels of sericin in the cornea and then increases the proliferation and migration, thus increasing the therapeutic effect of sericin, and treats the epithelial wound of the cornea (Noriaki Nagai et al., 2019).

5.4 Anti-inflammatory and antioxidants

Sericin's immunomodulatory and ROS-eliminating qualities make it a crucial component for wound healing. Antioxidant enzymes can inhibit free radical production and facilitate ROS removal in sericin-based hydrogel systems. Munir et al. prepared hydrogels using sericin in combination with silver nanoparticles and extracts of plants such as curcumin and banana peel powder to hasten wound healing. By lowering levels of proinflammatory cytokines, this study has additionally demonstrated antiinflammatory effectiveness (Munir et al., 2023). Similarly, Deenonpoe and his team discovered silk sericin's antiinflammatory potential (Deenonpoe et al., 2019). Xujie et al. patented a sericin-containing mouthwash that significantly enhances tissue repair and wound healing in the oral cavity. It can also treat periodontitis, gingivitis, pericoronitis, and other oral mucosal diseases. The mouthwash also has antibacterial and antiinflammatory properties, which are helpful in maintaining oral hygiene (Sericin-Containing Mouthwash and Preparation Method Thereof, 2024).

Some polyphenols possess antioxidant properties but need more stability due to their limited applications in the industry. Zhang et al. developed a ROS-triggered wound healing approach to prevail over these stability issues using anthocyanins encapsulated in harnessed silk sericin. This hairpin structure of bioactive sericin-based hydrogel helps enhance loading efficiency and maintain stability in diverse environmental conditions (Zhang et al., 2023).

Since sericin and curcumin exert antioxidant and antiinflammatory activities, researchers have hybridized sericin and curcumin to synergize their effects in biomedical use. Kanoujia et al. formulated curcumin-loaded sericin nanoparticles by desolvation method using genipin crosslinking, for use as an antiinflammatory and antioxidant (Kanoujia et al., 2021). Sleiman et al. prepared the 3D biohybrid composed of collagen and silk sericin (CollSS) enriched with microsphere containing Curcumin (C) and quercetin (Q) founded potential of antioxidants by measuring the level of ROS as well as by DPPH radical scavenging activity, which showed a decrease in ROS level by both CollSS and CollSS-CQ, but the presence of flavonoids (CQ) enhances the antioxidant property in a significant manner and Coll-CQ also shown 64.83% free radical scavenging activity where scaffold (CollSS) shown 13.45% comparatively lower than CollSS-CQ (Sleiman et al., 2024).

5.5 Diabetic wounds

Chronic wounds will lead to complications that are related to diabetes mellitus. Increased formation of ROS will lead to delayed healing of any chronic wound. To minimize this oxidation, the antioxidant property of sericin can be exploited. Silva et al. developed an in-situ silk sericin-based hydrogel formed by horseradish peroxidase (HRP) hybridization, which can be used as an advanced dressing for wound

healing. Studies conducted on diabetic mouse wound models have shown that the use of a hydrogel made from silk sericin can reduce epidermal thickness and wound margin distance. This hydrogel also helps protect against oxidative stress and promotes proper healing (Baptista-Silva et al., 2022). Wei et al. prepared the transparent injectable sericin-honey semi-interpenetrating network hydrogel and established an enhanced wound-healing process in an in vivo study (Wei et al., 2024).

5.6 Multidrug resistance infection

Some cases, such as deep burn wounds, were susceptible to resistance from multiple drugs that may cause severe infection. Depending on the thickness of the wounds, an extended time is required for the healing of deep wounds, thus increased chances of infection, exist. Bakadia et al. prepared vancomycin and gentamicin-loaded microsphere in sericin-based hydrogel. The combination of both drugs leads to a synergistic antibacterial effect, which improves the in vivo therapeutic effect as compared to free drugs and helps reduce the resistance (Bakadia, Zhong, et al., 2022).

6. Concluding remarks

In the textile industries, silk sericin was treated as sewage, leading to environmental pollution. To overcome this problem, researchers took it as a task to convert waste to best, which revealed that silk sericin had extensive applications in various fields. Extracting sericin from the cocoon of *B. mori* is easy and cost-effective. Sericin is a protein of natural origin that finds wide-ranging applications in the pharmaceutical and biomedical arena. It possesses exceptional biological and pharmacological properties, including antiinflammatory, antioxidant, antibacterial, immune response, and antitumor activities. Over the years, researchers have increasingly explored sericin in combination with natural and synthetic polymers to overcome various challenges. Researchers innovating on this fascinating topic of hybridized sericin have an excellent opportunity to explore and better understand this unique connection with wound healing. Sericin can be hybridized into nanomaterials, hydrogels, films, membranes, scaffolds, and microneedles; this can amplify the potential of sericin. In this chapter, we have highlighted the recently used method of preparation to hybridize sericin with different polymers, such as cross-linking, self-assembly, desolvation, repetitive freeze-thawing method, and co-blending method. This sericin hybridization with therapeutic agents will synergize its effect, opening a new gateway to deliver new therapeutic agents. We have reviewed silver nanoparticles extensively conjugated with sericin to form a promising wound-healing agent. In conclusion, we summarize sericin hybrid materials with a prominent approach to wound healing.

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Applications of sericin hybrid materials in pharmaceutical sectors

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Jibanjyoti Panda [1,3], *Yugal Kishore Mohanta* [1], *Rashmi Rekha Baruah* [1], *Balaji Doolam* [2] *and Debasis Nayak* [3]

[1]Nanobiotechnology and Translational Knowledge Laboratory, Department of Applied Biology, School of Biological Sciences, University of Science and Technology Meghalaya (USTM), Baridua, Meghalaya, India; [2]Department of Biotechnology, Chaitanya Bharathi Institute of Technology, Hyderabad, Telangana, India; [3]Department of Wildlife and Biodiversity Conservation, Maharaja Sriram Chandra Bhanja Deo University, Baripada, Odisha, India

1. Introduction

Sericin, a protein, is synthesized by the silkworm *Bombyx mori*, which is a member of the Lepidoptera order and Bombycidae family, both of which consist of holometabolous insects. *Bombyx mori*, a species known for its abundant production of sericin, reaches its peak sericin production during the final larval stage. Sericin, along with fibroin, is responsible for the formation of the silk thread utilized in cocoon construction. The cocoon serves as a protective structure that creates optimal conditions for the transformation of larvae into adult organisms (Baruah et al., 2023; Silva et al., 2022). Researchers have extensively investigated *B. mori* for its potential pharmaceutical applications, including wound healing, drug delivery, and various other purposes (Chouhan & Mandal, 2020). Sericin, a component primarily found in an amorphous state, exhibits increased solubility in water. It functions as a gum binder, serving to uphold the structural integrity of the cocoon (Sinna et al., 2020). Due to its hydrophilic nature, sericin, a protein, can be effectively eliminated or isolated from fibroin through a simplified thermochemical process referred to as "degumming" (Shitole et al., 2020a). The elimination of sericin from silk can be achieved through a multitude of methods. The experimental conditions involved in this study include elevated temperatures, potentially in conjunction with increased pressure through autoclaving. Additionally, an acidic environment was created using a solution primarily composed of citric acid. On the other hand, using a solution containing sodium carbonate resulted in an alkaline environment. Lastly, urea was also utilized as a component (Rajput & Kumar Singh, 2015). The observed separation technique exerted an influence on the

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solubility, molecular weight, and gelling properties of sericin (Saha et al., 2019). Sericin has been extensively investigated for its notable biochemical and biophysical properties, which have sparked interest in exploring its diverse potential applications. These products encompass a wide range of applications, including but not limited to the cosmetics and food industries, as well as biomedical coating materials utilized in anticoagulants, drug delivery systems, anticancer treatments, and tissue engineering endeavors (Wang et al., 2024). When sericin is incorporated into a serum-free medium for cell culture, it exhibits the ability to enhance cell proliferation. Also, using sericin alone or with matrices has been shown to help cells stick together and grow. Prospective resolutions for these stipulations encompass sericin membrane, three-dimensional framework, nanoparticle, composite, conjugated pharmaceutical, and recombinant sericin (Kunz et al., 2016).

Several investigations have been conducted to explore the properties of silk sericin. Dong et al. (2020) did a study to look at the hypoglycemic effect of sericin protein made from silk-processing waste and how to make it. The sericin protein was added to the regular diet of type 2 diabetic (T2D) mice at a concentration of 0.8% (g%) and administered orally. The oral protein, silk sericin hydrolyzate, is obtained through the process of boiling a solution containing 0.025% calcium hydroxide. The protein exhibited a notable reduction in fasting blood glucose levels and fasting plasma insulin levels. Additionally, it demonstrated significant enhancements in oral glucose and insulin tolerance, along with the stimulation of antioxidative activity. Dihan et al. (2019) conducted an investigation on the physicochemical and biological properties of silk-based products produced in industrial settings in comparison to regenerated silk fibroin. The aim of their study was to explore potential applications of these materials in the realms of biology and therapeutics. Upon comparative analysis with regenerated silk fibroin, the findings suggest that sericin exhibits potential as the optimal silk material for utilization in tissue engineering applications. Fatahian et al. (2017) conducted a study on the extraction process of sericin from the solution of silk gum effluent. Additionally, they examined the inherent characteristics of the extracted sericin. The antibacterial effects of sericin were further examined in bacterial models. The study's findings unveiled the potential for sericin extraction from gum effluent, thereby highlighting its inherent antibacterial properties. In their study, Li et al. (2020a) elucidated the synthesis and application of a nerve conduit composed of carbon nanotubes and sericin. This conduit exhibited desirable electrical conductivity and mechanical properties that are conducive to the process of nerve regeneration. Researchers were able to show that using an electrically conductive conduit made of carbon nanotubes (CNTs) and sericin along with electrical stimulation could be a good way to fix nerves that have been cut. Based on the scientific literature, only a small number of studies have been done to look into the biophysical and mechanical properties of silk sericin and its possible uses in different fields, with a focus on the medical field. The utilization of sericin for pharmaceutical purposes has the potential to yield significant economic, social, and environmental consequences. This chapter aims to elucidate the characteristics of sericin and provide an overview of the latest developments in utilizing this protein for pharmaceutical purposes (Fatahian et al., 2022).

2. Extraction methods of sericin from silk cocoons

Hydrolysis of sericin is the first step in the degumming process, followed by the separation of sericin and fibroin. Fig. 12.1 shows how this process results in the breakdown of peptide bonds. Because it does not dissolve in water and does not attract water, fibroin makes it easier to separate sericin from silk and get it out. Due to its hydrophilic nature, sericin exhibits limited solubility in aqueous environments. Detergents and soaps, such as the renowned Marseille soap, along with a sodium bicarbonate (Na_2CO_3) solution, are employed in the conventional technique of degumming silk within the silk industry (Lamboni et al., 2015). The aforementioned procedure demonstrates efficacy in the elimination of sericin from cocoons, leading to the retrieval of unadulterated and distinct fibroin suitable for utilization within the textile sector. The sericin that has been retrieved, nevertheless, has undergone significant degradation, leading to a reduction in its molecular weight and the loss of various functional characteristics (Biswal et al., 2022). The process of isolating soap from sericin presents considerable challenges. Hence, it is plausible that the sericin might retain remnants of soap, thereby impeding its suitability for utilization in biological or pharmaceutical contexts. Hence, various degumming methodologies have been devised to promote the retrieval of sericin over fibroin (Lamboni et al., 2015). Modifications in temporal parameters, thermal conditions, chemical augmentations, and various other influencing factors can be implemented across all aforementioned methodologies (Biswal et al., 2022; Lamboni et al., 2015). Various methodologies are occasionally employed in tandem to attain the desired yield and sought-after attributes of sericin. Thermal energy is introduced through the process of subjecting the cocoons to elevated temperatures, typically achieved by heating or boiling them in an aqueous medium, either with or without the application of elevated pressure using an autoclave

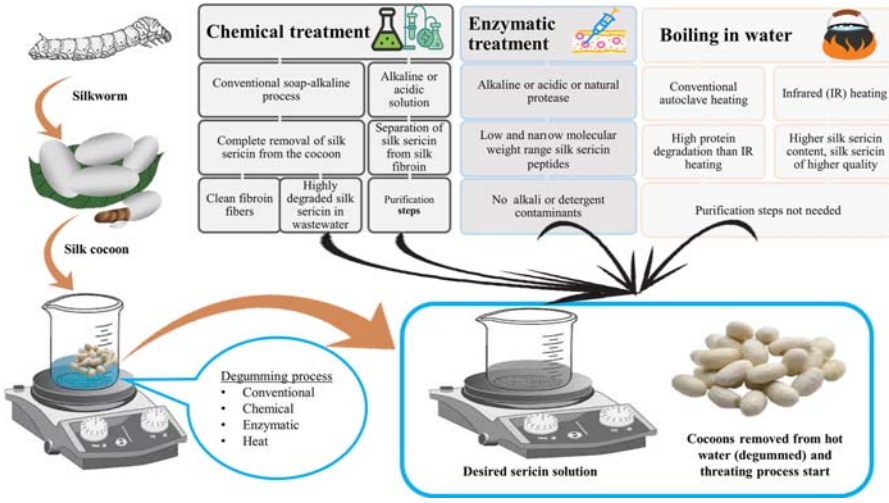


Figure 12.1 A schematic presentation of extraction methods of sericin from silk cocoons.

apparatus. The aqueous medium engages in interactions with the hydroxyl moieties present in polar amino acids, thereby inducing further segregation of sericin and fibroin (Silva et al., 2022). This phenomenon arises due to the inherent vulnerability of hydrogen bonding between the hydroxyl groups, which are exacerbated by the elevated temperature and pressure conditions. Due to its remarkable solubility in both alkaline and acidic solutions, sericin is effectively extracted from silk using these chemical agents (Çapar et al., 2015). The hydrolytic action of acids and bases facilitates the breakdown of sericin by cleaving the peptide bonds of amino acids, resulting in the liberation of sericin into the surrounding solution. In the context of sericin solubility enhancement, it is noteworthy that the presence of sodium carbonate can facilitate this process. This is due to the conversion of the carboxylic acid (-COOH) groups within the sericin molecules into carboxylate ions ($-COONa^+$), which is made possible by the strong hydration properties of sodium ions (Na+) (Kim et al., 2012). Proteolytic enzymes, such as alcalase, savinase, degummase, papain, and trypsin, can be used to extract sericin effectively (More et al., 2018). The hydrolysis of amino acid peptide bonds is catalyzed by specific enzymes, specifically those that facilitate the cleavage of the carboxyl group of lysine/arginine with the amino group (NH2) of the adjacent amino acid.

3. Characteristics of sericin

Sericin is a protein that exhibits a white or yellow coloration, lacks any discernible odor, possesses the ability to dissolve in water, and is characterized by a pleasant taste. The moisture content ranges from 10 to 17%. The evaluation of sericin's morphology revealed the presence of wrinkled particles, which can be attributed to the collapse of hollow spherical structures (Ghosh et al., 2017). In their research, Jadhav et al. found that the isolated sericin from silk had an amorphous structure in industrial wastewater. The extracted sericin had a round, smooth, bowel-like form (Salunkhe & Jadhav, 2018). Further, we present a comprehensive description of the significant characteristics exhibited by sericin, encompassing its molecular weight, solubility, gelling properties, isoelectric pH, and more (Fig. 12.2).

The molecular weight of silk sericin is contingent upon the specific extraction technique employed for its isolation. For instance, cocoons yield a molecular weight range of 40−400 kDa, while directly extracted samples from the worm exhibit a range of 80−310 kDa (Shitole et al., 2020b). The diverse literature reports have indicated variations in the molecular weight of sericin. For instance, one study involved the process of obtaining silk sericin a solution containing 1% sodium deoxycholate, followed by precipitation using equal volumes of 10% trichloroacetic acid. This particular method yielded sericin with molecular weights ranging from 17,100 to 18,460 (Silva et al., 2022). Additionally, it is noteworthy that the hot water extraction technique employed for sericin reveals a molecular weight (MW) of 24,000 as determined through gel electrophoresis. Conversely, the MW of sericin, when obtained via spray drying, falls within the range of 5000 to 50,000. When sericin is subjected to extraction using

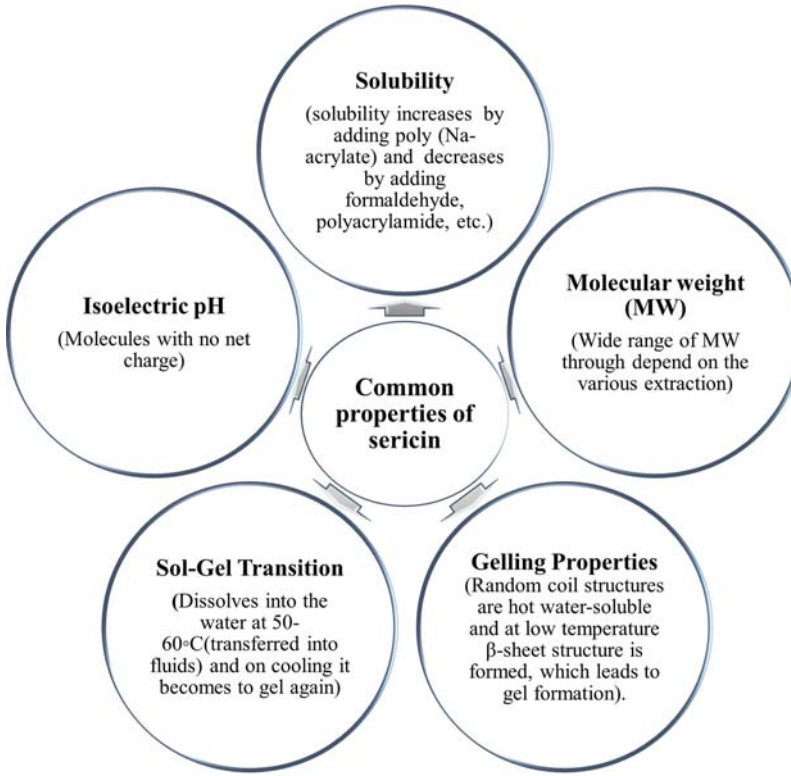


Figure 12.2 Illustration exhibiting some of the properties of sericin.

aqueous urea, it exhibits a molecular weight (MW) of 50,000 at a temperature of 100°C. However, through enzymatic action, the molecular weight of sericin has been observed to range between 300 and 10,000 (Seo et al., 2023). Upon reaching the culmination, the ranges of molecular weight (MW) would be contingent upon the diverse extraction conditions, encompassing the active type (alkaline, enzymes, acidic), temperature, processing time, pressure, pH, and other relevant factors. Sericin exhibits partial solubility in hot water. The correlation between the solubility of silk sericin and its amorphous and crystalline structures is evident. The amorphous region comprises a structure known as a random coil, which serves as the predominant molecular form of the highly soluble sericin. On the other hand, the β sheet, also referred to as the crystalline region, exhibits greater resistance to dissolution (Seo et al., 2023). Sericin undergoes a conformational change from its initial random coil conformation to adopt a more stable β sheet structure. This structural transition leads to a reduction in the solubility of sericin when exposed to water. Additionally, the solubility of sericin was enhanced through the incorporation of poly (Na-acrylate), whereas the presence of formaldehyde, polyacrylamide, and resin finishing agents resulted in a reduction in sericin solubility (Kunz et al., 2016; Silva et al., 2022).

The initial investigation conducted in 1994 revealed that the sericin protein displayed a rapid process of gel formation when subjected to lower temperatures (specifically 10°C) and maintained a pH level within the range of approximately 6−7 (Ghosh et al., 2017). Sericin is typically comprised of a combination of random coil and β-sheet structures (Padamwar & Pawar, 2004). As the conformational change from random coil to β-sheet structure occurs, it results in the formation of a gel-like sericin structure. The process exhibits reversibility when the sample is subjected to a temperature range of 50−60°C, resulting in gel formation upon subsequent cooling (Ghosh et al., 2017). This indicates that haphazard coil configurations possess solubility in hot water, while the low temperature induces a transformation of the sericin structure from the random coil conformation to the β-sheet conformation. This conformational change imparts the development of gel characteristics to the sericin (Lee et al., 2023).

Sericin demonstrates the intriguing property of sol-gel behavior, displaying a remarkable propensity to dissolve in water at temperatures ranging from 50 to 60°C, transforming into a fluid state. Upon cooling, it undergoes a fascinating transition, returning to its original gel state (Ghosh et al., 2017; Silva et al., 2017). The isoelectric pH, scientifically referred to as the point of zero net charge, corresponds to the specific pH value at which molecules demonstrate a complete absence of any discernible electric charge. The isoelectric pH is a well-defined concept in biology, referring to the pH value at which the concentration of hydrogen ions or other ions attains an equilibrium state, thereby establishing an environment that is electrically neutral. Hence, the determination of the isoelectric point with respect to the pH scale has emerged as a conventional procedure. The isoelectric point of sericin is estimated to be around 3.5 to 4.0 due to an elevated level of alkaline residues in amino acids.

4. Sericin-based hybrid materials and their pharmaceutical applications

Recent studies on sericin have revealed its remarkable biological properties, even in its discarded form. In recent studies, sericin has demonstrated its ability to augment cell adhesion and replication (Aramwit et al., 2010). Furthermore, it has been observed to induce cell differentiation (Nayak et al., 2013; Pasovic et al., 2018). These findings are particularly significant in the context of biomaterials, as sericin exhibits favorable biocompatibility and minimal immunogenicity. Furthermore, it is important to note that sericin exhibits remarkable antioxidant capabilities, effectively combating oxidative stress, and also demonstrates exceptional moisture retention abilities (Jena et al., 2018). The capacity of sericin to change, precipitate, or cross-link with other polymers allows for the creation of biomaterials with tunable dimensions, as well as properties like elasticity, strength, and biodegradability. Cosmetics, a field concerned with enhancing the appearance and health of the skin, has increasingly recognized the significance of cell biology and tissue engineering (Kunz et al., 2016). The potential medical and pharmacological advantages are synergistically augmented by the environmental merits of sericin retrieval and utilization (Liu et al., 2022). Due to its



Figure 12.3 Major pharmaceutical properties of sericin-based material.

inherent biological characteristics, as well as the ecological concerns arising from sericin's release as a byproduct of the textile sector, extensive research has been conducted on this protein for diverse applications across various industries. Henceforth, this analysis will concentrate on the prominent biomedical and pharmaceutical implementations of sericin, specifically in the realms of tissue engineering, drug administration, and additional applications encompassing metabolic disorders and cosmetic formulations (Fig. 12.3 and Table 12.1).

4.1 Antimicrobial

The possession of antibacterial qualities by a biomaterial is indicated when it is capable of either eradicating or inhibiting the proliferation of microorganisms. The management of infectious diseases has become a significant concern for healthcare systems in recent times. Infections throughout the healing process are a major clinical issue for wound care professionals. The presence of infections at wound sites has been observed to impede the healing process and elevate the likelihood of subsequent complications, both at the local and systemic levels (Manesa et al., 2020). Therefore, the utilization of biomaterials possessing antibacterial properties represents a valuable strategy for the production of biomedical products. Scientists think that cysteine, an amino acid with polar properties and no electric charge due to its sulfhydryl groups, is what gives sericin its antibacterial properties. The sulfhydryl groups then link up with oxygen or nitrogen through weak hydrogen bonds, making a chemically reactive compound that interferes with a number of enzyme reactions and metabolic processes in microorganisms. The antibacterial effects of sericin have been demonstrated to be effective against both Gram-positive and Gram-negative bacteria. The antibacterial properties of sericin were identified in a series of studies conducted by Ahamad and Kumar Vootla (Ahamad, 2019) against *Escherichia coli, Staphylococcus aureus,* and fungal strains including *Candida albicans* and *Aspergillus flavus*. Jassim and Al-Saree (Jassim et al., 2010) also observed that the growth inhibitory effect of sericin

Table 12.1 Promising pharmaceutical activities of sericin.

Pharmacological activity	Mode of use	Model used	Activity		Sources
			Upregulation	Downregulation	
Antihyperlipidemic activity	Silk protein with varying ratios of fibroin to sericin (F100 for pure fibroin, F81 for 81:19 fibroin to sericin, and F50 for 50:50)	High fat-fed mice	Increase in high-density lipoprotein (HDL-C); decrease in lipogenesis; control of adipokine production; increasing dietary sericin led to a magnifying of these effects.	Body mass index and improved lipid profile; total plasma cholesterol, triglyceride, atherogenic index, and free fatty acid concentration.	Seo et al. (2011)
	Silk cocoon extract	Cholesterol diet-induced hyperlipidemia and atherosclerosis in rabits	HDL-C concentrations and body mass index.	Arterial plaques' dimensions.	Ali and Arumugam Sarasa (2011)
	Oligopeptides extracted from sericin	Caco-2 cell line	–	Cellular absorption of cholesterol.	Lapphanichayakool et al. (2017)
	Oligopeptides produced from sericin and a high-fat diet	High cholesterol-fed rats	–	Plasma and non-HDL cholesterol.	Lapphanichayakool et al. (2017)
	Sericin on a high-fat diet	Caco-2 cell line	–	30% cholesterol uptake in a cell line; plasma and non-HDL cholesterol.	Limpeanchob et al. (2010)
	Sericin on a high-fat diet	High fat-fed rats	No changes were seen in body weight, total fat mass, or serum adiponectin.	Triglyceride, cholesterol, phospholipid, and free fatty acid levels in the blood; HDL-C, HDL-phospholipids, LDL-C, and LDL-TG; glycogen-6-phosphate dehydrogenase and malic enzyme, two lipogenic enzymes, and triglyceride (TG) in the liver.	Okazaki et al. (2010)
	Sericin on a high-fat diet	High-fat diet-induced obese mice	Lipid flushing, recovered through gastrointestinal morphometry.	Biochemical and biometric alterations brought on by obesity induction have not fully recovered; no influence on the mice's bowel transit time.	Regina Inês et al. (2020)

Antitumor an antioxidant activity	A sericin protein pretreatment	Mice with alcoholic hepatitis	Alcohol content in the urine; return to normal levels of antioxidant enzymes such MDA, GSH, and SOD that had been elevated; return of normal hepatic mitochondria; Normal histology with minor central vein congested at 1.50 g/kg of dosage.	Alcohol content of the blood.	Li et al. (2008a)
	Silk sericin	Enzymatic assay	Strong ability to quench free radicals such as hydroxyl, superoxide, and DPPH; strong antioxidant protection against linoleic acid peroxidation; high ferrous-ion chelating activity and strong reducing power.	–	Fan et al. (2009)
	Hydrolysates of silk sericin produced by several proteases	Enzymatic assay	Alcalase hydrolysates have more prominent radical scavenging and lipid peroxidation activity than other proteases, although all silk sericin hydrolysates show substantial reducing power and ferrous ion chelating activity.	–	Fan et al. (2010)
	Silk sericin	AH927 cutaneous fibroblast cells were oxidized by hydrogen peroxide.	When compared to cells treated with H_2O_2, viability is maintained at 35 ng/mL.	Cell release of malondialdehyde, lactate dehydrogenase, and catalase after sericin preincubation and subsequent H_2O_2 treatment.	Jagtapb and Khyade (2018)
	For the first 10 weeks, combine silk sericin with 1,2-diethylhydrazine.	1,2-Dimethylhy drazine challenged mice		Expression of c-myc and c-fos proteins; levels of 8-hydroxydeoxyguanosine, 4-hydroxynonenal, and inducible nitric oxide synthase protein. Incidence of colon cancer; number of colon adenomas; BrdU labeling index of colonic proliferative cells.	Zhaorigetu et al. (2001)

Continued

Table 12.1 Promising pharmaceutical activities of sericin.—cont'd

Pharmacological activity	Mode of use	Model used	Activity		Sources
			Upregulation	Downregulation	
	Silk sericin	Human colorectal cancer SW480 cell line	Producing caspase-3, which induces cell death; causing cells to enter an S-phase arrest.	Cell survival; inducing cell death by downregulating Bcl-2.	Kaewkorn et al. (2012)
	Sericin (silk) treatment	1,2-Dimethyl hydrazine treated rats	Antioxidant capacity.	Mucosal lipid peroxidation in the colon; the prevalence of abnormal crypt foci throughout the colon's surface area.	Zhaorigetu et al. (2007)
	Instantaneous application of topical sericin following UVB therapy	UVB-induced skin lesion in hairless mice	–	Skin lesion development (including lesion size and color intensity), epidermal thickness, PCNA, 4 HNE, and COX-2 protein expression, and inflammatory response.	Zhaorigetu et al. (2003a)
	After applying 7,12-dimethylbenz anthracene (DMBA) to the skin, sericin was applied immediately, and then UVB irradiation was administered twice weekly for a total of 22 weeks.	UVB-induced tumor promotion in the DMBA initiated mouse skin	–	Incidence and proliferation of tumors.	Zhaorigetu et al. (2003b)

Cardiovascular activity	Cocoon silk extract is used in a variety of conventional medicines.	Cardiotoxicity caused by isoproterenol in rats	–	Damage to the heart is reduced by lowering cardiac marker enzymes (CK-MB and troponin), the heart's weight in relation to the patient's body weight, the amount of myonecrosis, the number of inflammatory cells filtered in, and lipid peroxidation. Enhanced cardiac recuperation and antioxidant ability.	Mahmood et al. (2015)
	Preliminary treatment with silk cocoon extracts in ethanol	Rats with isoprenaline-induced myocardial infarction	–	Signs of inflammation, including heat, redness, dilated capillaries, and scarring detected by a pathologist; multiple cardiac enzymes and the heart's weight ratio both showed considerable enhancements.	Srivastav et al. (2013)
	The conventionally formulated pretreatment (Khamira Abresham Hakim Arshad Wala)	Doxorubicin-induced cardiotoxicity in rats	Antioxidant activity (restoring MDA and GSH levels).	Enzymatic alterations associated with heart tissue damage	Nazmi et al. (2011)

Continued

Table 12.1 Promising pharmaceutical activities of sericin.—cont'd

Pharmacological activity	Mode of use	Model used	Activity		Sources
			Upregulation	Downregulation	
Gastrointestinal protective activity	Gastrointestinal defense mechanism	High fat-fed rats	Mucin and fecal IgA, which measure gut immune and barrier functioning.	No significant variation in the fecal organic acids acetate and n-butyrate or the fecal secondary bile acid microbiota composition between the high fat-diet with and without sericin.	Okazaki et al. (2011)
	Sericin protein as a pretreatment	Gastric damage in mice caused by alcohol	Reduced blood alcohol content; recovery of stomach injury markers such as glutathione S-transferase, superoxide dismutase, and glutathione; mitochondrial repair in the stomach lining.	Alcohol content of the blood.	Li et al. (2008b)
	Pretreatment with sericin protein	Rats with constipation caused by atropine	The control group experienced a significant drop in fecal wet and dry weight; Wet and dry fecal weights did not differ in rats fed sericin; the sericin group (regardless of atropine treatment) had a higher water content than the control group.	–	Sasaki et al. (2000a)
	Combining sericin, white egg albumin, and microelements	Sprague–Dawley male rats	There is no difference in the urine excretion of Zn, Fe, Mg, and Ca, and all of them appear to be absorbed. Toward the end, weight, food intake, and stool dry weight were all steady.	–	Sasaki et al. (2000b)

Activities associated with complications of Hypoglycaemia	Acid-hydrolyzed silk peptides	Model of type 2 diabetes in nonobese, partially pancreate ctomized (Px) rats	Tolerance to glucose and maltose after oral administration; secretion of insulin; resistance to the loss of bone mineral density and lean body mass caused by paclitaxel.	–	Park et al. (2020a)
	High-fat diet with acid-hydrolyzed silk peptides	High-fat diet-induced obesity	Subcutaneous (SAT) and visceral (VAT) adipose tissue (AAT) adipogenic transcription factor expression is downregulated, suggesting weight gain suppression.	Increased levels of glucose and adipocyte size, HbA1c expression, ubiquitin proteasome activity, and accelerated expression of myoblast determination protein 1 (MyoD)/ myogenic factor 4 (myogenin).	Lee et al. (2020)
	Silk peptides that have been acid-treated	3T3-L1 adipocytes		Consolidation of lipids; C/EBP and PPAR expression.	Lee et al. (2020)
	The green sericin layer of a cocoon, extracted using ethanol.	T2DM mice	Increases in islet area and the number of insulin-positive beta cells; increased levels of insulin and hemoglobin A1c; increased ISI, SOD, and GSH-Px activity.	Better values for oral glucose and insulin tolerance; HOMA-IR; and activity levels of NF−B, IL-6, and TNF-.	Zhao et al. (2019)

Continued

Table 12.1 Promising pharmaceutical activities of sericin.—cont'd

Pharmacological activity	Mode of use	Model used	Activity		Sources
			Upregulation	Downregulation	
	Sericin hydrolyzate peptide fraction	Inhibition of α-glucosidase enzyme test	Acarbose-like α-glucosidase inhibition.	–	Fang et al. (2017)
	Silk sericin	T2DM rats	–	Increased expression of the growth hormone receptor and IGF-1 in the testes; enhanced serum growth hormone levels; enhanced serum growth hormone expression; enhanced serum testosterone and IGF-1 levels; enhanced spermatogenic activity.	Song et al. (2015)
	Five times a day after corneal injury, rats' eyes were injected with silk sericin.	Otsuka long-Evans Tokushima fatty rats (T2DM model) with corneal wounds	Healing and shrinking of the wound progress; complete healing within 48 h.	–	Nagai (2013)
	Silk sericin	Nerve cell damage in the sciatic nerve in T2DM rats	–	Increased neurofilament protein expression in the sciatic nerve; increased expression of nerve growth factor in the spinal ganglion and anterior horn cells of the lumbar spine (L4-6); increased expression of neuropeptide Y in these regions.	Song et al. (2013)

Neuropsychological activity	A syrup made from silk cocoon aqueous extract	Patients with mixed anxiety-depressive disorder	–	Compared to the control group, the median anxiety and sadness ratings at weeks 6 and 12.	Zeinalpour et al. (2021)
	Silk fibroin nanoparticles	Traumatic Brain injury model	–	Long-term neurological function recovery after brain injury; improved survival of primary neuronal and astrocyte cultures in 3D silk fibroin matrices compared to 2D plastic plates in oxygen-glucose deprivation.	Moisenovich et al. (2019)
	Enzymatic hydrolysis of the silk fibroin protein (FPEH)	Healthy adults, 55 years old on average	Improvements in recollection, efficiency at recalling information, drawing, and memory quotient as a function of dosing; Depending on the outcome, the best FPEH dose was either 400 or 600 mg; there were no documented side effects.	–	Kang et al. (2018)
	Preparation of silk amino acids (SAA)	Rats model for Parkinson's disease	Reduced neuronal death and dopamine and its metabolite losses caused by 6-OHDA treatment. Recovery from the pole test impairments brought on by 6-OHDA. Enhanced ipsilateral forelimb utilization in the cylinder test. The circling behavior caused by apomorphine in PD rats has improved.	–	Kim et al. (2011)

Continued

Table 12.1 Promising pharmaceutical activities of sericin.—cont'd

Pharmacological activity	Mode of use	Model used	Activity		Sources
			Upregulation	Downregulation	
Activities for wound healing and skin health	Pure natural silk dressing	Patients who have burns spanning more than 10% of their bodies	–	Scarring and more surgeries compared to those whose wounds were repaired with nylon mesh and collagen; high levels of contentment with the esthetic results; increased frequency of painful clothing changes; rapid reepithelization.	Schiefer et al. (2020)
	Silk sericin/AgNPs-functionalized sodium alginate hydrogel bandage	Rats with artificial wounds	Wound closure rate; absence of pus and inflammation.	On day 12, there was no evidence of infection or infection-related complications.	Tao et al. (2021)
	Dressing composed of AgNPs-sericin and poly (vinyl alcohol).	Rats with artificial wounds	Antimicrobial properties; rapid wound closure; increased healing time.	–	Tao et al. (2019)
	Hydrogels based on SF	Hypertrophic scarring in rabbits	In the group treated with SF hydrogel, the wounds were noticeably lighter and more closely matched the surrounding normal skin tone. a Smoother appearance of scars.	Hyperplasia of scar tissue index.	Li et al. (2020b)
	Sol-gel film made from silkworm cocoons	Artificial wound-created in rabbits	Speedy recovery from wounds.	Quick reduction of swelling and tissue damage; full, healthy epidermal regrowth.	Yu et al. (2017)

against *S. pneumoniae*, *Pseudomonas aeruginosa*, and *E. coli* was found to be augmented at higher concentrations ranging from 10 to 20 mg/mL. Following a 7-day treatment regimen involving the application of a 2% sericin solution, the researchers documented a decrease in colony count from an initial value of 146 to a final count of 29. The literature has documented that silk sericin possesses antibacterial properties as well as the ability to inhibit biofilm formation. A recent in vitro study by Aramwit and colleagues (Aramwit et al., 2020) looked at how well sericin stopped biofilms from forming and got rid of biofilms that were already there. The study's results showed that the three different ways of extracting sericin using urea, heat, and acid degradation were all good at stopping biofilm from forming. Among these methods, sericin extracted using urea demonstrated the highest level of antibiofilm activity against *Streptococcus mutans*. Tao et al. (2021) demonstrated a hydrogel-based potential antibacterial effect. They formulate a moldable and injectable semiinterpenetrating network hydrogel (SA/Se) by functionalizing sodium alginate with silk sericin, using calcium ions as the crosslinking agents. During this process, the phenolic hydroxyl group of tyrosine in sericin synthesized silver nanoparticles (AgNPs) in situ, enhancing the antibacterial qualities of the hybrid hydrogel. The hybrid hydrogel demonstrated a strong antibacterial effect by irreversibly disrupting the structure of bacterial membranes, leading to bacterial lysis and death of *E. coli, S. aureus,* and *P. aeruginosa* (Fig. 12.4).

4.2 Antioxidant and antitumor activities

The antioxidant properties of sericin have been well documented over an extended period of time. The suppressive effect of its antioxidant activity on lipid peroxidation in the intestine has been demonstrated, indicating its potential utility in mitigating the progression and metastasis of colon cancer (Cao & Zhang, 2016). In their study, You-

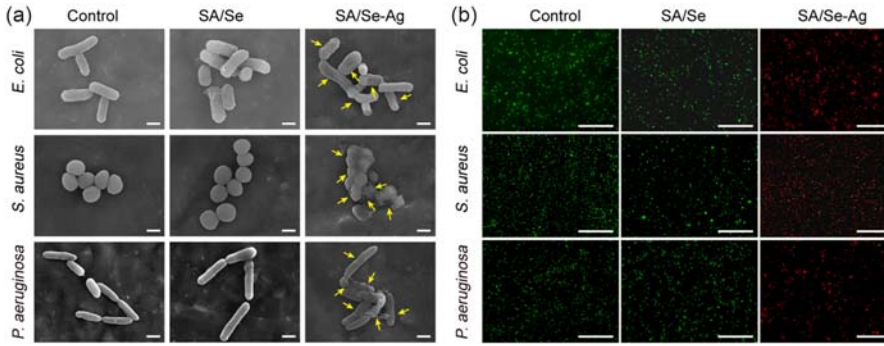


Figure 12.4 Antibacterial activity. (a) Destruction of bacterial membrane observed by SEM. Scale bar, 1 μm. (b) LIVE/DEAD staining assay. Scale bar, 100 μm.
From Tao, G., Cai, R., Wang, Y., Zuo, H. & He, H. (2021). Fabrication of antibacterial sericin based hydrogel as an injectable and moldable wound dressing. *Materials Science and Engineering: C, 119*, 111597. https://doi.org/10.1016/j.msec.2020.111597.

Gui et al. (Li et al., 2008a) employed a mouse model to investigate the effects of sericin on alcohol-induced liver injury. The authors specifically highlighted sericin's capacity to restore depleted levels of antioxidant enzymes, including glutathione (GSH), glutathione peroxidase (GSH-PX), catalase (CAT), and superoxide dismutase (SOD). Furthermore, it has been observed that sericin exhibits an antioxidative impact on the peroxidation process of linoleic acid as well as a noteworthy ability to scavenge hydroxyl, superoxide, and DPPH radicals (Fan et al., 2009). Separate in vitro research found that when compared to a control group, different silk sericin hydrolysates had significantly higher reducing power and ferrous ion chelating ability (Fan et al., 2010). The exposure of a feline fibroblast cell line to hydrogen peroxide resulted in a decrease in catalase activity and thiobarbituric acid reactive substances (TBARS), thereby supporting the notion that sericin possesses antioxidant properties. Furthermore, it was observed that cells subjected to sericin treatment exhibited a noteworthy increase in cell viability and restoration of cellular membranes, thereby indicating the potential of sericin as a viable option for cancer treatment (Jagtapb & Khyade, 2018).

Anticancer treatment can benefit especially from the mixing approach for the production of silk-based drug delivery systems (DDSs). The different cell types that make up a tumor make it not a homogeneous tissue (Fig. 12.5). Drug carriers may thus be advantageously modified to target cells of the tumor microenvironment in addition to cancer cells. Anticancer therapy may target stromal cells including cancer-associated fibroblasts (CAFs), angiogenesis-related cells (endothelial cells, pericytes), and immunological cells including tumor-associated macrophages (TAMs).

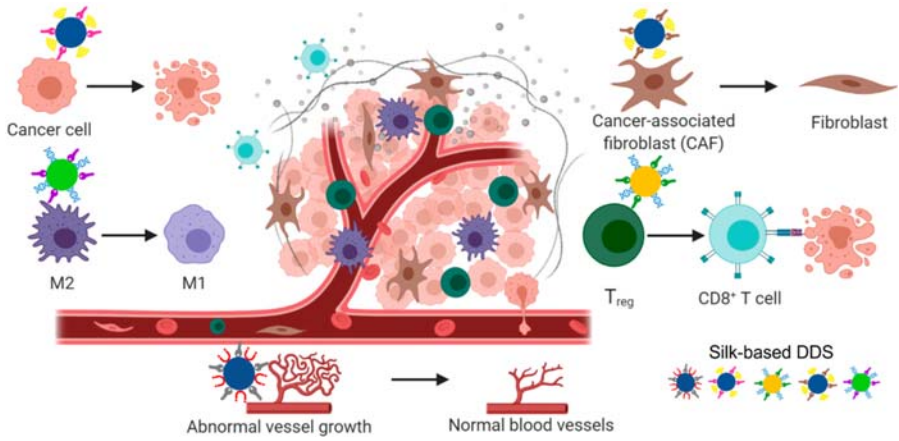


Figure 12.5 Tumor microenvironment (TME) and possible anticancer therapeutic targets. Tumor-associated macrophages (TAMs/M2), lymphocytes T_{reg}, angiogenesis-related cells (endothelial cells, pericytes), cancer cells, and immunological cells as possible targets of a silk-based medication delivery system for treatment.
From Florezak, A., Deptuch, T., Kucharczyk, K. & Dams-Kozlowska, H. (2021). Systemic and local silk-based drug delivery systems for cancer therapy. *Cancers, 13*(21), 5389. https://doi.org/10.3390/cancers13215389.

Anticancer oligotherapeutics have been effectively delivered to macrophages in vitro using spheres fashioned of bioengineered MS2KN silk (Kozlowska et al., 2017). They are now being studied in a rat breast cancer model as DDSs. One way to imagine cancer treatment is to administer silk spheres that are designed to give different medications to different cell types either simultaneously or successively (Fig. 12.5). Furthermore, this technology is general and maybe applicable to several kinds of cancers; for instance, immunotherapy-tested silk particles in breast cancer may be modified to treat immunosuppressed TME in other cancer types. Future research might also reveal new chemicals linked to TME cells and cancer.

When mice were given 1,2-dimethylhydrazine, the good effects of sericin on colon adenocarcinoma, cell growth, and nitric oxide production were seen. These effects were demonstrated following the administration of a dosage of 30 g/kg of sericin over a period of 115 days (Zhaorigetu et al., 2001). To test the effects of sericin, an in vitro experiment was performed within two distinct molecular weight ranges on the SW 480 cell line of human colon cancer. The effects of tiny sericin on cell viability were observed to be greater through the activation of caspase-3, down-regulation of Bcl-2 expression, and increased cell cycle arrest at the S phase (Kaewkorn et al., 2012). In an experimental study utilizing a rat model to investigate colon carcinogenesis, the administration of sericin at a concentration of 3% demonstrated a notable reduction in both oxidative stress levels and the occurrence of tumors in the colon. A study conducted by researchers has demonstrated that sericin possesses the ability to mitigate the occurrence of redness, diminish the size of lesions, and decrease the probability of tumor formation and metastasis as a result of exposure to ultraviolet radiation emitted by the sun (Zhaorigetu et al., 2003a). In their study, they conducted a comprehensive investigation into the impact of sericin on tumor promotion in mouse skin tumorigenesis models induced by 7,12-dimethylbenz (alpha) anthracene (DMBA) and 12-O-tetradecanoylphorbol 13-acetate (TPA). Initially, sericin was administered in a topical manner onto the skin of female ICR mice that had been initiated with DMBA. Subsequently, tumor growth was treated by employing TPA. The protective capacity of soricine was evidenced by a decrease in tumor formation and proliferation. In the second step of the experiment, sericin was administered topically to the dorsal skin of mice, after which a 24-hour period was allowed to elapse before the initiation of the double TPA treatment procedure. Histological changes caused by inflammation, such as increased cell growth and leukocyte infiltration, were greatly reduced by pretreatment with sericin. The protein levels of c-fos, c-myc, and COX-2 in the epidermis of healthy skin were likewise diminished. The results of these studies show that silk sericin might help protect against the growth of skin tumors by reducing oxidative stress and inflammation (Mumtaz et al., 2023).

4.3 Cardioprotective activities

Several studies have been conducted to examine the potential cardiovascular benefits associated with silk cocoons. The impact of different formulas of isoproterenol-induced cardiotoxicity pretreatment on Wistar rats was investigated in an in vivo study conducted by Mahmood et al. (2015) and revealed the exhibition of cardioprotective

effects by cocoon silk extract. The results indicated that the silk formulations possess the ability to mitigate heart damage, enhancements in heart recovery, cardiac antioxidant capacity, and lipid peroxidation, as well as decrease in cardiovascular marker enzymes (such as CK-MB and troponin). In a similar manner, the administration of ethanolic extracts derived from silk cocoon (known as Abresham) prior to the induction of a myocardial infarction with isoprenaline (ISO) demonstrated cardioprotective effects. This was observed through the reduction of inflammatory response, redness, capillary dilation, and scar formation in comparison to the group treated solely with ISO. The study also demonstrated improvements in the ratio of heart weight to body weight as well as the levels of various cardiac enzymes (Srivastav et al., 2013). In addition, the administration of silk cocoon extract prior to exposure to doxorubicin, a drug known for its potential cardiotoxicity, resulted in a significant reduction in cardiac-related enzymatic changes and tissue injuries in Wistar albino mice (Nazmi et al., 2011).

4.4 Controlled release applications

In order to navigate the limitations mentioned earlier, the utilization of controlled-release formulations emerges as a prominent strategy within the realm of pharmaceuticals. Conventional dosage forms facilitate rapid release, which may lead to patient noncompliance in achieving the desired therapeutic effect during the administration of diverse dosing regimens. Based on the literature review, it has been observed that both sericin and SA exhibit promising characteristics in terms of their ability to undergo cross-linking, copolymerization, and blend formation with various other polymers. Amino group in silk sericin confers polarity to its functional groups, resulting in an increase in the viscosity of the solution and a reduction in the leakage of the blend. Furthermore, a concoction comprising silk sericin (2.5%), salicylic acid (2.8%), and diclofenac sodium (2.0% w/v) has been employed to facilitate the protracted discharge of diclofenac sodium. In addition to the rapid and complete liberation of diclofenac sodium by the sericin-free formulation within a mere 45 min, the blend containing the drug exhibited an impressive entrapment efficiency of 81.06%. Furthermore, the presence of high-viscosity sericin significantly delays the release of diclofenac sodium, extending the liberation time from 240 to 360 min. Alginate is responsible for providing gastroresistance to particles. The utilization of Weibull release kinetics (R2:0.9986) was additionally taken into account to analyze the drug release behavior from the sericin−SA blend in the dissolution profile (Vidart et al., 2018). This biological phenomenon encompassed cellular expansion, extracellular matrix degradation, molecular movement, and molecular conformational adjustments. Another investigation revealed the utilization of a controlled-release methodology involving a combination of sericin and silk fibroin. The amalgamation of silk proteins sericin and fibroin was accomplished by Srisuwan et al. through the utilization of the water-in-oil emulsification technique. In this instance, the blue dextran functions as a placebo, mimicking the experimental conditions. The dissolution rates of microparticles composed of a 75:25 sericin:fibroin blend was observed to be 81%, 50%, and 62%, respectively. Following an initial rapid release, occurring within a span of 3 hours,

attributed to the drug concentration gradient resulting from matrix swelling, the composites proceeded to gradually release the remaining drug payload over a duration of 48 h at a temperature of 37°C and a pH of 7.4. This phenomenon arises due to the dissolution or surface erosion of the sericin and fibroin constituents. As per the authors of the paper, the sericin microparticle exhibits an initial phase of rapid medicine release within the first 3 hours, followed by a subsequent phase of gradual release throughout the remaining duration. The presence of fibroin within a sericin mixture induces conformational alterations, transitioning the sericin from a disordered coil structure to a sheet-like arrangement. Consequently, this modification influences the dissolving characteristics of the blend. Hence, the alteration in release dynamics may potentially confer greater advantages (Srisuwan et al., 2017).

4.5 Application in cosmetics

The incorporation of sericin into cosmetic formulations, such as creams and shampoos, has been found to result in various beneficial effects. These include enhanced hydration and elasticity, improved cleansing with reduced irritation, as well as antiaging and antiwrinkle properties (Kunz et al., 2016). Additionally, sericin has been shown to effectively prevent chapping and brittleness of the nails. The applications of these substances are primarily attributed to the inclusion of amino acids containing hydrophilic side chains, which constitute approximately 80% of the composition. Notably, serine, which accounts for 30%−33% of the amino acid content, exhibits a significant ability to absorb water. Sericin has the capability to create a film that is soft and smooth when applied to the skin, thereby serving as a barrier against water loss (Shitole et al., 2020a).

The study conducted by Padamwar et al. (2005) examined the in vivo moisturizing impact of sericin on human skin. The results revealed that sericin reduced impedance while simultaneously increasing the levels of hydroxyproline and hydration in the epidermal cells. The observed rise in hydration levels was attributed to the occlusive properties of sericin, which effectively hindered the process of transepidermal water loss, a key factor in the occurrence of skin dryness. The moisturizing efficacy exhibited no significant impact on the topographical structure of the epidermis. The authors maintain that sericin exhibits a comparable amino acid composition to filaggrin, a constituent of the stratum corneum, and plays a role in the inherent moisturization of the skin. Consequently, sericin possesses significant moisturizing properties. The presence of dryness is a distinguishing feature observed in several skin disorders, including atopic dermatitis and ichthyosis. These conditions are associated with a reduction in the concentration of free amino acids within the outermost layer of the skin, known as the stratum corneum. Kim et al. (2012) investigated the effectiveness of silk proteins, specifically fibroin and sericin, as a therapeutic intervention for atopic dermatitis using an animal model. The researchers found that the inclusion of 1% sericin in the diet over a period of 10 weeks resulted in a notable enhancement in epidermal hydration. The ingestion of sericin resulted in an elevation in triglyceride and free amino acid levels. Additionally, there was an upregulation of peroxisome proliferator-activated receptor (PPARγ), peptidylarginine deiminase-3 (PAD3), and

caspase-14. These molecules play a crucial role in enhancing the expression of profilaggrin and facilitating the degradation of filaggrin into free amino acids, ultimately leading to the improvement of dry skin conditions. Hence, sericin emerges as a promising adjunctive therapeutic option for managing dry skin conditions, including atopic dermatitis (Kunz et al., 2016).

4.6 Extended and sustained release applications

The utilization of a combination of silk sericin and sodium alginate was employed in order to extend the duration of release for the antihypertensive drug valsartan. In a concise manner, the researchers generated a concoction comprising valsartan, sericin, and sodium alginate in specific proportions (2.0:2.5:1.0% W/V). The remarkable gelling capacity of alginate can be attributed to the existence of divalent ions. The sericin present in the blend is responsible for the diverse range of applications facilitated by the cross-linking process. The observed phenomenon led to an extended and sustained liberation of valsartan, with approximately 94% of the compound being released after a duration of 28 h. This outcome can be attributed to the formation of crosslinks between salicylic acid and sericin. The authors observed a decrease in drug leakage and incorporation capacity (82.75%, 2.61%) when exposed to a high concentration of salicylic acid. This phenomenon was attributed to the drug's ability to form crosslinks with the salicylic acid. However, the maximum drug loading capacity ($30.09 \pm 1.21\%$) is attained when using the ideal concentration of sericin. The formulation utilizing alginate and sericin exhibited remarkable drug loading capabilities and a protracted drug release profile (Freitas et al., 2019). The sericin−salicylic acid matrix, loaded with ibuprofen, as developed by Freitas et al. utilized polyethylene glycol as a chemical crosslinking agent. The matrix was analyzed and found to have a particle size distribution ranging from 0.80 to 1.08 mm. The drug entrapment efficiency exhibited a range of 73.01%−94.15% across formulations that possessed the optimal concentration of sericin and drug ratio. This shows how important the concentration of sericin is, especially its polar functional groups like hydroxyl and carboxyl, when it comes to how well it traps drugs. During the process of nanoparticle synthesis, it has been observed that sericin and salicylic acid exhibit robust crosslinking behaviors. This cross-linking phenomenon plays an important role in preventing the unwanted leakage of drugs from the nanoparticles. However, the presence of salicylic acid influences the rate at which the medication is released. Specifically, when the mass fraction ofsalicylic acid reaches 2.8%, it results in a gradual and consistent release of the medication. This distinctive experimental outcome is predicated on the observation that highly interconnected nanoparticles of salicylic acid exhibit reduced solvent infiltration, thereby influencing the swelling characteristics (Freitas et al., 2018).

4.7 Gastrointestinal protective activity

Extensive research has been conducted to investigate the impact of silk cocoons on digestive function. Using rats fed a high-fat diet, Okazaki et al. (2011) examined how sericin affected the luminal environment of the intestine. The results of the study

indicate that sericin exhibited beneficial effects in reducing the occurrence of colon cancer and ulcerative colitis in rats subjected to a high-fat diet. These effects were observed through alterations in the immune and barrier functions of the intestines. In an independent investigation employing a mouse model to simulate alcohol-induced gastric injury, the researchers observed that sericin possesses the capacity to rectify the compromised architecture of gastric mucosal mitochondria and mucosal irregularities in the mouse stomach, relative to the control group. This restoration is achieved through the augmentation of antioxidant enzyme activity as well as the promotion of "first-pass metabolism" in the liver and an enhanced rate of ethanol excretion in the urine (Li et al., 2008b). According to a study conducted by researchers, it was observed that rats administered with atropine and subsequently fed sericin exhibited a notable reduction in the occurrence of constipation. The oral administration of sericin resulted in a significant enhancement in the bioavailability of essential microelements such as zinc, iron, magnesium, and calcium (Sasaki et al., 2000a). Silk fibroin—based nanoparticles have garnered significant attention in the field of medical research due to their notable antiinflammatory properties and capacity to promote mucosal healing. Consequently, these nanoparticles have been extensively explored for their potential therapeutic applications in the treatment of inflammatory bowel disease (IBD), colon cancer (CRC), and the mitigation of associated symptoms in CRC patients. Other benefits include the fact that the sequences are biodegradable, biocompatible, easy to self-assemble, less likely to cause an immune response, and easy to control.

4.8 Hypoglycemia activities

The capacity of silk cocoons to lower blood sugar levels has been extensively investigated and documented in scientific research. The in vitro study showed that when insulin-resistant HepG2 cells were given silk fibroin peptides, their metabolisms of glucose and fat were improved. By enhancing glucose uptake and promoting glycogen storage while concurrently reducing triglyceride (TG) levels (Yang et al., 2019). An investigation was undertaken to assess the impact of an ethanolic extract obtained from the green cocoon shell of the silkworm, which is rich in flavonoids, through an in vitro methodology. The analysis revealed significant antioxidant, antiinflammatory, and antihyperglycemic properties. The antihyperglycemic effects were attributed to the inhibition of two enzymes, alpha-amylase and alpha-glucosidase, which are known to be involved in the development of hyperglycemia (Wang et al., 2020). In a separate investigation, it was observed that rats subjected to partial pancreatectomy exhibited enhanced oral glucose tolerance and insulin tolerance, along with increased insulin expression activity. These findings provide evidence of the antidiabetic properties associated with silk peptides (Park et al., 2020a). High-fat diet-induced overexpression of glucose transporter 4 (GLUT4) and uncoupling protein 3 (UCP3) in relation to glucose uptake and mitochondrial activity suggests that dietary silk peptides have an inhibitory effect on blood glucose levels that is dose-dependent in mice (Lee et al., 2020). The study suggested the enhanced cellular insulin sensitivity, as

well as improvements in testing for insulin and glucose tolerance in the mouth, along with reduced blood glucose levels, following a 7-week administration of an ethanolic extract derived from the sericin layer in a mouse model of type 2 diabetes (Zhao et al., 2019). Various hypotheses have been proposed to explain the mechanisms through which the consumption of silk cocoons lowers blood sugar levels in hyperglycemic diabetic models. Several mechanisms have been identified that contribute to the beneficial effects of the compound under investigation. These mechanisms include the inhibition of α-glucosidase, the upregulation of important enzymes involved in insulin metabolism and glycolysis, such as glycogen synthase, GSK3, GLK, PFK1, PKM2, and AMPK, and the ability to promote pancreatic cell growth and regrowth (Dong et al., 2020; Fang et al., 2017; Park et al., 2020b).

4.9 Inhibition of devitrification

When compared with crystalline structures, it is commonly observed that the amorphous state of the drug exhibits a higher energy content. This implies that the amorphous or metastable forms of the medications pose a significant risk. Through a series of progressive changes, it undergoes a gradual metamorphosis, ultimately assuming a state characterized by the formation of crystals (Al-Obaidi et al., 2017). A plethora of empirical evidence showcases the capacity of polymers and proteins to effectively stabilize amorphous pharmaceutical formulations. The intermolecular interactions, specifically hydrogen bonding and/or electrostatic interactions, observed between medicines and polymers and proteins are in accordance with the probable mechanism responsible for stabilizing the amorphous state. The investigation conducted by Jadhav et al. delved into the functional properties of sericin within binary solid dispersions containing poorly soluble or hydrophobic pharmaceutical compounds, namely lornoxicam, meloxicam, and felodipine. Physical mixing, ball milling, solvent evaporation, and spray drying are among the techniques employed in the production of solid dispersions containing sericin and medicinal substances. The hydrophilic nature of sericin can be attributed to the structural arrangement of its amino acid chain. Hydrogen bonding, the van der Waals force, and electrostatic attraction collectively contribute to the enhancement of sericin's stability in its solid state, while the hydroxyl, carboxyl, and amino groups actively inhibit the process of nucleation. Based on the findings of these investigations, it was concluded that the spray-dried solid dispersion comprising 7.4%, 8.23%, and 18.31% crystallinity of lornoxicam, meloxicam, and sericin, respectively, exhibited the highest degree of formulation stability. After studying the stability of solid dispersion for 3 months, it was seen that spray-dried felodipine-sericin solid dispersion still had a microcrystalline stable amorphous state and a dissolution performance of more than 85%. The available evidence suggests that sericin has the capacity to inhibit approximately 90% of the devitrification process. This means that it has a good chance of being used to stabilize naturally occurring amorphous proteins that use hydrophilic and hydrophobic drug-binding sites (Salunkhe et al., 2019).

4.10 Skin health and wound healing activities

Sericin is a protein that is found in silk cocoons. It has the potential to be used as a wound-healing agent in dressings because it is biocompatible, helps keratinocytes and fibroblasts grow, promotes cell division, and keeps moisture in for a long time (Tao et al., 2019). A clinical trial was conducted to assess the efficacy of utilizing pure silk dressing in the management of superficial burn injuries that encompassed over 10% of the total body surface area. Rapid re-epithelialization was successfully attained, thereby circumventing the need for uncomfortable dressing changes. Additionally, patients expressed a high degree of satisfaction with respect to both scarring and cosmetic considerations (Schiefer et al., 2020). There has been a significant amount of research and experimentation focused on the development of sericin-based composite products. Various approaches, materials, and formulations have been utilized in order to enhance the antibacterial and physiochemical characteristics of sericin. This study presents the development of a newly designed semiinterpenetrating hybrid hydrogel for the purpose of treating wound injuries. The hydrogel is made of silver nanoparticles (AgNPs) and sodium alginate that has been modified with silk sericin. After a duration of 50 h, the hydrogel exhibited a retention rate of over 5% in phosphate-buffered saline. Additionally, the swelling ratio was measured to be 32. The hydrogel demonstrated notable effectiveness in terms of its antibacterial activity (Dong et al., 2022). Tao et al. (2019) showed that *Staphylococcus aureus* and *Pseudomonas aeruginosa* cannot grow in silk sericin/polyvinyl alcohol sponges with in situ biomimetic AgNPs. This was achieved through the sponges' antibacterial activity and their ability to suppress biofilm formation. The application of sponges in a Wistar rat model of skin laceration resulted in an expedited progression of wound healing. This was achieved through the promotion of re-epithelialization, angiogenesis, and collagen deposition. A separate investigation revealed that the application of a sericin/agarose (50:50) gel, containing lysozyme exhibited enhanced wound healing capabilities attributed to its distinctive characteristics. The aforementioned characteristics encompassed a remarkable capacity for water retention and a powerful antimicrobial efficacy against *Escherichia coli* and *Staphylococcus aureus*, while exhibiting no detrimental effects on healthy cells (Yang et al., 2018). Furthermore, the wound healing potential of the ZnONPs-polydopamine-coated sericin/PVA composite film formulation has been demonstrated through the enhancement of medicinal properties such as hydrophilicity, swell ability, tensile strength, elongation, and antibacterial activity (Ai et al., 2019). Nevertheless, silk fibroin has demonstrated potential for promoting the restoration and preservation of skin health through its ability to enhance cellular proliferation, migration, adhesion, and the expression of associated proteins (Vidya & Rajagopal, 2021). Hydrogel-based wound healing was shown by Tao et al. (2021). They use calcium ions to crosslink sodium alginate and silk sericin to make a moldable and injectable semiinterpenetrating network hydrogel (SA/Se). The phenolic hydroxyl group of tyrosine in sericin generated AgNPs in situ. SA/Se−Ag group wound contraction ratio was 99% after 12 days in an animal investigation, demonstrating it can promote wound healing (Fig. 12.6). This new hydrogel may aid wound healing and tissue engineering (Tao et al., 2021). An optimal wound dressing should possess the capacity to impede

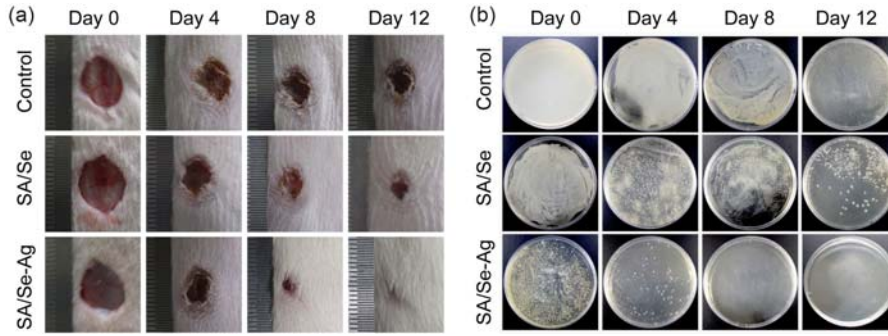


Figure 12.6 Wound healing activity. (a) Wound on day 0, 4, 8, and 12 after surgery. An open wound was used as the control. (b) Wound exudates culture.
From Tao, G., Cai, R., Wang, Y., Zuo, H. & He, H. (2021). Fabrication of antibacterial sericin based hydrogel as an injectable and moldable wound dressing. *Materials Science and Engineering: C, 119*, 111,597. https://doi.org/10.1016/j.msec.2020.111597.

bacterial infiltration and efficiently eradicate microorganisms. *Staphylococcus aureus* is the primary causative agent of wound infections. In this experiment, *S. aureus* was employed to infect the wound in order to assess the bactericidal efficacy of the hydrogels.

In an animal model of burn injury, using injectable hydrogels that contained silk fibroin led to better wound healing, collagen deposition, and blood vessel growth (Dong et al., 2022). When hypertrophic scars were treated with a hydrogel that had 3% silk fibroin in it, the scars looked a lot better. This was achieved through a reduction in pigmentation intensity, decreased tissue density, and enhanced alignment of collagen fibers (Li et al., 2020b). In a study by Yu et al. (Guan et al., 2020), it was possible to find convincing histological evidence demonstrating the successful reconstruction of the epidermis and the speedy healing of wounds. These findings were observed through the utilization of silk fibroin sol−gel films. The wound dimensions exhibited a decrease of approximately 30% following a 10-day period of therapy involving the application of fibroin biomaterial dressings. Subsequently, an additional reduction of 11% was observed after 15 days of treatment (Yu et al., 2017). In contrast, the comparison group did not receive any form of treatment. Novel formulations of silk and its constituent elements have been recently developed for the purpose of addressing various dermatological conditions. These encompass nanoporous films, silk fibroin microparticle dressing encapsulating insulin, lyophilized silk fibroin dressing (Salunkhe et al., 2018), and nanopowder dispersed as aerosols (Chou et al., 2021; Li et al., 2017; Liu et al., 2021).

4.11 Solubility enhancement applications

Salunkhe and his colleagues found that sericin-containing effluent from sericulture could be used to make poorly soluble medicines more bioavailable. Silk sericin's hydrophilic properties and possible binding sites may help dissolve and solubilize poorly

soluble drugs. To make binary solid dispersions of poorly soluble medicines and sericin, the researchers used physical mixing, ball milling, solvent evaporation, and spray drying. 1:0.5, 1:1, 1:1.5, 1:2, 1:2.5, and 1:3 was the drug−sericin ratios. The study found that with the increase of sericin concentration the Gibbs free energy decreased and the sericin interaction increased (1:1). Polar drug groups connected to the sericin activities via hydrogen, electrostatic, and van der Waal forces, which destabilized the acrystalline form. Curiously, the physical combination with sericin reduced the medication's crystallinity. In this case, the drug's crystallinity was actively suppressed by sericin's amorphous nature. In addition, the sericin showed a hollow, bowel-shaped morphology when mixed with meloxicam and lornoxicam, which resulted in a lot of exposed surface area for its size. An increase in solubility of up to 8 to 10-fold (drug: carrier ratio 1:2 w/w) is resolved, with meloxicam (98.81%) dissolving better than lornoxicam (98.37%) dissolving better than felodipine (97.11%) dissolving in 120 min compared to pristine drugs (26.72%, 29.14%, and 22.75%, respectively). The felodipine binary mixture's rounded, smooth surface lowered its dissolution and solubility. Drug loading, dissolution, solubility enhancement, and drug distribution are all areas where the scientists believe sericin could benefit from its unusual shape and structure. According to forecasts (Salunkhe et al., 2018), the future of solubility and the sericulture industry may depend on sericin. Lipophilic lipid management medicine fenofibrate (FF) is a pharmaceutical agent. Due to its low water solubility (3 g/L) and sluggish dissolution rate, FF has a low oral bioavailability. Parisi and coauthors looked into whether or not sericin could boost bioactivity in FF. The drug absorption (in vitro) of sericin-poly-(ethylcyanoacrylate) nanospheres is 72.9%, which is greater than that of pure drug, and the nanospheres are generated by interfacial polymerization in aqueous environments. After being created, these synthetic nanospheres exhibited remarkable mucoadhesive and hydrophilic properties. Following incubation for 3 h, the intestinal mucosa retained approximately 61% of the loaded FF. Mucin and sericin interact electrostatically, and this is what gives mucoadhesive characteristics. More than 70% of FF is absorbed by the body through the digestive tract, according to the in vivo study. In contrast, the FF-loaded nanospheres had a reduced lipid content. When compared to the hypercholesterolemic group, serum levels of alanine transaminase (ALT) and aspartate transaminase (AST) in the FF-sericin-poly-(ethylcyanoacrylate) nanospheres treated group were 28% and 21% lower, respectively. For poorly water-soluble medications, the ability to create sericin/poly (ethylcyanoacrylate) nanospheres implies an innovative synthetic method for administering drugs (Parisi et al., 2015).

4.12 Tissue engineering and drug delivery systems

Silk proteins have been used to make different composites for drug delivery and tissue engineering because they are biocompatible, their mechanical properties can be changed, and they have the ability to heal themselves (Wattanavijitkul et al., 2024). In this study, a variety of techniques, including freeze-drying, gas-foaming, salt-leaching, and electrospinning, are utilized to construct diverse biological structures. These structures encompass fibers, capsules, spheres, nano-based materials, and

porous three-dimensional frameworks such as sponges, hydrogels, foams, and scaffolds. These architectural designs have gained significant traction in the fields of tissue engineering and implantable devices (Cheng et al., 2018; Wani et al., 2020). From a biological perspective, it is widely recognized that silk fibroin−based structures have proven to be effective in facilitating the transportation of both small molecules, such as phytochemicals, and larger molecules, such as proteins and genes. These formations have demonstrated reliable capabilities for delivering therapeutic agents in a controlled manner, either through localized, systemic, or intracellular pathways. Additionally, these silk fibroin−based formations can exist in their natural state or be modified on their surface to enhance their functionality (Cheng et al., 2018). Akrami-Hasan-Kohal et al. (2021) have successfully engineered a drug delivery system that ensures a controlled release of dexamethasone sodium phosphate. This system involves the integration of chitosan nanoparticles loaded with the aforementioned drug into a hydrogel composed of silk fibroin, known as SFH/DEX-CSNPs. The findings exhibited a well-connected permeable matrix framework that exhibited a steady release of DEX in accordance with the initial-order model kinetics over a span of 16 days, accompanied by a minimal initial exploded relief.

In the following investigation, a mixture of a drug called hydrochloride microparticles was created using inhalable silk fibroin. The method of drug delivery that was utilized demonstrated an augmentation in the drug loading content as well as an enhancement in the mucosal penetration activity and lung accumulation rate. Additionally, it exhibited remarkable cytocompatibility and biosafety, as reported in reference (Lin et al., 2021). Furthermore, the proficient transportation of anticancer agents while minimizing associated side effects and addressing safety considerations is a fundamental characteristic of drug carriers employed in the field of cancer treatment (Nguyen et al., 2019). One recent study attempted to address this issue by decorating zeolitic imidazolate framework-8 with pH-responsive nano-based silk sericin in order to transport doxorubicin. The formulation exhibited enhanced stability, a mechanism of drug release triggered by acidic conditions, effective internalization by cellular structures, and demonstrated antitumor activity when combined with doxorubicin (Li et al., 2021). Similarly, a separate investigation sought to assess the effectiveness of a complex formed by grafting low-molecular-weight polyethyleneimine onto silk fibroin in packaging plasmid DNA containing the inhibitor of growth 4 and interleukin-24 genes. This study revealed that the complex not only enhanced the transfection of the human lung adenocarcinoma cell line but also exerted a notable inhibitory effect on the proliferation of these cancerous cells. Furthermore, it is noteworthy to mention that no notable deleterious impacts on healthy cells were documented (Bahremand et al., 2024; Niu et al., 2021).

Recently, there has been a significant focus on the utilization of silk-based biological substances for the purpose of reconstructing organ defects, with a particular emphasis on connecting tissues such as cartilage and bone (Zuluaga-Vélez et al., 2021). In a study conducted by Lee S. and colleagues, they produced an injectable form of hydrogels composed of gellan gum, silk fibroin, and chondroitin sulfate (GG/SF/CS) ternary components. These hydrogels were designed to promote the regeneration of cartilage tissue, and various proportions of the components were utilized in their fabrication. The

remarkable mechanical and physicochemical characteristics of the hydrogels were validated based on the results obtained from the swelling test, degradation rate analysis, compression test, and their inherent property of shear thinning. The selection of the 0.5 Gg per 3.5% solution of sodium fluoride/calcium sulfate formulation was made for conducting experiments both within controlled laboratory environments (in vitro) and within living organisms (in vivo). The chondrocytes enclosed within the hydrogel exhibited diminished toxicity, enhanced cellular attachment and growth, as well as the manifestation of cartilage-specific extracellular matrix (ECM) and genes (SOX9, COL-2, and AGG) (Lee et al., 2021). A recent study conducted in a laboratory setting examined the process of endochondral ossification using decellularized cartilage-derived extracellular matrix (CD-ECM) combined with a scaffold made of silk fibroin. This scaffold also contained human bone marrow−derived mesenchymal stem cells (hBMSCs). The study found that this combination had a significant impact on both the early and late stages of the cells' differentiation, particularly in terms of their hypertrophic phases. Additionally, the expression of certain markers associated with bone formation, such as IBSP, OSX, and COL1A1, was found to be significantly increased when compared to a scaffold that did not contain CD-ECM. Similarly, the utilization of the CD-ECM/silk fibroin scaffold resulted in the manifestation of heightened calcium deposition, the secretion of alkaline phosphatase, and the preservation of sulfate glycosaminoglycan content (Jeyakumar et al., 2021).

5. Consequences and toxicity levels

The utilization of silk cocoons, composed primarily of biocompatible components, has existed since prehistoric times. However, there is a scarcity of noted evidence pertaining to the toxicological aspects of silk cocoons. Furthermore, it is worth noting the inclusion of the United States Food and Drug Administration (FDA). Instead of silk sutures, a well-known biological scaffold made of fibroin called SERI has been used to strengthen soft tissue, especially in the repair of the abdominal wall (Jewell et al., 2015; Madden et al., 2020). The safety profile of sericin extracted from water has been thoroughly examined through a range of preclinical methodologies. The bacterial reverse mutation test, the micronucleus test on mammalian erythrocytes, and the chromosomal aberration test on mouse spermatogonia are all examples of genotoxicity testing. Additionally, the sub-chronic toxicity of sericin has been evaluated in Sprague−Dawley rats over a period of 90 days. In the last section, we talked about both in vitro and in vivo genotoxicity tests. The results showed that, compared to the negative control, sericin did not have any mutagenic or genotoxic properties. Throughout the duration of a 90-day sub-chronic exposure period, no fatalities were observed that exhibited a statistically significant association with the administered treatment. Weight, food intake, blood hematology and biochemistry components, urine indices, and histopathology results all showed no statistically significant alterations. The researchers found that the no-observed-adverse-effect level (NOAEL) of sericin, as determined in the study, was 1 g/kg/day for both male and female rats

(Qin et al., 2020). The safety profile of silkworm extract powder was also evaluated in rats using the same assays. Consequently, the oral administration of the substance resulted in a lethal dose exceeding 5000 mg/kg, and no untoward effects were documented during a 90-day period of powder ingestion. The researchers ultimately established the No-Observed-Adverse-Effect Level (NOAEL) for silkworm powder extract to be 2000 mg per kilogram per day for male and female rats (Heo et al., 2013). While there were instances where the principle was breached in certain extraction techniques at elevated rate (Aramwit et al., 2010), the outcomes derived from the MTT assay indicated that silk sericin solutions obtained through different silk extraction methods did not manifest any cytotoxic properties toward mouse fibroblast cells. This was observed even when exposed to concentrations as high as 40 g/mL for a duration of 24 h. No aberrant clinical signs, changes in biochemical or gross pathological markers, erythema, edema, scarring, or skin reactions were found in a separate study looking into the safety of silk protein films compared to a control group (Padol et al., 2011). Furthermore, a substantial body of studies has been conducted to look at the safety characteristics of silk and fibroin at the concentrations employed in cosmetic products (Johnson et al., 2020). Over a period of 14 days, the acute toxicity caused by giving sericin by mouth at doses of 500, 1000, and 2000 mg/kg did not cause any significant changes in the body weight, feces, respiratory rate, or visual characteristics that were tested. In contrast, the subacute toxicity test conducted over a period of 4 weeks using identical doses did not yield any discernible toxicological effects. Nevertheless, it was observed that when administered at the highest dosage, certain instances of inflammation or abnormalities in the essential organs were documented.

Ultimately, it was concluded that the NOAEL falls below 2000 mg/kg, thereby signifying its safety (Regina Inês et al., 2020). Nevertheless, there exist certain claims regarding the potential negative impacts purportedly associated with silk and its constituent elements. Following the meticulous process of isolating pure fibroin may be able to reduce the documented instances of an increased inflammatory reaction occurring after consumption of silk (Madden et al., 2020). Also, there is some evidence that silk fibroin might make amyloidogenesis worse, even though it is linked to a lower risk of getting amyloidosis (Tsukawaki et al., 2016). Furthermore, the phenomenon of silk sensitization was initially documented in the context of the pathophysiology of childhood asthma and its impact on the severity of the condition. This observation was made through a cross-sectional study involving children residing in a rural province of China renowned for its sericulture (Celedón et al., 2001).

6. Bibliometric analysis

An attempt has been taken to reflect a wide range of date (including number of scientific publication and patents) of 2 decade through bibliometric analysis. **All the date were exported from the PubMed using desired keyword**. In between 20 years, there are a lot of publication related to sericin has added to the scientific community throughout the world (Fig. 12.7). More than 550 numbers of publication have been

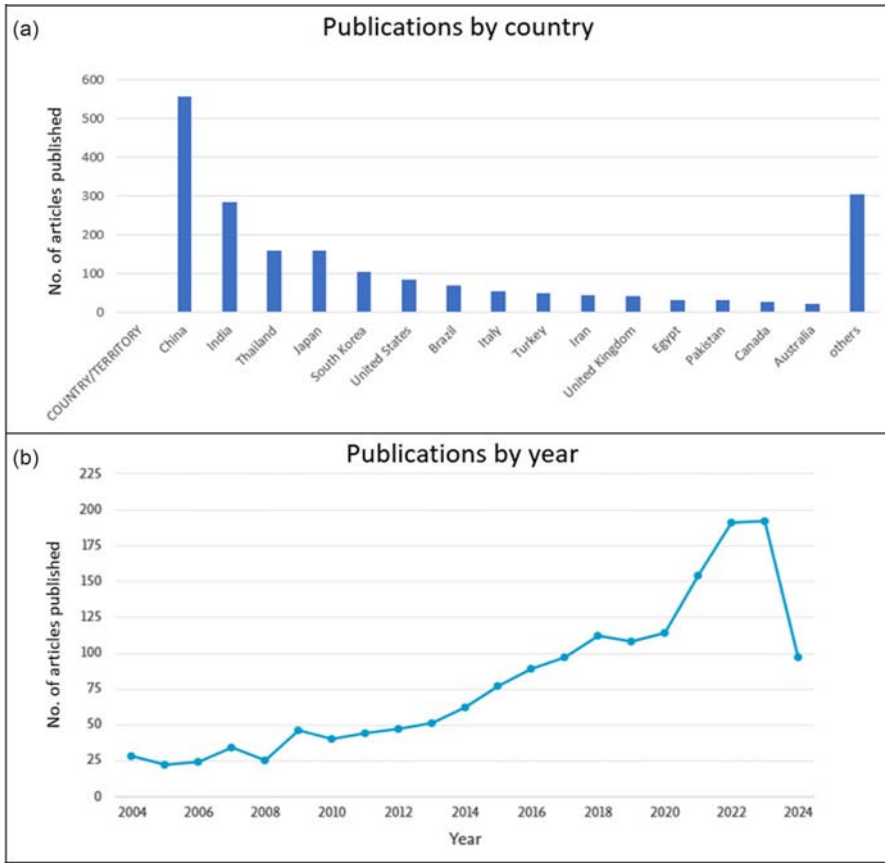


Figure 12.7 (a) The bar chart illustrates the number of research articles published by various countries and territories from 2004 to 2024. China leads with the highest number of publications, followed by India and Thailand. The chart provides a clear comparison of research productivity across different nations. (b) The line chart shows the number of research articles published each year from 2004 to 2024. The trend indicates significant growth in publications over the years, with noticeable increases in recent years. This chart highlights the overall increase in research activity and productivity over the 2 decades. (c) The bar chart illustrates the number of patents granted by various patent offices from 2004 to 2024. The United States Patent and Trademark Office leads with the highest number of patents granted, whereas the United Kingdom Intellectual Property Office granted the least. The chart provides a clear comparison of the patent grants across different offices. (d) The bar chart shows the number of patents granted each year from 2004 to 2024. The trend indicates significant growth in patents over the years, with noticeable increases in recent years. This chart highlights the overall increase in patent grants and innovation over the 2 decades.

done by China followed by India (near about 300 publication). Maximum (near about 190) number of publications has been reported in the year of 2022 as well as 2023. In recent year (2024), there are almost 100 number of publications has been recorded. In

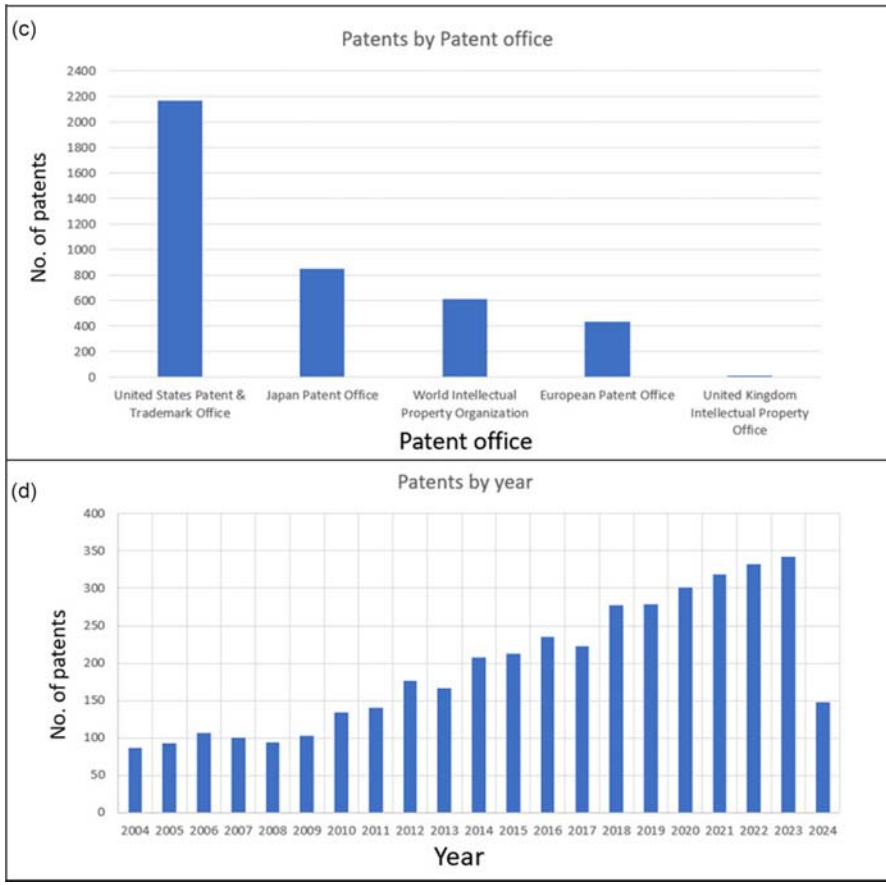


Figure 12.7 cont'd.

addition to this, many patents have been published between these 20 years (2004 and 24) (Fig. 12.7). United Kingdom Intellectual Property Office has published more than 2100 numbers of patents followed by Japan Patent office almost more than 800 number of patents. The rate of patents publication gradually increases every year. Most of the patents have been published in the year of 2023, till date. In current year, almost 100 numbers of patents already published, and it may progress in future.

7. Challenges and opportunities

The viability of the silk industry is under threat as a result of challenges pertaining to the economic valuation, accessibility, and requisite resources for the cultivation of silkworms and the subsequent production of silk. While acknowledging the notable economic value of silk, it is important to recognize the potential for generating various

renewable and sustainable by-products throughout the processing stages. Sericin, a proteinaceous substance found in silk, is commonly disposed of as a detrimental byproduct within the textile sector. The captivating biological activities exhibited by sericin have garnered recognition as a biomaterial possessing remarkable potential for applications in the fields of biomedicine and pharmacology. The recovery of sericin from wastewaters generated by the silk industry holds substantial commercial, social, and environmental importance.

The distinctive characteristics of sericin, as elucidated in this investigation, render it a highly promising contender for application in various biological and pharmacological contexts. One of the extensively studied methodologies in the realm of biomedicine involves the examination and utilization of sericin. This entails the advancement of drug delivery systems that encompass sericin in various forms such as films, nanoparticles, foams, hydrogels, fibers, and other analogous materials. Sericin, a proteinaceous substance, has been widely employed in tissue engineering due to its remarkable ability to facilitate cell adhesion and proliferation. It plays an important role in various biological processes such as tissue reconstruction, repair, and the regeneration of skin epithelial cells. Notably, sericin has demonstrated significant utility in the realm of bone tissue engineering and the healing of wounds. Sericin, a protein found in silk, facilitates the development of environmentally friendly, compatible with living organisms, and capable of natural decomposition products, all while maintaining an affordable price point. Due to its remarkable versatility in terms of its ability to form combinations with both natural and synthetic polymers, as well as its official recognition and approval by the Food and Drug Administration (FDA), sericin presents notable benefits when compared to alternative natural biomaterials. Despite the numerous potential applications and advantages of silk sericin, it exhibits certain limitations that impede its widespread utilization within the field of biomedicine. The initial stage in ensuring the economic viability of the silk industry involves selecting an extraction technique that ensures a reliable physicochemical profile and improved biological functionality. For the successful implementation of this approach at an industrial scale, it is imperative that it exhibits both sustainability and scalability. Furthermore, silk sericin, a biologically derived substance, exhibits certain limitations in its application across diverse biological domains (He et al., 2018). Furthermore, the rheological properties and inadequate mechanical characteristics of silk sericin prevent its direct application in drug delivery systems or as scaffolds for tissue engineering. Consequently, the generation of sericin-based scaffolds is commonly achieved through their integration with complementary constituents (Hu et al., 2020).

Sericulture harbors the promising prospect of evolving into biofactories that generate proteins, lipids, and polysaccharides with biomedical and pharmaceutical applications in forthcoming times. This development is particularly captivating, known as the sustainability predicament and the captivating biomedical possibilities associated with sericin and other byproducts derived from the rearing of silkworms. The thread that silkworms spin, scientifically known as *Bombyx mori*, is a fascinating example of a composite fiber consisting of two distinct components: water-repellent fibroin and water-loving sericin. Sericin, a significant component found in abundance, is commonly extracted and unfortunately discarded into wastewater as a byproduct

during the intricate process of transforming *Bombyx mori* cocoons into silk fabric, which is primarily utilized in the textile industry. The presence of this effluent poses a significant threat to the well-being and survival of various species of aquatic organisms, as well as the overall balance and functioning of the ecosystem. The utilization of this biomaterial, which possesses notable economic, social, and environmental implications, has garnered considerable interest due to the detrimental polluted environments caused by the disposal of sericin, along with its advantageous attributes.

8. Conclusion

The abundance of benefits makes silk sericin highly appealing. The sericin-based composites are notable for their ability to serve as carriers, effectively releasing their active component at a specific rate and targeted location. Here, the most important uses of silk sericin in biomedicine are covered in a number of contexts. It is determined that sericin has several applications in the biomedical field, such as enhancing site-specific delivery of drugs, promoting wound healing, acting as an antibacterial agent, and many more. Further research is required to develop sericin applications for commercial use, as they are currently only being tested in laboratory settings. The use of silk sericin in various sectors requires further improvement in order to fully exploit its intriguing and diverse qualities, such as its potential to build innovative materials. Therefore, it may be inferred that silk sericin holds great potential as a protein for biomedical purposes.

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Applications of sericin hybrid materials in cancer treatment

13

Sericin—Application in cancer treatment

Anitha Mamillapalli, Sireesha V. Garimella, Brinda Goda Lakshmi Didugu and Haroon Rashid
Department of Life Sciences, School of Science, GITAM (Deemed to be University), Visakhapatnam, Andhra Pradesh, India

1. Introduction

Sericulture is an agriculture-based industry. The rearing of silkworm larvae comes under the agriculture sector, and postcocoon processes come under the industry. India is the second largest producer of silk in the world, with the uniqueness of producing four different silks—mulberry, tasar, muga, and eri. Mulberry silk is produced by *Bombyx mori (B. mori)*. It is an insect of commercial importance as silk production is done at an industrial scale. Silkworms are used as experimental models to study genetics, genomics, and disease. Apart from its usage as a textile, silk has a lot of biomedical and cosmetic applications. Silk is produced from a pair of silk glands in the silkworm. They are modified exocrine glands, morphologically and functionally separated into anterior (ASG), middle (MSG), and posterior gland (PSG) regions (Perdrix-Gillot, 1979) (Fig. 13.1). The DNA of silk glands undergoes repeated endoreduplication and the nuclei look highly branched with DAPI staining.

Silk is majorly made of two proteins, namely fibroin and sericin. Fibroin constitutes 70%−80%, while sericin constitutes 20%−30% of total silk (Silva et al., 2022). Fibroin is synthesized by the PSGs. Fibroin is a partly crystalline and fibrous protein. Sericin is majorly produced by MSG. It coats the core silk fibroin and comes out from the anterior silk gland as a fiber. Sericin belongs to a family of glycoproteins and is classified as a globular protein. The conversion of alpha helix to β-sheet structure in sericin makes it form a gel. It is an amorphous protein with many polar amino acids. Sericin is produced after degumming silk fiber. It is a byproduct during the manufacturing of silk in the textile industry (Lamboni et al., 2015).

Silk sericin, a natural compound, can be coupled with several molecules to form nanoparticles, and can be used in biomedical applications such as drug delivery vehicles in cancer treatment. The wide use of silk in the biomedical field is due to its biodegradability, biocompatibility, less toxicity, and enhanced permeability (Elahi et al., 2021).

Cancer is a disease characterized by abnormal cell growth, forming malignant tumors and invading tissues, affecting any body part. Despite numerous treatment

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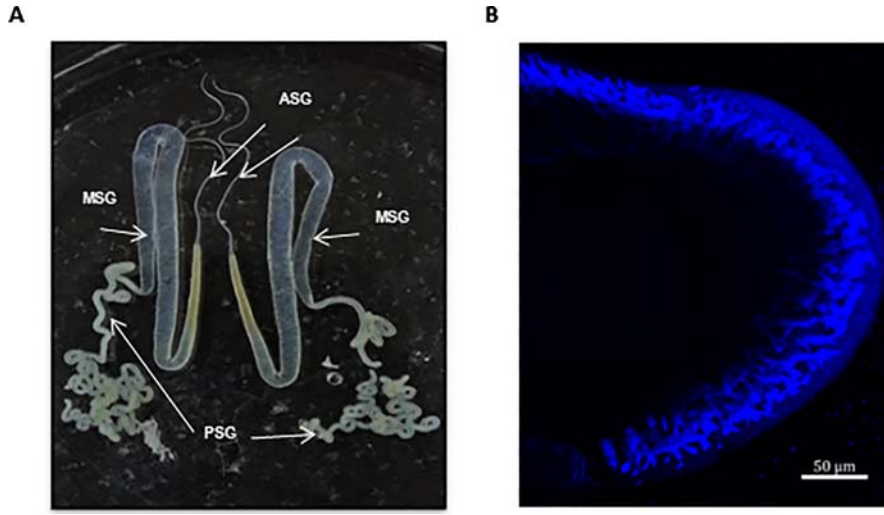


Figure 13.1 A pair of silk glands in the silkworm, *Bombyx mori*. (a) Silk gland of *B. mori* at day 7 of fifth instar stage (b) cross section of MSG showing branched nuclei stained with DAPI.

options available to cure the disease, cancer remains the cause of high mortality. The need of the hour is for novel drugs and the delivery of the drug to precise tumor locations. Sericin has a chemopreventative effect, which may be attributed to various pathways, such as inhibition of cell proliferation, cell apoptosis, stopping of angiogenesis, and its effect to arrest the cell cycle (Lifshitz et al., 2001; Sun et al., 2004). Targeting apoptosis is also one of the major approaches to the prevention of cancer (Huerta et al., 2006; Lifshitz et al., 2001; Sun et al., 2004). In this chapter, we discuss the molecular nature of sericin, the role of sericin as a potential anticancer agent, and a promising delivery agent for cancer therapy. We also discuss the growing importance of sericin as a hybrid material and the limitations or challenges associated with using sericin in cancer therapy.

2. Characteristics of sericin genes

Five distinct types of sercin genes are reported namely *Ser 1*, *Ser 2*, *Ser 3*, *Ser 4*, and *Ser 5*. The expression of the *Ser* gene varies during the life cycle of the silkworm (Table 13.1). *Ser1* codes for four mRNAs, *Ser2* gene codes for two mRNAs, and *Ser3* gene codes for one mRNA. Sericin is composed mainly of three polypeptides of 400, 250, and 150 kDa. *Ser4* gene expression is observed in the silk gland till the fourth instar and fourth molt. Sericin 4 protein is highly expressed in the silk secreted during the beginning of the fourth instar when compared to the silk secreted at the

Table 13.1 List of sericin genes with expression details.

S. No.	Gene	Gene ID	Position on chromosome 11	Size	Expression	References
1	*Ser1*	101740082	2513096–2543046	23 kb	MMSG and PMSG	Liu et al. (2020)
2	*Ser2*	100379325	5313784–5326519	12 kb	AMSG	Michaille et al. (1990)
3	*Ser3*	100136948	4981825–4988066	6.6 kb	AMSG	Liu et al. (2020)
4	*Ser4*	–	4782596–4822998	7.3 kp	MMSG and PMSG	Dong et al. (2019)

Table 13.2 Summary of the sericin proteins and their characteristics.

S. No.	Protein	Molecular weight (kDa)	Solubility in hot water	Nitrogen content (%)	Site of occurrence	References
1	Sericin 1	20–100	Soluble	17.2	Innermost layer	Kunz et al. (2016)
2	Sericin 2	100–200	Soluble	16.8	Intermediate layer	
3	Sericin 3	200–400	Insoluble	16.6	Inner layer	
4	Sericin 4	280, 260	Soluble	16	Outer layer	Dong et al. (2019)
5	Sericin 6	467 kDa	Soluble	16	Inner layer	Wu et al. (2023)

instar end (Dong et al., 2019). Sericin 1, sericin 2, and sericin 3 are three abundant proteins in the *B. mori* silk (Dong et al., 2013). Sericin 6 is also reported (Table 13.2).

From the first to fifth instar, the middle part of the MSG (MMSG) and the posterior part of the MSG (PMSG) express the *ser 1* gene, but the anterior part of the MSG (AMSG) expresses the *ser 3* gene after day five of the fifth instar (Takasu et al., 2010). It is also reported that the *Ser 3* gene is expressed in the anterior and middle part of the MSG (Takasu et al., 2007) (Fig. 13.2).

From the first instar to day 5 of the fifth instar, the AMSG synthesizes sericin 2 proteins. From the first to the fourth instar, the percentage of sericin 2 in silk rises (Dong et al., 2013). Sericin 2 functions as an adhesive protein that helps in binding the cocoon to substrates like tree branches or mulberry leaves (Kludkiewicz et al., 2009).

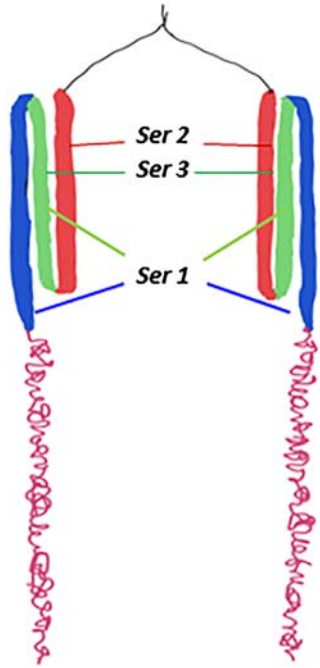


Figure 13.2 Pictorial representation of silk gland. Pictorial representation of silk gland showing different regions of middle silk gland with encoded sericin genes.

3. Sericin—Physical and chemical properties

Silk cocoon has three layers—outer, middle, and inner layers, respectively. Each of these layers contain sericin of 15%, 10.5%, and 4.5%, respectively. The gum binder sericin, which is amorphous and water-soluble, keeps the structural integrity of the cocoon. It is characterized by the occurrence of amino acids, with strong polar side chains namely, amino, carboxyl, and hydroxyl groups. The high content of serine, aspartic acid, and glycine is reported (Kunz et al., 2016). Serine is the most prominent amino acid in all sericin proteins (Fig. 13.3).

More hydrophobic amino acids of sericin have been associated with enhanced antioxidative capabilities (Chen et al., 1995). The fibroin threads that make up the dense and closed structure of the cocoon are joined together by sericin. Fibroin protein comprises of two subunits of 25 and 370 kDa in equimolar proportion that are joined covalently together by disulfide bonds. Sericin is a glue protein molecule that has a molecular mass ranging from 10 kDa to more than 400 kDa and is categorized into three types: sericin A, B, and C (Fig. 13.3). Hydroxyl, carboxyl, and polar amino acids of sericin play a crucial role in the human body's metabolic pathways (Table 13.3). It has numerous medicinal applications in wound healing and tissue engineering. It is reported to have neuroprotective, antioxidant, antihypertensive, anticancer, antidiabetic, and antiaging properties. Sericin has also become a

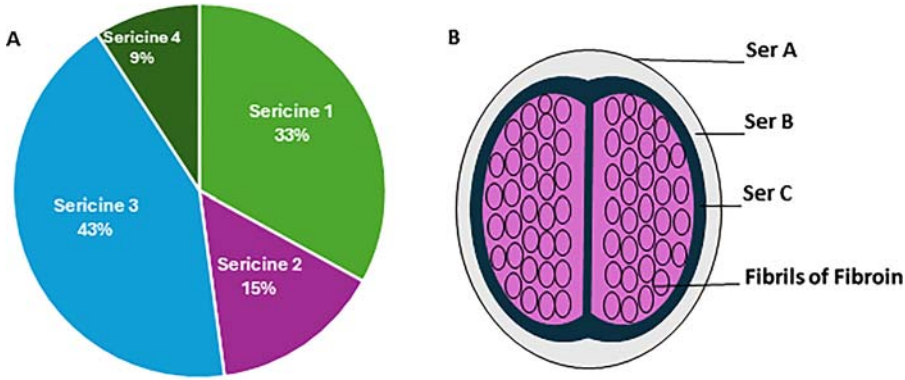


Figure 13.3 Composition of serine in various sericin proteins. (a) Percentage composition of serine in various sericin proteins. (b) Pictorial representation showing cross-section of silk fiber.
Adapted from Dong, Z., Guo, K., Zhang, X., Zhang, T., Zhang, Y., Ma, S., et al. (2019). Identification of *Bombyx mori* sericin 4 protein as a new biological adhesive. *International Journal of Biological Macromolecules, 132*, 1121−1130. https://doi.org/10.1016/j.ijbiomac.2019.03.166.

Table 13.3 Amino acid composition of sericin protein.

S. No.	Amino acid	Percentage composition (%)	Isoelectric point (pI)	Polarity
1	Serine	30−33	5.68	Hydrophilic
2	Glycine	16−19	5.97	Hydrophilic
3	Aspartic acid	14−16	2.97	Hydrophilic
4	Threonine	8−10	5.86	Hydrophilic
5	Glutamic acid	7−9	3.22	Hydrophilic
6	Isoleucine	4−5	6.4	Hydrophobic
7	Alanine	2−3	6.01	Hydrophobic
8	Phenylalanine	1−2	5.76	Hydrophobic
9	Valine	1−2	6.01	Hydrophobic
10	Leucine	1−2	6.03	Hydrophobic

hopeful drug delivery method for chemical-based drug therapy, particularly in the form of biodegradable capsules.

4. Significance of sericin hybrid materials

Sericin, which is hydrophobic, can be easily modulated to prepare hybrid materials. Silk sericin hydrogel crosslinked with horse radish peroxidase (HRPO) showed

elevated thermal stability. These hydrogels showed highly crosslinked structures with 50 μM mean pore size suitable for accommodating cells and allowing them to proliferate. This is an important requirement in the wound-healing process (Baptista-Silva et al., 2022). Sericin-honey hydrogels were shown to be effective for in-vivo wound-healing properties in mouse models (Wei et al., 2024). Sericin biopolymer is also applied for bioremediation. Development of nano-flowers of high-molecular-weight sericin (high-molecular-weight sericin hybrid nanoflowers [HMW-ShNFs]) combined with copper showed enhanced peroxidase activity. These were also shown to significantly enhance the degradation of the antibiotic ciprofloxacin, thus making it an eco-friendly material (Koshy et al., 2024). Sericin is also widely studied in the cosmetic industry due to its hydration, antioxidant, and wound-healing properties. Melanogenesis induced by ultraviolet radiation was significantly reduced by the silk sericin due to its antioxidant and antityrosinase activities (Kumar & Mandal, 2019a, 2019b). Bacterial cellulose modified with hyaluronic acid (HA) and silk sericin (SS) was proved to be better for cosmetic and wound dressing properties due to the enhancement of tensile strength and moisture content values (Wang et al., 2020). The enhancement of β sheet structures by mixing silk fibroin with silk sericin without the use of chemical crosslinkers is a suitable biomaterial for skin regeneration (Byram et al., 2024). Studies showed that alginate/graphene oxide/sericin/nanohydroxyapatite nano hydrogels stimulated bone formation with sericin contributing to macrophage polarization (Fu et al., 2023). Sericin-diamond-ZnO (SDZ) structures prepared by doping sericin are fabricated for high-performance long-life UV photodetectors. Sericin played a role in increasing energy levels in the conduction band and improved UV absorptivity (Saravanan et al., 2020). Crosslinking of sericin with glutaraldehyde and hydrogen peroxide/horseradish peroxidase (H_2O_2/HRP) resulted in a hydrogel with enhanced fluorescent properties, which can be used as a bioprobe or tracer in medical applications (Zhang et al., 2024). Silk sericin has the potential to chelate metal ions and is valuable in removing metals from various sources. Sericin nanocoating with anthocyanin was tested with zinc and aluminum and found to be very effective in estimating real-time removal of metal ions (Yao et al., 2022).

The anticancer drug, cisplatin and cisplatin-based sericin nanocarriers, caused cytotoxicity in MCF-7 cells. The combination of sericin and cisplatin showed enhanced cell viability when compared to cisplatin alone, indicating controlled drug release by a gradient decrease in the cell viability and highlighting sericin-based nanocarriers as promising drug delivery agents (Bahremand et al., 2024).

Thus, the available data shows that the usage of sericin as a hybrid biomaterial is increasing in an exponential manner, covering all fields like pharmaceutical, cosmetic, energy harvesting, and medical fields (Fig. 13.4).

In the medical field, it is shown to be used in bone regeneration, skin regeneration, wound healing, controlled drug release, reduction in melanization, management of inflammatory diseases, and many more.

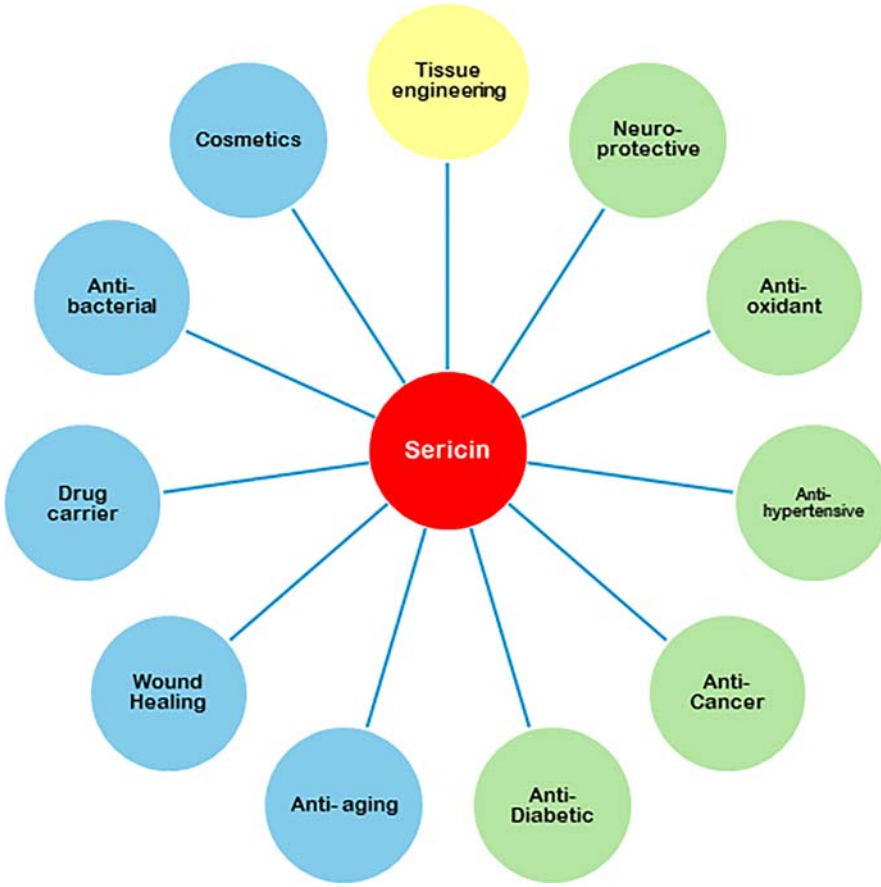


Figure 13.4 Usage of silk sericin in several industrial and medical applications.

4.1 Publications related to sericin

The importance of sericin for different biomedical fields has been explored in the recent past, and more research work has been published in the past 10 years (Fig. 13.5).

The publications with "sericin" search term retrieved from PubMed data showed that the publications number has surged from 2000 to 2024. The total number of publications on silk and biomaterial was 4587, sericin—biomaterial was 268889, sericin—cancer was 4031186, and sericin—cancer—biomaterial was 28717. The increasing trend in the number of publications on sericin is due to its significant role in the biomedical, cosmetics, and pharmaceutical industries. Sericin may also contribute to advancement in healthcare.

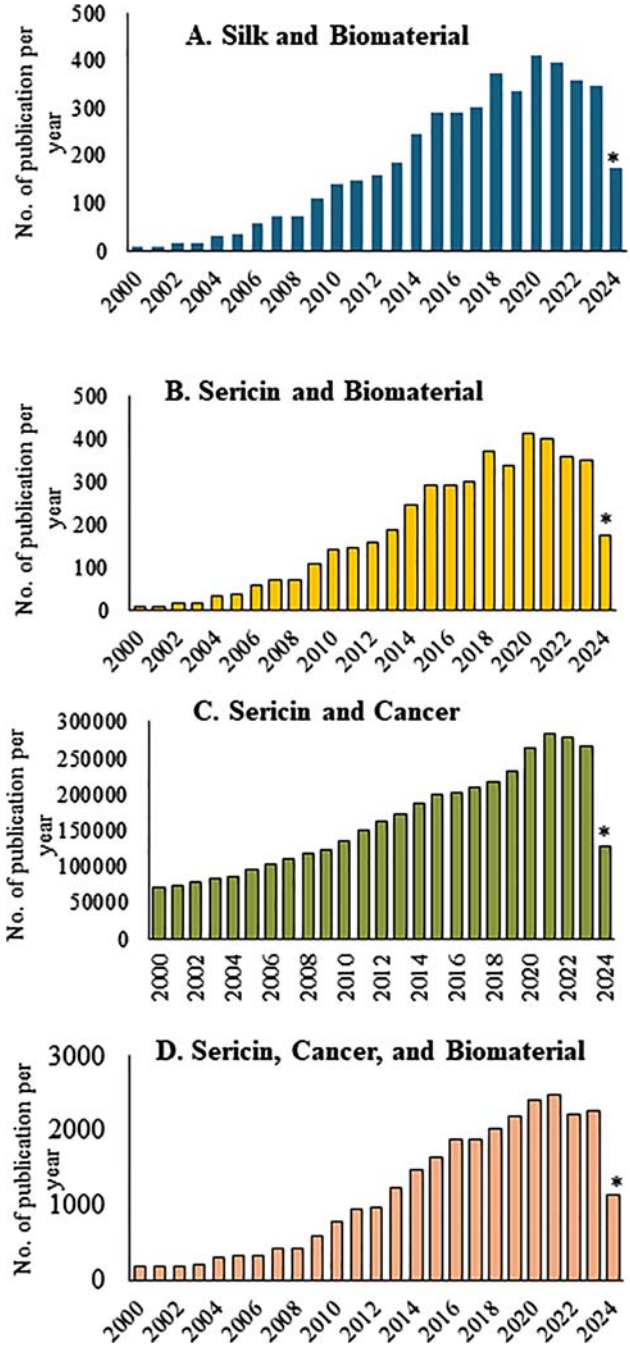


Figure 13.5 Image representing number of publications related to sericin and cancer in PubMed. Number of publications based on different search terms retrieved from PubMed data. The total number of publications on (a) silk and biomaterial, (b) sericin and biomaterial, (c) sericin and cancer, and (d) sericin, cancer, and biomaterial. The data arefrom 2000 till *May 2024.

4.2 Patents related to sericin

Sericin is gaining interest due to its unique properties, including biocompatibility, biodegradability, and antioxidant activities, leading to innovative applications across industries. Sericin patents cover a wide range of processes and applications. Key areas of innovation include methods for efficient extraction, preparation of sericin-containing composition, and development of new applications. The number of patents based on different search terms retrieved from "Google Patents" showed an increasing tendency (Fig. 13.6).

The total number of patents from 2000 to 2024 on silk and biomaterial was 1508, sericin and biomaterial was 361, and sericin cancer and biomaterial was 101. The biocompatibility and affinity of sericin with tissues promote wound healing by facilitating the formation of a microenvironment for tissue regeneration. It can induce fibroblast proliferation and collagen production. The invention related to methods for promoting wound healing using silk-derived proteins such as sericin film, sponge, and gel is entitled "Methods of promoting wound healing using silk-derived proteins." The important patents associated with silk as biomaterials are listed in Table 13.4.

Sericin's properties can find innovative applications in cancer treatment, drug delivery systems, wound healing, antioxidant and anti-inflammatory, and as a scaffold for cancer cell study. Target-specific delivery is one of the important steps in cancer research. The approaches to deliver chemotherapeutic drugs to target cancer tumor by advanced methods is the need of the hour.

5. Sericin and cancer

5.1 Sericin and its role in cell cycle regulation/cell proliferation

Cell cycle is a complex process which involves different phases—G1, S, G2, and M. During these stages, cells grow and divide to give rise to daughter cells. The process is highly regulated. Many studies in different cancers show dysregulated cell proliferation. Any defect in the cell cycle control mechanisms leads to excessive cell divisions, which can lead to cancer. Sericin has been initially used in growing many different kinds of cell lines to supplement bovine serum albumin (BSA) in cell culture and was found to be safe. However, sericin, when mixed with polyphenols and flavonoid compounds, showed anticancer activity. The effect was found to be due to elevation in pro-oxidative stress. This effect was found to be caused by all sericin produced from different silkworms—*B. mori*, *A. assamensis*, and *P. ricini*. The high level of oxidative stress generation led to cell cycle arrest (G1 phase) in the breast cancer cell line (MCF-7), epidermoid carcinoma cell line (A-431), and oral cancer cell line (SAS) (Kumar & Mandal, 2019a, 2019b). Nanoparticles prepared from sericin stimulated arrest in the sub-G1 and S-phase, in a concentration-dependent manner in estrogen-receptor positive MCF-7 and triple-negative breast cancer cell line (MDA-MB-231) (Mumtaz et al., 2023). The study of sericin in MDA-MB-468 cells reported a cell cycle arrest at the G0/G1 phase and lowered the CDK4, which is important in controlling the progression

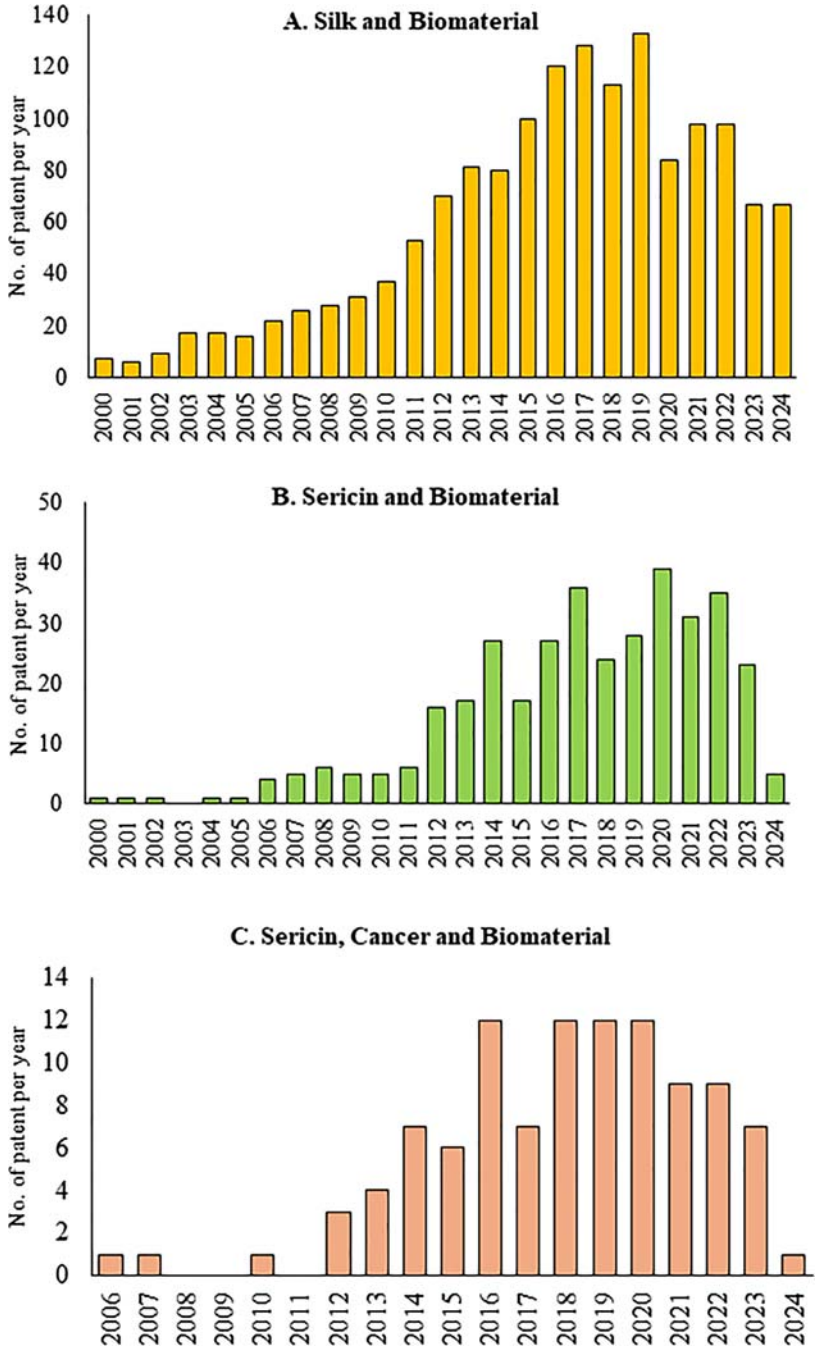


Figure 13.6 Number of patents related to silk and biomaterial (A), sericin and biomaterial (B), sericin, cancer and biomaterial (C) as reported in Google Patents.
Data was retrieved from Google Patents.

Table 13.4 List of notable patents with silk as a biomaterial.

S.No.	Patent No.	Patent title	Inventor	Date of publication
1	US Patent 6284786	Method of isolating sericin from silkworm and uses thereof	M. Takasu T. Yamada T. Tsubouchi	4th Sept, 2001
2	US Patent 7060857	Sericin hydrogel, its production method, and uses thereof	H. Kameda M. Takasu T. Yamada	13th June, 2006
3	US-11110206-B2	Silk sericin-based hydrogel, methods and uses thereof	Ana, Sara Isabel, Sandra Cristina Paulo Jorge	9th Sept, 2021
4	US Patent 7816378	Sericin-based biocompatible material and method for producing the same	H. Kameda M. Takasu T. Yamada	19th Oct, 2010
5	US Patent 8399020	Cosmetic composition containing sericin	K. Sato Y. Kobayashi	19th Mar, 2013
6	US Patent 8912181	Sericin-containing composition for wound healing	P. Aramwit S. Kanokpanont T. Srichana	16th Dec, 2014
7	US Patent 9126060	Sericin-based scaffold for tissue engineering	P. Aramwit S. Kanokpanont T. Srichana	8th Sept, 2015
8	US Patent 10441597	Sericin-derived nanoparticles for drug delivery	K. Tsukada Y. Kojima	15th Oct, 2019
10	JP-2019519596-A	Methods of promoting wound healing using silk derived proteins	Abdel-Nabi, Walid Rosenblatt, Mark Lawrence, Brian Infanger, David	11th July, 2019
11	US Patent 11383092	Sericin-infused bandages for accelerated wound healing	D.L. Kaplan J. Zhu	19th July, 2022
12	EP patent 3221677A1	Method for producing sericin microcapsules and their application	T. Tsukada T. Nakajima	4th Oct, 2017
13	CN102559824A 824A	Sericin for biological material and preparation method thereof	Hunan Nanfang Biotechnology Co Ltd	22nd Oct, 2014
14	CN117982438A	Ophthalmic sericin freeze-dried powder and preparation method thereof	Zhuohe Pharmaceutical Group Co ltd.	7th May, 2024

of cells from the G1 to S phase (Niu et al., 2021). In another study, sericin acted as a key regulator of the G/S progression in hepatocytes. Sericin is linked to a rise in the proportion of cells in the S phase and a decrease in the G0/G1 phase (Huang et al., 2018). It was also tested in 3D cell culture models due to its mechanical strength, more compressibility, and porosity along with swelling nature. Sericin−alginate−chitosan microcapsules were used for hepatocyte culture and cryopreservation. The positive effect of sericin is attributed to its increase in collagen. The sericin upregulated CCR6, EGFR, and FOS genes, which are involved in cell proliferation (Table 13.5). The signal from the CCR6 is transduced, and Src, PI3K, AKT1, JNK1, and NFkB1 are activated, and finally, MMP9 is upregulated. This shows that sericin can regulate cell cycle and promote proliferation in hepatocytes by the CCR6-activated pathway (Huang et al., 2018). Therefore, the proposed mechanism of the cell cycle regulation by sericin is through enhanced activation of growth factor receptors that, in turn, upregulate the survival pathway genes and promote tumor cell cycle progression (Fig. 13.7).

Recent studies showed the effect of sericin as an anticarcinogen against liver tumors induced by diethyl-nitrosamine (DEN) in male mice (Bakr et al., 2024).

5.2 Effect of sericin on apoptosis of cancer cells

Sericin was reported to suppress colon tumors for the first time in rat models. The effect of pure sericin was tested in colon cancer cell lines (SW480) and normal FHC colon cells (Zhaorigetu et al., 2001). The low-molecular-weight sericin of 61−132 kDa was shown to induce apoptosis of SW180 cells by increasing caspase-3 activity and by downregulating antiapoptotic protein, Bcl-2 levels. This resulted in a decrease in cell viability in cancer cells than in normal cells. This study also reported that both extrinsic and intrinsic pathways of apoptosis are induced by low-molecular-weight sericin (Kaewkorn et al., 2012). Investigation on sericin as an anticancer drug on triple-negative breast cancer (TNBC) cell proliferation showed promotion of cellular apoptosis by causing cell cycle arrest at G0/G1. The PI3K/Akt signaling pathway, which is enriched in TNBC (based on dataset analyses), was inhibited by sericin in TNBC MDA-MB-468 cells. Sericin treatment upregulated Bax and Cyto-C protein expression while downregulating Bcl-2 protein expression in MDA-MB-468 cells, indicating sericin's potential to induce cellular apoptosis by both extrinsic and intrinsic pathways of apoptosis (Niu et al., 2021) (Fig. 13.8 and Table 13.6).

Antheraea proylei J (oak tasar) silk-derived sericin was demonstrated to induce apoptosis in a caspase-dependent manner in cervical cancer (Hela) and lung cancer (A549) cell lines via the MAPK pathway (Devi et al., 2024). Thus, sericin has anticancer properties, which can be attributed to its simulation of apoptotic pathways.

5.3 Sericin as a drug carrier in cancer therapies

Cytotoxic drugs aimed at removing tumor cells have deleterious effects on normal cells too. The focus of the current cancer therapies is to reduce the effects of the drugs on normal cells and to precisely deliver the drug to cancer cells and enhance their

Table 13.5 Gene expression changes in hepatocytes treated with sericin.

S. No.	Role	Gene Name	Gene Function	Change	References
1	Cell cycle and cell proliferation	CCR6—C−C Motif Chemokine Receptor 6	CCR6 binds to ligand CCL20 which induces inflammation.	+	Rujimongkon et al. (2021)
2		EGFR—Epidermal growth 22 factor receptor (EGFR)	Binding of EGFR to its receptor promotes the cell growth and differentiation.	+	Huang et al. (2018)
3		FOS	It plays an important role in signal transduction, cell proliferation and differentiation.	+	Huang et al. (2018)
4		Src	Increase growth rates and invasion characteristics of tumors and decreases apoptosis.	+	Huang et al. (2018)

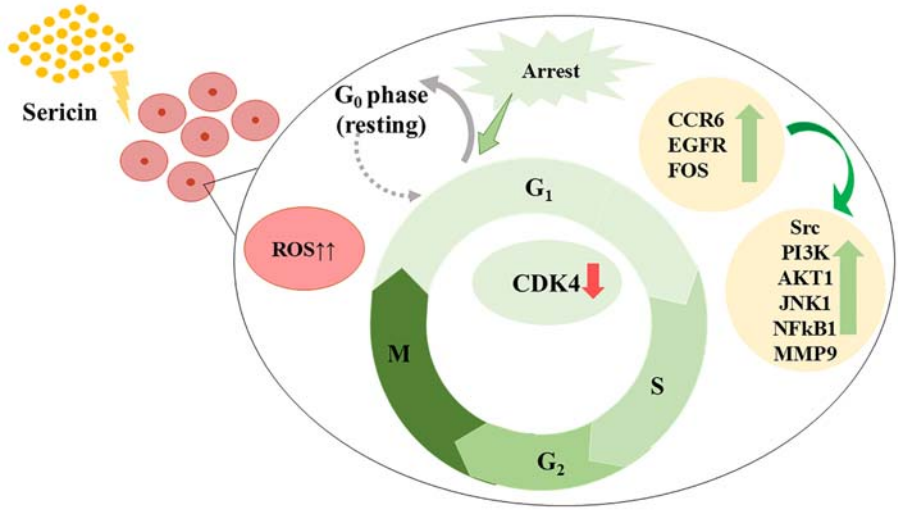


Figure 13.7 Mechanism of cell cycle arrest in the cells treated with sericin. Green arrows indicate the upregulation of genes, and red arrows indicate the downregulation of genes.

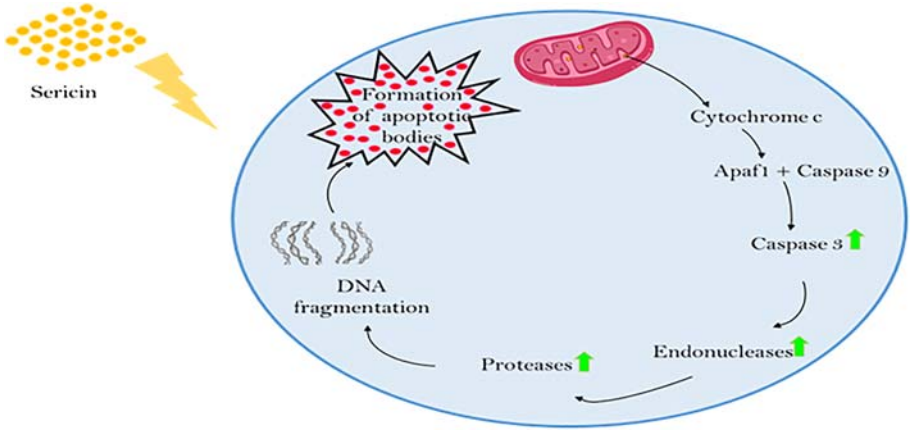


Figure 13.8 Sericin causes apoptosis of cancer cells by the activation of various pathways.

efficiency. Targeted drug delivery is the need of the hour for accurate drug release to the tumor cells, thereby improving the bioavailability. Numerous natural and synthetic polymers have been tested to enhance drug delivery to tumor cells. Silk-based nanoparticles have been extensively studied to deliver anticancer agents like paclitaxel, doxorubicin, floxuridine, methotrexate, etc. Silk fibroin, the medical material approved by the US Food and Drug Administration (FDA), has been widely used in the postoperative suture, tissue regeneration, and drug delivery system. Apart from silk fibroin, silk sericin has also been shown to have immense potential as drug carrier (Florczak et al., 2020).

Table 13.6 Gene expression studies of sericin-treated cancer cells.

S. No.	Role	Gene name	Gene function	Expression levels	References
1	Cellular apoptosis	Bcl2	Regulates cell death by controlling the mitochondrial membrane permeability. Inhibits caspase activity either by preventing the release of cytochrome *c* from the mitochondria and/or by binding to the apoptosis-activating factor (APAF-1).	−	Mandal and Kundu (2009), Niu et al. (2021)
2		Bax	Release of cytochrome *c* into the cytosol and activates caspase-3.	+	Kumar and Mandal (2019a,b), Mandal and Kundu (2009)
3		Cyt-c	Cyt *c*, the peripheral protein of the mitochondrial inner membrane (IM), acts as an electron shuttle.	+	Kumar and Mandal (2019a,b)
4		p53	The gene activates a tumor suppressor causing growth arrest or apoptosis, mediated by stimulation of BAX and FAS antigen expression or repression of Bcl-2 expression.	+	Kumar and Mandal (2019a,b)
5		Casp 3	Involved in the activation cascade of caspases responsible for apoptosis execution. It cleaves PARP1, activates SREBPs, and triggers cell adhesion in sympathetic neurons. It also cleaves IL-1 beta, inhibits AKT1, and acts as an inhibitor of type I interferon production during virus-induced apoptosis. It also promotes phosphatidylserine exposure on apoptotic cell surface.	+	Kumar and Mandal (2019a,b)
6		Casp 8	Activated caspase-8 can activate downstream caspases directly or indirectly by cleaving the BH3 Bcl2-interacting protein, which releases cytochrome *c* from mitochondria and activates caspase-9 in a complex with dATP and Apaf-1.	+	Kumar and Mandal (2019a,b)
7		Casp 9	Caspase-9's binding to Apaf-1 causes the protease to become activated, which in turn promotes Caspase-3 or Caspase-7 to cleave and become active. Promotes apoptosis brought on by DNA damage in an ABL1/c-Abl-dependent way. Poly(ADP-ribose) polymerase (PARP) is proteolytically broken down.	+	Kumar and Mandal (2019a,b)
8		NDUSF1	The mitochondrial membrane respiratory chain NADH dehydrogenase (Complex I) core subunit is crucial for electron transfer, ubiquinone acceptor, and assembling complex I, forming super complexes with ubiquinol-cytochrome reductase complex (Complex III).	−	Ampawong et al. (2018)
9	Anti-inflammation	COX	Inducible immediate-early gene product whose synthesis in cells can be upregulated by either mitogenic or inflammatory stimuli.	−	Aramwit et al. (2013)
10		iNOS	Induced in response to cytokines and bacterial products in inflammatory and tissue cells, and its overproduction is associated with the pathophysiology of various inflammatory diseases.	−	Aramwit et al. (2013)

In addition to the antiproliferative and proapoptotic effect of pure sericin protein, sericin-made nanoparticles or sericin conjugates efficiently induce apoptosis in cancer cells. Sericin-conjugated silver nanoparticles significantly inhibited cell proliferation in breast cancer cell lines MCF-7 and MDA-MB-231 after 72 h of treatment and also induced apoptosis and nuclear fragmentation. Expression studies showed prominent stimulation of cell cycle arrest and stress-related genes such as cyclin-dependent kinase inhibitors (CDKN1A, CDKN1B) and GADD family genes. Nuclear DAPI staining showed significant induction of apoptosis and nuclear fragmentation in MDA-MB-231 cells at a concentration of 1 mg/mL for both sericin and sericin-AgNO3 NPs. The spindle-shaped MB231 cells changed their shape, lost their original spindle outlook, and appeared more rounded (Mumtaz et al., 2023).

Hu et al. prepared chitosan/sericin nanoparticles of 200−300 nm size with 50% encapsulation efficiency and pH-dependent drug release ability. The DOX−SSC−NPs were indicated to mitigate the systemic toxicity of Dox in mice while maintaining the antitumor efficacy of the drug (Hu et al., 2018). The introduction of poly-C-benzyl-L-glutamate (PBLG) chains onto sericin particles (SS-PBLG) significantly improved their micelle stability in aqueous solution and doxorubicin carrying capacity. SS-PBLG-Dox nano-micelle exhibited more antitumor potential in anthracycline drug-resistant (ADR) cell lines MCF-7/ADR and HepG2/ADR, both in vitro and in vivo, as compared to the same dose of free doxorubicin (Guo et al., 2018). *A. pernyi* silk sericin (AS) has been used as a template to nucleate hydroxyl-apatite (HAp) nanoneedles to form porous sericin−HAp nanocomposite microspheres (ASMs) that had a Dox encapsulation efficiency of 62% and were toxic to HeLa cells (Shuai et al., 2017). In another approach, folate-conjugated *B. mori* silk sericin nanoparticles (FA-SND) were generated via self-assembly. These nanoparticles (50 nm) specifically targeted human oral epithelium carcinoma KB cells that are rich in folate-receptor. The FA-SND nanoparticles were endocytosed into lysosomes, where the acidic microenvironment promoted a rapid release of Dox that was then transported to nuclei exerting toxicity (Huang et al., 2016). In another interesting strategy for targeted drug delivery, B. *mori* sericin-coated meso-nanoparticles (MSNs) were loaded with Dox and tested in multidrug resistant MCF-7 cells. The sericin coating of MSNs prevented the premature leakage of the entrapped Dox from MSNs before the particles could reach the targeted cells, and on reaching the tumor, sericin's cell-adhesive property enhanced the uptake of SMSNs by the tumor cells that, in turn, were transported into perinuclear lysosomes where the drug was released. These SMSNs reported promising results in-vitro and in-vivo (Liu et al., 2016). Sericin derived from a nonmulberry silk cocoon, *A. mylitta* was used for paclitaxel (PTX) delivery. The average size of obtained silk sericin-poloxamer (SS−P) NPs was ∼100 nm in diameter that could be maintained during prolonged storage and incubation. These drug-loaded nanoparticles showed efficient cytotoxicity toward MCF-7 cells when compared with the free drug (Mandal & Kundu, 2009). The newly formulated sericin/propolis/fluorouracil nanoparticles exhibited clear-cut cytotoxic effects through the PI3/Akt/mTOR in both in vitro and in vivo colon cancer models (Diab et al., 2024).

Silk sericin also appears to be a promising delivery agent for plant-derived substances in cancer therapy. Saraf and associates developed curcumin-loaded sericin

nanoparticles, whose basic pH improved their absorption, sustained release, and anticancer effects (Kanoujia et al., 2021).

Suktham et al. analyzed the effect of resveratrol-loaded sericin NPs against Caco-2 human colorectal adenocarcinoma cells and BJ skin fibroblasts. Sericin-based NPs resulted in high encapsulation levels (71%−75%) and intracellular internalization efficiency (97%) compared with free resveratrol and exhibited a cytotoxic effect on cancer cells without affecting the normal cells (Suktham et al., 2018). Apart from anticancer drugs and natural products, sericin was successfully used to formulate nanoparticles for nucleic acid delivery. Yalcin et al. investigated the delivery of siRNA into Hep-2 laryngeal cancer cells using albumin-sericin nanoparticles (Alb-Ser NPs). NPs were loaded with siRNA targeting casein kinase 2 (CK2), absent, small, or homeotic-like (ASH2L), and cyclin D1 (CCND1) genes, which are overexpressed in Hep-2 cells. The silencing effect achieved by individual administration of Alb-Ser NPs targeting the mentioned above genes was significantly higher (45%−65%) compared with naked siRNA and resulted in significant cytotoxicity of targeted cells (Yalcin et al., 2019).

Silk proteins can be conjugated to inorganic molecules. The particles obtained from such composite material may offer advantages in both cancer diagnosis (e.g., magnetic resonance imaging [MRI]) and therapy (like targeted drug delivery, and hyperthermia). Silk fibroin and spider silk have been extensively used in these studies, while data with sericin are limited. Phototherapy, represented by PDT and photothermal therapy (PTT), is considered a prospective therapeutic approach for cancer therapy with minimal invasion and high efficiency. PDT is related to the application of light absorbed by the photosensitizing (PS) agent and is used in conjunction with molecular oxygen to release singlet oxygen that is highly cytotoxic. In a study, hydrophilic sericin was modified with hydrophobic cholesterol and a tumor-targeting agent, folic acid (FA-Ser-Chol) to effectively encapsulate IR780, a PS agent (FA-Ser-Chol-IR780). These micelles were efficiently taken up by FA receptor-positive gastric cancer cells. Upon the cellular uptake and NIR laser irradiation, micelles showed remarkable PDT and PTT cytotoxicity toward BGC-823 cells (Deng et al., 2019).

5.4 Antioxidative properties of sericin and its role in cancer

Sericin has important biological characteristics that make it useful in many different contexts. Free radicals and reactive metabolites, commonly referred to as oxidants or reactive oxygen species (ROS), are formed in excess and can be eliminated by antioxidant defense systems. The antioxidant activity of sericin is among its most important advantages. Various publications have reported the inhibition of lipid peroxidation, neutralization of free radicals, ROS-scavenging, and antityrosinase action as antioxidant properties of sericin (Fig. 13.9).

Sericin has been investigated for its antioxidative qualities and its possible involvement in cancer. Cancer and other disorders, particularly those that affect the immune system, are thought to be influenced by the effects of oxidative stress. Studies have investigated the antioxidant potential of sericin by measuring the prevention of lipid peroxidation in mouse brain extracts. When compared to controls, which showed more oxidation, it was shown that tissues incubated with sericin for a longer period

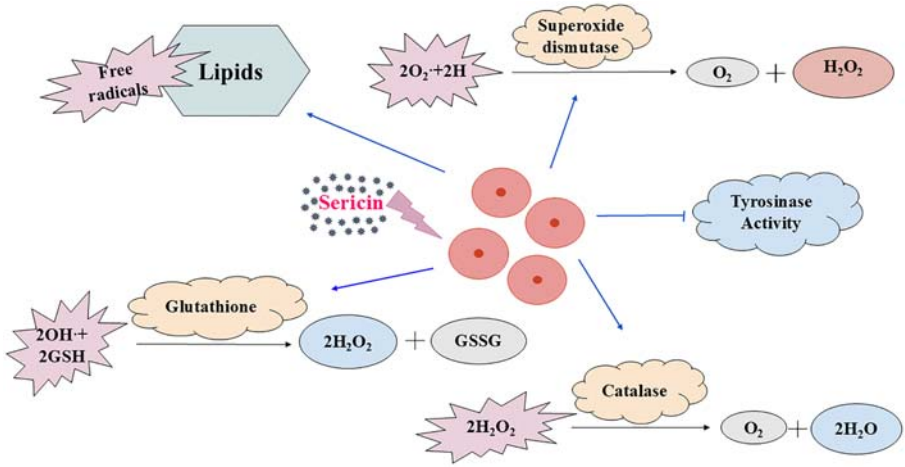


Figure 13.9 Schematic representation of the antioxidant potential of sericin. Adapted from Kato et al. (1998), Kumar and Mandal (2017).

of time showed fewer compounds derived from lipid peroxidation. In related work, hydrogen peroxide was used to cause oxidative stress in feline fibroblasts, and the samples incubated with sericin also showed strikingly reduced levels of lipid peroxidation byproducts (Jadhav et al., 2018).

Sericin protein can reach the rectal zone intact since it is resistant to human proteases. This trait led researchers to look into sericin's role in colon cancer. Two investigations on mice revealed a link between sericin consumption and a decrease in the frequency of colon cancers. In mice, colon carcinogenesis was generated for this aim, and sericin was administered orally to the animals. The inhibitory action on tumors and its connection to antioxidant activity were studied histologically. Examinations of the target tissue's cellular proliferation and oxidative stress showed a decreased adenoma incidence and minor oxidative stress in sericin-administered samples (Zhaorigetu et al., 2001).

Thiol group compounds are active antioxidants and confer protection in cell damage. The administration of 30 mg sericin powder to 12-week-old rats showed significantly higher native thiol and total thiol levels in the plasma. This suggests that sericin could be used as an antioxidative and cancer-preventing agent, facilitating lung tissue proliferation (Yazicioglu et al., 2024).

Sericin's low digestibility makes it an effective antioxidant, antitumor, antimicrobial, anti-inflammatory, anticoagulant, colon health promoter, and protective against obesity. These properties also enable its use in tissue engineering and drug delivery (Kunz et al., 2016). Undigested sericin may inhibit intestinal oxidative stress, which leads to a decrease in cell proliferation (Zhaorigetu et al., 2001). On lowering the oxidative stress, inflammatory reactions, and the endogenous tumor promoter TNF-α, the silk protein sericin, inhibit mouse skin tumor formation induced by 7,12-dimethylbenz[a]anthracene (Zhaorigetu et al., 2003). The addition of sericin powder

to bread enhanced its antioxidative properties, suggesting sericin proteins could be beneficial for human health (Takechi et al., 2014).

5.5 Role of sericin in the improvement of mitochondrial architecture

Mitochondria are important cellular organelles that are shown to be involved in many cellular processes of eukaryotic cells like cell proliferation, cell death, and calcium homeostasis. They are sites of many biochemical reactions like oxidative phosphorylation, tricarboxylic acid cycle, gluconeogenesis, etc. They also contain DNA that varies in copy number and sequence with evolution.

There are a minimum of five different mechanisms that were shown where mitochondria participate in cancer initiation and progression: Mutation in DNA, oxidative stress, cell death, metabolic reprogramming, and cell proliferation.

In nearly all eukaryotic cells, mitochondria are biosynthetic, bioenergetic, and signaling organelles. It has been demonstrated that these organelles' dysregulated function is crucial for carcinogenesis, tumor growth, and tumor dissemination. In a tumor, the mitochondria are reprogrammed. Some oncoproteins or tumor suppressors, such as IDH1/2, SDH, and FHs, function within mitochondria, producing oncogenic metabolites that start tumor development. Many other oncoproteins or tumor suppressors, however, directly or indirectly affect mitochondrial function, reprogramming mitochondrial metabolism to cause tumor transformation. The exterior and inner membrane architecture of the mitochondria, which dictate their bioenergetic capacity, organize themselves into highly ordered networks. According to a recent study, oxidative phosphorylation involved in tumors' affect glucose flux reduced both mitochondrial activity and cytoskeleton-based motility, which resulted in the restricted perinuclear location of mitochondria in these cancer cells.

Several studies revealed that sericin-treated rats had highly expressed levels of several mitochondrial energy maintenance proteins, including HDHD3, SDHA, ATPSA, ECHDC3, and ETFA. It is also well known that the pathophysiology of nonalcoholic steatohepatitis (NASH) is significantly influenced by the impairment of fatty acid oxidation or energy production in the mitochondria. This shows that sericin enhances mitochondrial architecture via altering the activity of caspase-3 and DRP1, which reduces the severity of hepatic steatosis (Ampawong et al., 2018). Sericin antioxidant effects preserved mitochondrial structure by regulating Tu, NADH-ubiquinone oxidoreductase, and prohibitin-2. It also modulated lipid metabolism in hepatocytes.

Sericin regulated the apoptotic (NDUFS1) and autophagic (TUFM and PHB2) mitochondrial proteins. Sericin treatment reduced the number of dysmorphic mitochondria in the rats. Additionally, proteomics investigation demonstrated a correlation between the expression of the proteins OAT, GOT2, ACSM1, HADH, and BDH1 with a decline in lipid accumulation and hepatocyte injury. The expression of CPS, AD, UOX, SARDH, and DMGDH was increased, which decreased hepatic steatosis and improved other liver functions (Ampawong et al., 2018).

Thus, the administration of sericin can control cancer progression by checking various mitochondrial activities.

6. Challenges and opportunities of using sericin for cancer treatment

Sericin can encapsulate the drug and protect it from degradation before it reaches the targeting site (Suktham et al., 2018). Investigations on the appropriate synthesis of silk sericin nanoparticles for resveratrol drug encapsulation proved them to be very efficient drug nanocarriers (Suktham et al., 2018). Sericin's film-forming ability creates a barrier over wounds, while its hydrophilic nature retains moisture, promotes faster healing, and improves recovery times for surgical wounds in cancer patients reducing the risk of infection and enhancing tissue regeneration. Sericin nanoparticles also possess low cytotoxicity immunotoxicity, biocompatibility, and higher nutritional significance. Sericin extraction is carried out by several methods. Degumming the *B. mori* cocoons and extracting sericin with water by boiling for 3 hrs at 100 °C was shown to be safe to use in food-related products (Qin et al., 2020). Sericin was shown to cause apoptosis in normal colon cells and cancer colon cells (Kaewkorn et al., 2012). Though most of the literature shows the applications of sericin as an anticancer agent, its usage needs to be checked, as nontargeted delivery can lead to the death of normal cells. In the cited publication, the authors showed the death of colon cancer cells and the proliferation of normal colon cells with sericin treatment. Studies showing more mechanistic details need to be addressed. A study on the rat models showed higher than 30 mg of sericin caused liver and kidney problems (Yazicioglu et al., 2020). Therefore, the dose of sericin administration also needs to be taken care of in biomedical applications.

7. Conclusion

Sericin is a silk protein, a natural polymer produced and secreted by the silk gland of insect *B. mori*. Sericin is a water-soluble glycoprotein and comprises 25%−30% of the cocoon weight; it is a hydrophilic protein characterized by the presence of 18 amino acids, with strong polar side groups (hydroxyl, carboxyl, and amino groups) and high content of serine, aspartic acid, and glycine, thus making it a potential player as a polymer in many biomedical applications like tissue engineering, cosmetic industry, and biomedical domain. Sericin has been reported to be a promising anticancer agent owing to its antiproliferative and apoptosis-inducing ability. Interestingly, sericin was demonstrated as a key player in cell cycle regulation in several cancer cell lines, though the exact mechanism is not yet elucidated. There are few studies to show the antioxidant property of sericin and the role of sericin in altering the mitochondrial structure and function that can affect tumor survival and propagation. Hence,

many other aspects of sericin that can promote it as a promising anticancer therapeutic remain to be explored.

Several groups across the globe have exploited the physical and chemical properties of silk sericin and silk fibroin in the preparation of drug carriers. These drug transport systems were studied to ferry many synthetic and natural compounds, peptides, and small RNA precisely to the target tissue in a variety of disease models such as cancer, neurodegeneration, inflammation, etc. In cancer biology, the boundaries of sericin-based drug delivery have not been limited to chemotherapeutic options alone but are now being promoted as potential agents that can aid in the diagnosis of cancer as well as in novel cancer treatments like photo-dynamic therapy. There is an urgent need for studies to focus on the drug-loading ability of the sericin-based nanoparticles, long retention times in circulation, and their targeted delivery to the tumor cells, which would contribute toward sericin-based oncotherapies in the clinic.

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Sericin in nutraceutical, food engineering and packaging applications

14

Anjali[1], *Prince Kumar Sonu*[1], *Mulaka Maruthi*[2] *and Vidyullatha Peddireddy*[1]
[1]Department of Nutrition Biology, School of Interdisciplinary & Applied Sciences, Central University of Haryana, Mahendergarh, Haryana, India; [2]Department of Biochemistry, School of Interdisciplinary & Applied Sciences, Central University of Haryana, Mahendergarh, Haryana, India

1. Introduction

Silkworms have served as a vital component of various industries, providing a natural protein product called silk with a wide range of benefits from ancient times. Sericin is a protein produced by *Bombyx mori*, a holometabolous insect belonging to the *lepidoptera* and *Bombycidae* orders. *B. mori* produces a large amount of Sericin at the end of the fifth larval stage, and together with fibrin, forms the silk thread used for the production of cocoon, a structure that provides ideal conditions for the appearance of the metamorphosis of the adult larva (Kundu et al., 2008). A streamlined thermochemical procedure known as "degumming" can be used to remove or separate sericin from fibroin, because it is a hydrophilic (soluble in hot water) protein. Silk fibers form 97% of total protein of which 70%−80% of total protein is fibroin and 20%−30% is sericin, and remaining are carbohydrates, pigment, waxes and minerals (Kongkachuichay et al., 2002). Based on the source of silkworm sericin protein feed, it is classified into two main categories, mulberry and nonmulberry sericin. Mushroom selenium is synthesized by *Bombyx mori*, a silk worm that feeds exclusively on mushroom plants and synthesizes important, commercially valuable selenium proteins. Likewise, *Samia cynthia ricini*, *Antheraea assamensis*, *Antheraea mylitta*, *Antheraea paphia* and others synthesize nonmulberry or Vanya sericin. In addition, the characteristics of sericin, it may depend on the diversity of silkworms, primary plants, and other environmental conditions (Jena et al., 2018). Sericin is a glue protein that binds silk filaments tightly. Silk sericin consists of 17 amino acids, including serine, histidine, glycine, threonine, tyrosine, glutamine, and aspartate amino acids. Sericin's exceptional qualities and possible use in the dietary supplement field have been shown in earlier research. Sericin is harmless and nonallergenic, demonstrating good biocompatibility. Furthermore, it has several beneficial properties, including antibacterial & antioxidant actions. Various dietary supplements' compatible nature and consistency have improved when sericin has been added as a component. Sericin, for example, has been shown in trials to improve the taste of bread, potato dough, and dressings for salads (Zhu et al., 2024).

Science and Technology of Silkworm Sericin. https://doi.org/10.1016/B978-0-443-21736-4.00014-3
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The silk sericin protein has been the subject of numerous articles and patents during the last 20 years. According to Google Scholar, approximately 21,400 publications and 1400 patents have been filed since 2003 (Figs. 14.1 and 14.2). As there have been many publications in past 20 years, silk sericin can be proposed as emerging area, and in future, it might be useful to treat many other diseases. Indeed, because of its distinctive characteristics and potential uses, silk sericin is becoming a fascinating topic to investigate in numerous additional fields such as textiles, drug delivery, biomedical applications, cosmetics with skin care, biodegradability, environment sustainability, and advanced materials etc. Silk sericin has demonstrated potential in biomedical applications including scaffolds for tissue engineering, wound healing materials, and drug delivery systems. It is useful in regenerative medicine because of its biocompatibility and capacity to promote cell development (Saad et al., 2023). The hydrating and antioxidant properties of sericin make it a popular ingredient in skincare and cosmetics. It is a common ingredient in antiaging products since it helps increase

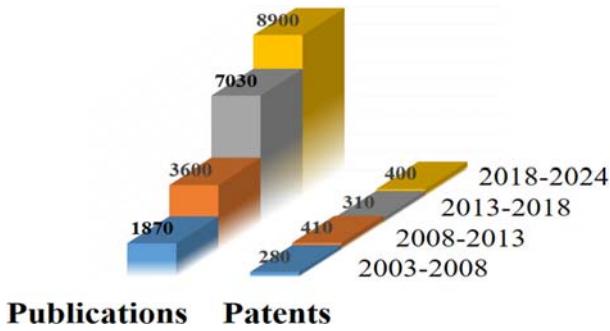


Figure 14.1 Total number of sericin based patents and publications in past 20 years (2003−24).

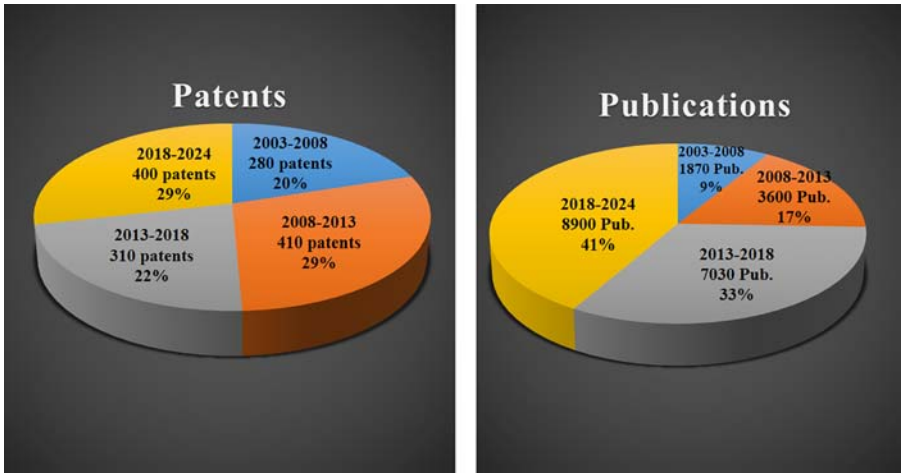


Figure 14.2 Graph showing number of sericin based publications and patents in every 5 years from 2003 to 2024.

skin's softness and moisture (Sarangi et al., 2023). Sericin is being investigated in the textile industry for its capacity to give materials functional qualities like improved dyeability, UV protection, and antibacterial activities. It might result in the production of high-performing, environmentally friendly textiles (Veiga et al., 2024). When viewed alongside synthetic alternatives, the manufacture of silk is often regarded as sustainable. Sericin isolation and usage can further improve the sustainability of silk processing through waste reduction and the creation of value-added goods (Silva et al., 2022). Researchers are investigating the potential application of sericin in the production of advanced innovative substances, including films, membranes, and coatings, due to its mechanical durability and capacity to form films (Seo et al., 2023). The distinct biochemical structure and adaptable qualities of silk sericin have led to a broad surge in interest across a wide range of industries and scientific fields.

Sericin has been discovered to possess antibacterial and UV-resistant characteristics, rendering it appropriate for implementation as a biomaterial (Pachhiappan et al., 2023). Moreover, sericin has shown antioxidant properties, as proven by its impact on skin fibroblast cell lines that were exposed to hydrogen peroxide for a duration of 24 hours. The characteristics of sericin have also rendered it beneficial in the realm of biomedical applications. For instance, low molecular weight sericin is employed in the domains of cosmetics, food additives, and pharmaceuticals. Conversely, high molecular weight sericin is utilized for the purpose of wound dressings and the advancement of biodegradable biomaterials. These characteristics, coupled with the commendable cytocompatibility and low immunogenicity of sericin, position it as a promising candidate for utilization in biomedical fields such as tissue engineering, wound healing, and regenerative medicine. Nonetheless, there exist certain constraints in the application of sericin in the realm of biomedical applications. One drawback pertains to the limited formability of sericin, attributable to its amorphous framework and elevated polar amino acid content. This serves to curtail their potential for fabrication into diverse shapes and structures. Another concern lies in the immunological response that ensues when sericin is employed as a biomaterial (Kwon & Seok, 2018). In contemplating the medical implementation of sericin, it is imperative to acknowledge that the immune system possesses the capacity to identify it as an alien substance. Consequently, this recognition can elicit an inflammatory reaction within the body, potentially leading to rejection or unfavorable consequences. In addition, the properties and composition of sericin diverge, contingent on whether it originates from mulberry silk or nonmulberry sources. This introduces further intricacy to their utilization within the medical realm.

However, it is imperative to draw attention to unique characteristics or recent advancements that differentiate sericin from alternative materials, or emphasize its expanding applications, which leads to significant novelty of sericin in this book chapter. Sericin-based functional foods have the potential to treat and prevent diseases such as osteoporosis (Jin et al., 2024), diabetes mellitus (Zhang et al., 2024), and ulcerative colitis (Wang et al., 2023). They are also used to enhance the stability and extend the shelf life of food products such as protein bars that include oral sericin (Zhu et al., 2024). The aforementioned studies represent contemporary research on sericin, rendering it innovative in its characteristics.

2. Silk sericin

Sericin, recognized as silk protein, represents a profoundly adaptable biomaterial that has engendered considerable scholarly scrutiny in recent times. It is procured from the cocoons of silkworms, which necessitate specialized nourishment to yield cocoons of superior quality, and the nutritional value of white mulberry leaves (*Morus alba*) satisfies this prerequisite. These leaves contain water (81.72%), fat (0.57%), protein (1.55%), fibers (1.47%), carbohydrates (14.21%), and other small compounds (0.48%), such as minerals (Imran et al., 2010). Leaf proteins are synthesized by cocoon gland cells and stored immediately in the lumen, where they are transformed into silk fibers. During the sewing process, silk passes through the aorta gland and is then ejected through the opening of the death. The result is a delicate double-fiber filament coated with a gum called sericin. This helps form silk boxes because they function as bonds that maintain their structural integrity. The obtained structure, oval in shape, is a safe haven during larval metamorphosis in which it becomes a pupa (Dash et al., 2007) and has long been utilized in the production of silk fabrics. It is recently that scientists have begun to investigate its potential for various clinical applications. Comprising approximately 20%−30% of silk fiber composition, sericin plays an important role in coating fibroin protein which makes up the majority of the silk filament (Dou & Zuo, 2014). During the isolation process of silk fibroin, the removal of sericin is essential to minimize inflammatory reactions and enhance biocompatibility. This focus on the removal stems from studies highlighting how certain components of sericin can induce immune responses when they encounter the living tissues. Eliminating these potentially problematic elements through proper purification procedures during extraction processes or refining techniques, such as degumming methods using chemical agents such as sodium carbonate or boiling water baths at pH levels near neutral (approximately seven) (Fig. 14.3). Sericin exhibits distinctive characteristics that render it optimal for biomedical applications. Sericin is a hydrophilic macromolecule with exceptional aqueous assimilation and sustenance properties. This attribute enables sericin to function as a moisture modulator, rendering it especially suitable for incorporation in hair care and cosmetic commodities. The capability of sericin to retain moisture aids in enhancing the hydration and consistency of hair, thereby rendering it suppler and easier to manage (Giovannelli et al., 2021). In addition, sericin has been discovered to possess antioxidant and antimicrobial characteristics. Its antioxidant properties render it advantageous for safeguarding against free radicals and oxidative stress, which have the potential to induce premature aging and inflict harm upon the skin. In addition, the antimicrobial features of sericin make it highly effective in preventing infections and promoting wound healing (Siritientong et al., 2013).

3. Sericin in nutraceutical applications

The protein sericin, obtained from silk fibers, has garnered substantial attention in recent years due to its varied potential health benefits. Due to its hydrophilic nature, it can

easily dissolve in water making it a promising nutraceutical that could potentially be incorporated into a variety of food and beverage products, thereby enhancing its availability among consumers. Moreover, sericin exhibits numerous advantageous characteristics that render it an enticing option for promoting overall welfare (Song et al., 2018). Unlikely, research studies have indicated that sericin demonstrates antioxidant activity, thereby providing protection to the body against oxidative stress and minimizing the harm caused by detrimental free radicals. Furthermore, sericin demonstrates anticoagulant characteristics that could have advantageous implications for individuals prone to blood-clotting disorders or cardiovascular ailments. Furthermore, investigations have indicated the antiinflammatory characteristics of sericin, implying its potentiality in ameliorating persistent inflammation and potentially alleviating indications connected with inflammatory ailments such as arthritis or inflammatory bowel disease (Deenonpoe et al., 2019). Moreover, sericin possesses antimicrobial characteristics, rendering it a prospective contender for combating bacterial infections and diminishing the peril of foodborne illnesses. The capability of sericin to augment cell attachment and proliferation has engendered significant attention as a nutraceutical. This particular quality of sericin has been extensively examined and utilized in various cell culture techniques, thereby making it a promising candidate for implementation in regenerative medicine and tissue engineering. As a result, the diverse biological functions displayed by sericin further enhance its potential as a valuable nutraceutical (Sahu et al., 2016). Additionally, the moisture-regulating capability and resistance to ultraviolet radiation exhibited by sericin make it a suitable component in cosmetic formulations aimed at enhancing skin hydration and safeguarding against solar harm.

3.1 Sericin nutritional benefits

Sericin has high levels of lysine, leucine, and valine—three necessary amino acids for human well-being. The synthesis of proteins, tissue repair, and regular growth and development relied on these amino acids. In diets deficient in sufficient protein, sericin, as a full-protein source, can be a beneficial supplement that promotes the functioning of the immune system, muscular fitness, and metabolic functions. The body can effectively break down and absorb nutrients found in sericin due to its high digestibility. This increases its bioavailability and assures that the human body can properly use the amino acids and other bioactive substances incorporated into sericin (Silva et al., 2022). Because sericin can scavenge free radicals and lessen oxidative stress, it demonstrates antioxidant activity. Since free radicals are linked to aging as well as chronic illnesses, antioxidants aid in defending cells against harm. Sericin significantly can support cellular wellness and generalized protection against antioxidants in nutraceuticals. Oral sericin use has been demonstrated to enhance skin's moisture and flexibility. It promotes the formation of collagen and preserves the skin's water-retaining barrier, each of which are necessary for keeping skin healthy and looking young. In contrast to other proteins like soy or dairy, sericin is non-allergenic and less prone to trigger allergic responses. As a result, it is a good choice for people looking for alternative sources of protein but have dietary allergies or sacrifices (Veiga et al., 2024).

3.2 Bioactive properties of sericin in nutraceutical applications

Silk-derived sericin has several bioactive characteristics that make it appropriate for use in nutraceutical products. These qualities enhance its potential positive health effects and useful roles in improving overall wellness. Sericin has strong antioxidant properties because it is a scavenger of free radicals and reduces oxidative stress. Free radicals are unstable substances that have the potential to harm cells and are implicated in the emergence of several chronic diseases, such as diabetes, cardiovascular disease, and cancer (Zhang et al., 2024). Sericin may assist in moderating the body's response to inflammation, promoting overall inflammatory balance and supporting health by reducing the synthesis of proinflammatory chemicals and cytokines. Sericin also improves the skin's ability to function as a protective layer, shielding it from contaminants and UV rays. Sericin is a useful component in skincare products and nutraceuticals that aim to improve skin health because it also accelerates the healing of wounds and may have antiaging properties (Miguel & Álvarez-López, 2020). Sericin might be involved in the regulation of glucose and metabolism of lipids, among other metabolic control processes. Its ability to enhance glucose tolerance, cholesterol levels, and general metabolic health parameters has been studied.

3.3 Formulation of sericin-based nutraceuticals

The process for producing sericin-based nutraceuticals includes producing goods that utilize sericin's advantageous qualities for uses in promoting health and wellness. The particular health advantages that the nutraceutical seeks to supply, such as support to the immune system, improvement of skin health, antioxidant properties, or metabolic management. This will direct the choice of further components and formulation methods (Saad et al., 2023). The additional components like antioxidants, prebiotics, probiotics, vitamins and minerals that improve the nutraceuticals health profile, effectiveness, and sensory aspects. Sericin can be taken as protein supplements as it is hypoallergic with powdered vitamins and minerals for health benefits. Sericin can be added to formulation of gummies in combination with sugar substitutes, flavorings, and colorants (Seo et al., 2023). Sericin may be a component in topical creams, serums, or ointments for skin and hair care as it constitute antioxidant activity and maintain skin hydration and block UV radiation (Sarangi et al., 2023).

3.4 Role in metabolic health

Silk-derived sericin has demonstrated encouraging potential as a means of supporting metabolic health through various processes. The ability of sericin to raise HDL (good) cholesterol levels and decrease LDL (bad) cholesterol has been investigated concerning producing healthy profile of lipids. This is because sericin lowers blood cholesterol levels overall by improving excretion of bile acids and intestinal blockage to reduce the absorption of cholesterol (Silva et al., 2022). Sericin lowers oxidative stress and inflammation, which are crucial in the emergence of arterial plaques, which could assist in avoiding the onset of atherosclerosis. Sericin may be able to enhance the

metabolism of glucose and insulin susceptibility (Wei et al., 2022). Research conducted on rodent models has indicated that administration of sericin can lower fasting glucose levels of blood and enhance insulin susceptibility, potentially due to its anti-inflammatory and antioxidant attributes. Chronic metabolic conditions including obesity and glucose intolerance are associated with persistent inflammatory processes and oxidative damage. Sericin may assist improve universal metabolic fitness by reducing these parameters due to its antiinflammatory and antioxidant qualities (Silva et al., 2022). The prebiotic properties of sericin may encourage the development of advantageous gut flora. Metabolic health maintenance depends on a healthy microbiota of guts since it affects immunological response, inflammation, and absorption of nutritional components (Matran et al., 2023). Therefore, sericin demonstrated a crucial role as nutraceutical for healthier maintenance of metabolic health.

3.5 Dietary supplement

Dietary fibers have gained considerable recognition in recent years because of their significant role in enhancing overall well-being and providing protection against various chronic diseases. Sericin, a silk-derived protein, has recently garnered attention. Sericin stands out for its exceptional water solubility and ability to encapsulate the fibroin fibers found on the surface of silk (Liu et al., 2018). In addition, sericin exhibits impressive attributes, including moisture regulation capabilities, UV radiation shielding properties, antibacterial activity, potential anticancer effects, and anticoagulant functions (source). The unique combination of these diverse qualities makes sericin an ideal candidate for integration into the diet as an invaluable source of dietary fiber (Qin et al., 2020). Moreover, incorporating this innovative inclusion not only enhances the nutritional composition of foods, but also holds promising additional health benefits. Sericin functions as a prebiotic, promoting the growth of beneficial bacteria in the gut and improving overall gut health (Song et al., 2018). Furthermore, sericin has been found to enhance intestinal absorption of essential minerals such as iron, zinc, calcium, and magnesium (source). This heightened absorption of minerals can contribute to the prevention of nutrient deficiencies and optimization of overall bodily functions.

4. Sericin in food engineering

4.1 Functional food

Sericin, a protein present in unprocessed silk, has attracted considerable interest as a potential functional food. Historically, sericin was viewed as mere waste during the processing of silk and was, therefore, not utilized. Nevertheless, researchers have now come to appreciate the financial and societal advantages that can be derived from reclaiming and reusing sericin (Liu et al., 2022). This protein exhibits diverse biological properties, elevating its potential as an ingredient in dietary supplements and other practical uses. Most of studies introduced sericin as dietary and nutritional

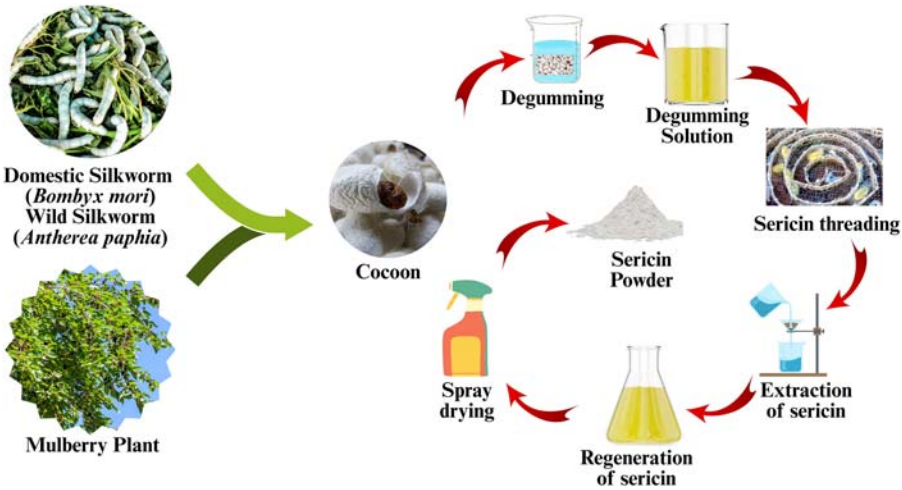


Figure 14.3 Sericin is obtained from the cocoon of *Bombyx mori* through the process of degumming in hot water. Subsequently, the cocoons are eliminated, leading to the availability of sericin for the purpose of threading. After that sericin regenerated through spray drying into powder form for its different applications.

supplement in food industry to improve health condition. Sericin based functional food (SBFF) used to treat bone related disease called osteoporosis. SBFF play therapeutic role in bone loss by osteoblast resorption (Jin et al., 2024). For example, sericin exhibits antioxidative, anticancerous, and wound healing activities that can contribute to overall health benefits. Furthermore, studies have shown that sericin has dietary fiber-like activity owing to its protease resistance. SBFF used to treat various disease due peroxidation of lipids and colonic inflammation by increasing reactive oxygen species amount (Wang et al., 2023). For example, silk sericin exhibit shelf life extension or protection of food degradation with its biodegradability and elasticity used for edible coating of fruits and vegetables. It was earlier mentioned that tomatoes extended their shelf life with same freshness and less degradability for around 40 days due to their resistance to oxidation and retention of moisture absorption (Seo et al., 2023).

4.2 Salad dressing

Sericin silk protein having emulsification property, which enables it for salad dressing. It consist of water soluble (hydrophilic) and insoluble (hydrophobic) AA (amino acid), gets adsorbed on the interface of oil in water emulsion to reduce tension in interface between them with their stabilization resulting, emulsion of firm dressing of salad with high "molecular weight" sericin (>280−300 Kda), emulsifying agent (Züge et al., 2017). Basically, fat and acids are two components of salad dressing in different varieties. It can be more complex by addition of spices and herbs in flavoring. Sericin is mixed vigorously with rape seed oil and vinegar to produce the stable emulsion in salad dressing (Takechi et al., 2011) (Table 14.1).

Table 14.1 Applications of sericin in food engineering.

Application	Properties
Salad dressing Bread making	Emulsifying agent for stabilization of food Improved nutritious value due to high fiber content Enhanced moisture absorption, and antifrosting property etc. Improved texture and color of bread with sericin concentration

4.3 Bread making

Sericin is added to the dough when baking bread to enhance its nutritional value. Due to its high fiber content, sericin-infused bread is suitable for diabetics. Sericin with different merits in the food industry i.e., easy availability, nontoxicity, admirable vapor absorbent ability, high content of fiber, decent emulsifying and antifrosting silk sericin (SS) protein with antioxidant properties. The color, hardness, and flavor of the bread are significantly altered when sericin levels are too high (>10/1000 g of flour) (Ghosh et al., 2017) (Table 14.1). It is said that the bread's color darkens, the texture hardens, and swallowing the bread becomes challenging. The internal structure of bread slices made of sericin in its varying specific volumes having various amount of sericin protein in it, investigated by SEM (Scanning electron microscopy) imaging. One slice of bread can contain up to 300−330 mg of sericin. A sensory analysis of bread upto "2 g" of additional silk sericin protein is revealed (Takechi & Takamura, 2014).

5. Sericin in packaging

5.1 Edible coating material

Sericin, which can be used as a fat-free edible coating substance, comes from silk waste and offers a more affordable and sustainable source of protein. While blocking the action of the enzyme polyphenol oxidase, it has the potential to improve fruit texture and color and diminish fruit weight loss. Sericin, an active ingredient, boosted the mechanical strength of edible coatings when combined with a protein, such as whey hydrolysate (in a restricted amount of around 0.1%). By incorporating polysaccharides, proteins, and gums into sericin-based films, antioxidant, antibacterial, and adjustable water barrier properties can be added, improving the functional qualities of edible films. Forming agents of films include a variety of biopolymers, including polysaccharides, amino acids, and triglycerides (Wang et al., 2010). Sericin protein is a biodegradable compound which can be broken down into small molecules by organisms, and do not cause any harm to environment and human health. Therefore, it can be helpful for protecting fruits and vegetables in their hydrolysate condition with an edible covering. Sericin is modified by crosslinking with different polymers due to its biodegradability, elasticity, and its strength. Tomatoes can be kept for longer at 25°C and 70% relative humidity by using an edible covering layer based on sericin

and incorporating chitosan, aloe vera, and glycerol (Liu et al., 2022). The polarity of the sericin molecule determines whether SS films are "hydrophobic" (water insoluble) or "hydrophilicity" (water soluble). Using more polarity results in the production of a silk sericin protein film with increased wetness. On the other hand, when sericin hydrolysate is combined with sericin film, the moisture content and molecular weight decrease, increasing the water-vapor permeability. The antioxidant activity of sericin hydrolysate with film is enhanced due to the synthesis of flavonoids and alkaloids, in addition to the total amount of phenols, surpassing that of sericin film alone. Flexible sericin films are produced through the combination of glycerol and polysaccharide polymers known as "glucomannan" (Seo et al., 2023) (Table 14.2). Sericin based films usually protect fruits and vegetables from microbial attack and their degradation due to their antibacterial and antioxidant effects (Silva et al., 2022).

Case studies: 1. A study by Yun et al. (2016) showed that a plasticizer i.e., glycine used with sericin for its elongation properties. Glycine exhibits synergistic effects on sericin films with molecules of water, increasing its elasticity. Moreover, as the amount of glycine in the sericin film increased, it led to rise in elasticity of the films. Later, the moisture content and β-sheet structure also somewhat increased. Thus, moisture content of film rises as a result of plasticization with glycine (Yun et al., 2016).

2. Another study by Oh et al. (2021) showed that Maillard reaction of sericin-glucose was triggered by using sericin films with strong crosslinks to generate glucose and heat treatment, which improved the limited physicochemical capabilities of sericin. According to the author, the development of the chemical crosslinking reaction based on the Maillard reaction greatly strengthened the intrinsic imperfections of the sericin film, such as its mechanical attributes and water repellency, also gave the film antioxidant and UV protection traits. Therefore, food oxidation can be managed and shelf life can be extended by adding glucose to form a sericin coating (Oh et al., 2021).

5.2 Extension of shelf life and preservation

The shelf life is extended by using a sericin-based (1.5%) edible coating substance that contains chitosan (1%), aloe vera (1%), and glycerin (1.5%) solution with water by dip-coating on tomatoes. The tomatoes' freshness and lifespan after 40 days of storage at temperature around 25°C and 70% moisture were compared relatively (Seo et al., 2023). SEM was used to measure the coating layer's thickness and semipermeable characteristics while lycopene levels, pH, total soluble solids (TSS), titratable acid content (TA), and weight loss were also investigated. The covering material made of edible ingredients and based on sericin stopped tomatoes from becoming rigid and losing weight. The TA of fruit was improved while pH, TSS, lycopene amount, total phenolic content, and antioxidants stayed low with storage time in comparison with uncoated tomatoes (Tarangini et al., 2022). Sericin films with glycine as plasticizer were formulated for the extension of shelf life or storage time. Water had a synergistic effect on sericin films to increase their flexibility, while an increase in glycine content also slightly boosted the film's moistness and beta-sheet structure. Glycine acts as a plasticizer in sericin films, increasing the degree of wetness in the films (Seo et al.,

Table 14.2 Application of silk sericin in food packaging (Seo et al., 2023).

Application	Composition	Properties
Edible coating	Protein	Improvement in mechanical strength i.e., whey protein
	Hydrolysate	Declination of molecular weight and moisture content, with increase in antioxidant activity
	Ag/ZnO Np	Improvement in adhering properties with antibacterial activity
	Glycerol	Flexibility in edible film as glucomannan, with surface improvement
	Polysaccharides	Functional and water absorption qualities improvement with antibacterial, antifungal and antioxidant activity
Shelf life extension and preservation	Glycine	Act as plasticizer to increase the firmness and moistness with flexibility
	Nanoparticles	Increase in antibacterial and antimicrobial activity with extension of life span
	Chitosan, aloe vera, glycerin	With water, prevent weight loss and stiffness as well as decline in TPC and antioxidant capacity

2023). In order to ensure that food is safe, sericin with edible coating materials uses nanoparticles to prolong the shelf life and their preservation by extending storage duration (Deepika et al., 2023) (Table 14.2).

6. Sericin's interplay with food components: Health and safety implications

Sericin, a prominent component of silk, has garnered increasing attention for its potential applications in the food industry. The silk protein, which typically envelops the fibroin core, exhibits remarkable properties that can be harnessed to enhance various food-related functionalities. Silk fibroin has been widely recognized for its favorable mechanical properties, flexibility, and slow-release capabilities, making it a popular choice for bone tissue engineering (Yao et al., 2016). Similarly, the acidic nature of sericin's side chains can induce the mineralization of calcium phosphate, an important process in bone formation (Yao et al., 2016).

Recent research has shed light on the versatile interactions between sericin and various food components. Silk-based materials, optimized through selective pressure to perform at the biotic-abiotic interface, can be leveraged to impart new functionalities and opportunities in the food industry (Zhou et al., 2018). For instance, the use of ionic liquid-dissolved silk fibers has enabled the fabrication of diverse silk-based composites, including blends with natural biopolymers, synthetic polymers, and inorganic

materials (Heng et al., 2022). These silk-based materials have found applications in areas such as artificial skin coatings, biomedical sensors, and drug delivery systems, showcasing their potential for food-related applications as well (Heng et al., 2022).

Furthermore, the incorporation of silk-based materials into food products can potentially improve their mechanical performance, as preliminary studies have suggested the use of silk fibers as micro-reinforcements to enhance the properties of polymeric-based structural composite materials (Cheung & Lau, 2006). The biodegradable and highly crystalline nature of silk fibers, coupled with their superior tensile strength, make them an attractive alternative to traditional reinforcing materials, such as glass and synthetic organic fibers (Cheung & Lau, 2006).

Sericin has been shown in recent studies to provide beneficial nutrients and can improve health outcomes when used as a dietary supplement in food products. Sericin lowers blood cholesterol and enhances the mitochondrial structure of the liver. Furthermore, sericin has antioxidant impacts on peripheral organs including the brain. The strong antioxidant properties of sericin and high hydroxyl amino acid content might decrease oxidative damage in the peripheral tissues and brains of a group of individuals. According to the aforementioned results, sericin, when added to food items as a supplement to the diet, may have a beneficial effect on mitochondrial activity and the breakdown of cholesterol, leading to established health advantages. In the estrogen-deficiency osteoporosis model, sericin can be used as a useful dietary material for the prevention of osteoporosis and its treatment because of its high concentration of serine, which can impair osteoclast functioning. This research also made use of heat-degraded sericin extracts, which are less harmful and better suited for industrial manufacturing and the creation of functional foods (Jin et al., 2024).

In conclusion, the unique properties of sericin and its interactions with various food components present promising opportunities for enhancing the health and safety of food products. By leveraging the versatile capabilities of silk-based materials, the food industry can explore innovative solutions to address challenges and develop novel, high-performance products that cater to consumer demands for sustainable and environmentally friendly options.

7. Toxicity, biocompatibility, regulatory aspects of sericin & safety assessments in food applications

It is imperative to take into account the toxicity and biocompatibility of sericin in food applications to guarantee the safety of consumers. The process of determining sericin's potential to hurt or have negative effects on humans is known as toxicity assessment. There were no harmful effects or mutagenic alterations in the liver, kidney, or spleen of rats given sericin orally. Sericin appears to be safe and nonmutagenic based on the scientific data that is currently available from *in vitro* and *in vivo* research. These results validate the safe utilization of sericin in the food, pharmaceutical, and biomedical industries (Qin et al., 2020). Sericin is a silk protein molecule with potent hydrophilic qualities that offer useful biochemical and biodegradable traits. Its capacity to display antibacterial,

antioxidant, anticancer, and antityrosinase qualities is what is thought to be responsible for its biocompatibility. Sericin is a proteinaceous substance that shows promise for use in the food industry for several purposes, such as food packaging and functional food items. Studies are being conducted both in vitro and in vivo to evaluate the tissue reaction, inflammatory responses, immunological compatibility, and general safety of sericin when it comes into contact with biological fluids or tissues (Saad et al., 2023).

8. Technical and economic challenges of sericin-based functional foods

The food sector is always looking for novel and innovative approaches to provide nutritional foods that provide individuals with greater wellness positive aspects (Rodgers, 2004). A topic of particular curiosity is the application of a protein called sericin, which comes directly from the cocoons of silkworms to foodstuffs. Sericin's distinctive physicochemical and biological features of sericin have led to its recognition as a potentially useful component (Zhou et al., 2018). Yet, there are a variety of financial and technical obstacles to overcome in order to commercialize sericin integration into food products successfully.

8.1 Technical challenges

One of major technological hurdle during processing of food and storage is ensuring the bioavailability and stability of sericin (Day et al., 2009). Similar to substantially bioactive molecules, sericin is susceptible to different environmental elements like heat, light, and oxygen, which can cause its beneficial qualities to diminish (Raddatz & Menezes, 2021). Moreover, the organoleptic features of the final goods may be impacted by adding sericin to the substrate of food, which may have an effect on consumer acceptance (Redgwell & Fischer, 2005). The currently available extraction procedure for sericin is time-intensive and laborious, which may restrict its scalability. It is crucial to develop extraction techniques that are more economical and efficient. Special formulating and manufacturing methods are needed for sericin-based functional foods to preserve their bioactive attributes and guaranteed customer approval. Functional foods based on sericin might not be as stable or have as long of a shelf life, which could work against them in the marketplace. It is essential to increase their durability and longevity by using inventive packaging and restoration methods.

8.2 Economic challenges

The requirement for functional foods based on sericin is still growing, and it can take some time for the market to grow to the point where large-scale production is financially feasible. The extraction, formulation, and processing costs of sericin can be substantial, which makes it difficult to manufacture competitively priced sericin-based functional meals. Economically, one of the biggest obstacles to sericin's broad application in the food business may be the expense of its extraction and purification

(Raddatz & Menezes, 2021). A variety of extraction and purification techniques are both affordable and effectively essential to increasing the viability of sericin-based functional food from a financial perspective for food producers.

Research and development in this sector are nevertheless motivated by the potential health benefits of sericin, which include its antiinflammatory, antioxidant, and wound healing qualities (Day et al., 2009; Rodgers, 2004). In future decades, sericin-based dietary supplements may be successfully commercialized if regular attempts are made to maximize the inclusion of sericin into food items while conserving their gustatory value and cost.

9. Scalability of production

It is essential to create scalable production methods that can efficiently and profitably provide functional foods based on sericin. Silk sericin is made by a laborious procedure that involves extracting and purifying the protein from silkworm cocoons. Historically, large-scale industrial scaling has been challenging due to this process' high manpower and resource requirements. Furthermore, the low yield and restricted supply of silkworm cocoons have impeded the widespread application of sericin-based products. To get over these problems, experts have investigated a number of ways to improve the scalability of sericin manufacturing. Two examples of advanced manufacturing techniques that can be used in this manner are recombinant gene expression and genetic modification. Artificial spider thread-like silk proteins that are functionally and structurally identical to authentic silk sericin have been produced owing to these approaches. Investigators have produced sericin-like thread proteins with greater influence over their features and in higher numbers by utilizing biologically synthetic approaches (Kiseleva et al., 2020).

The scalability of silk sericin manufacture can be addressed using a number of innovative techniques, each with specific advantages and disadvantages. One approach that seems promising is electrospinning, which could result in sericin nanofibers with controlled diameters by adjusting the electrospinning procedure and the properties of the polymeric solution. An example of an economical strategy for creating tiny nanofibers is an effective manufacturing of sericin nanofibers with shiny exteriors at concentrations of 50% and 60% of weight. The typical sizes decreased as the voltage used was increased (Zhang et al., 2011). A different strategy uses genetically modified silkworms to produce synthetic proteins in the silk glands, like human acidic fibroblast growth factor (r-haFGF). The technique has shown a significant rise in yield of proteins with its bioactivity, indicating the possibility of large scale production of functional sericin-based resources (Wang et al., 2015). Moreover, the formation of silk threads with enhanced strength and manufacturing effectiveness as a result of an aberrant expression of sericin in the posterior silkworm's gland provides a practical and environmentally friendly means of increasing sericin output (Chen et al., 2022). Taken together, these tactics demonstrate that silk sericin production may be increased through the use of gene editing and modern manufacturing techniques, potentially

leading to more extensive commercial and therapeutic applications. Collaborations between the public and private sectors can aid in the sharing of knowledge, the distribution of resources, and the management of risks, all of which contribute to the development of more efficient and scalable manufacturing processes.

10. Other potential applications (Table 14.3)

10.1 Antibacterial agent

Sericin exhibits varying antibacterial activity depending on degumming process for its extraction. Sericin obtained by water and sodium carbonate degumming processes can inhibit gram −ve or +ve food borne pathogenic bacteria i.e., *Escherichia coli* and *Streptococcus aureus*. As the sericin concentration is enhanced, its antibacterial activity also improves (Seo et al., 2023).

Table 14.3 Other potential application of sericin (Seo et al., 2023).

Other application's	Properties
Antibacterial	Promotes cell apoptosis with prevention of reproduction and growth of cell Inhibit gram +ve and −ve bacterial growth i.e., *Escherichia coli* and *Streptococcus aureus* in combination with other bioactive compounds
Antioxidant	Oxidative stress protection and decline in ROS, prevention of free radical chain reaction by stabilizing them Antioxidant activity is inversely correlated with the size of its molecules High Se and Thr, hydroxy (−OH) group with chelating trace elements i.e., Cu and Fe
Anticancer	Induction of apoptosis by self-assembly in breast MCF-7 cancerous cells Regulatory element Bcl2 induces or promotes cell death and encourage caspase-3 activity at last stage of cancer Causes cell shrinkage, changes in cancerous cells shape and size, with cell cycle arrest and preventing tumor growth
Antiaging	With the inhibition of apoptosis and enhances synthesis of type 1 collagen Vitamin C is also improved with great antiaging and antiwrinkle ability, also improve skin flexibility Good moisture retaining capacity to use in cosmoceutical industries to prevent skin problems i.e., dermatitis
Antiinflammatory	Antiinflammatory compounds containing i.e., hydroquinone and pyrogallol Phenolic compounds in conjugation more effective to decline the activity of 15-lipoxygenase "(15-LOX)"

10.2 Antioxidant activity

ROS (reactive oxygen species) are the free radicals released during cellular metabolism are highly reactive and toxic due to their instability. In food industry, BHA (butylated hydroxyanisole) and BHT (butylated hydroxytoluene) are man-made antioxidants with greater potential that are less expensive. Sericin has the potential to be an antioxidant due to its −OH (hydroxyl group) with high serine (Se) and threonine (thr) which may chelate trace metals like copper and iron. Sericin have free radical scavenging activity by stabilizing them to prevent the oxidative damage. Sericin's antioxidant activity is inversely correlated with the size of its molecules. Thus, its molecular size can be decreased for boosting its free radical scavenging or "antioxidant" action. In terms of oxidative processes, silk sericin is a common protein and a safe ingredient that can improve food quality over time in cosmetic foods and products (Seo et al., 2023).

10.3 Antiaging activity

A blend of sericin and silk fibroin powder has a high-water solubility and the ability to absorb moisture. Sericin protein also promotes the synthesis of type 1 collagen and inhibits apoptosis, which is why it is used in cosmetics for nails, skin, and hair to increase skin pliability and antiaging and antiwrinkle properties. Because sericin has potent antiaging properties and reduces wrinkles caused by oxidative stress, vitamin C was also enhanced. Thus, sericin has been successfully employed to treat skin conditions including dermatitis and eczema in the cosmoceutical sectors through the use of moisturizers and creams, among other products (Seo et al., 2023).

10.4 Anticancer activity

In addition to its antioxidant properties, sericin protein has demonstrated the ability to suppress multiple types of cancer cells. As sericin levels rise, the viability of cancer cells treated with sericin decreases. Silk sericin nanoparticles cause MCF-7 breast cancer cells to self-assemble and undergo apoptosis (Kumar & Mandal, 2019). Bcl-2 is an energetic component in the final stage of cell death that causes the death of malignant cells in the colon. It is a regulatory element that either promotes or inhibits cell death, or "apoptosis," and arises in the activity of caspase-3. In the meantime, sericin inhibits the effects of BCL-2, which also has anticancer properties. The anticancerous properties of sericin include inducing apoptotic mechanisms, which may help prevent angiogenesis, interrupt the tumor growth cycle, and regulate tumor growth (Seo et al., 2023).

10.5 Antiinflammatory activity

The silk sericin's fused phenolic components, such as pyrogallol and hydroquinone, confer additional antiinflammatory properties. The inflammatory disorders are associated with both NO (nitric oxide) and 15-LOX (15-lipoxygenase). 15-LOX is an important lipid mediator that promotes inflammation by converting arachidonic acid to

leukotriene. However, a rise in NO also intensifies inflammation (Omar et al., 2022). The assay of inhibition of "15-lipoxygenase" (15-LOX) and "nitric oxide" (NO) production were employed to evaluate the antiinflammatory properties of CS (control sericin), PS (pyrogallol-sericin conjugate), and HS (hydroquinone-sericin conjugate). The results showed that PS was more effective than "CS" and conjugated sericin hydroquinone (HS). Several biomedical applications use SS in conjunction with other biomaterials (Seo et al., 2023).

11. Conclusion

Bombyx mori silkworms are the source of the silk protein known as sericin. The process of threading after sericin extraction from silk cocoons is known as degumming. Following that, silk sericin (SS) was employed in a number of industrial applications, including food packaging, drug engineering, cosmetics, and nutraceuticals. It is very effective in healing wounds, skin ulcers, diabetes, and inflammation. In order to preserve and lengthen the shelf life of fruits and vegetables, sericin can be utilized to build biodegradable edible biofilm. Sericin also possesses antibacterial, antioxidant, antiinflammatory, and antiaging properties. SS is also helpful in functional food compositions with higher antioxidant properties for salad dressing and potato bread. Different nutraceuticals are made into medications using SS for medical uses. Because silk sericin contains a variety of amino acids, including glycine, aspartic acid, serine, tyrosine, and others, it has bioactive qualities that can be used to treat several diseases, including diabetes, osteoporosis, inflammation, and low cholesterol. SS possesses unique qualities such as flexibility, biodegradability, photoprotective qualities for use in cosmoceuticals, and the ability to create films for skin protection and food preservation with extended shelf life. Sericin has been utilized in recent studies to treat conditions including osteoporosis and diabetes mellitus, among others. Thus, SS may be employed in the future to treat any other illness. The ecological problem, the intriguing biological potential of sericin, and other waste products from silkworm production may lead to the development of a biofactory in the future that manufactures proteins, lipids, and carbohydrates for pharmacological and medicinal uses.

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Applications of sericin hybrid materials in textile industry

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Mandira Mondal, Bharti Rana, S. Wazed Ali and Mangala Joshi
Department of Textile and Fibre Engineering, Indian Institute of Technology Delhi, New Delhi, India

1. Introduction

Silk sericin has emerged as a highly sought-after sustainable product for the textile industry in recent years due to its eco-friendly nature and economic advantages. Utilizing waste goods in the textile sector is becoming more popular today as an environmentally responsible strategy. In addition to the positive effects of waste reduction for pollution control, sericin treatment of textiles from the degumming waste liquor promises a significant source of profit for silk growers as well. Sericin's features, notably antioxidant properties, antibacterial activity, UV protection, biocompatibility, biodegradability, nontoxicity, and ease of absorption and moisture release, make it a suitable finishing agent for eco-friendly textile treatments (Kaur et al., 2013; Martínez et al., 2017). In lieu of harmful chemicals, ecological methods, and biochemicals are increasingly being used in textile finishing procedures.

Considering a variety of specific uses, sericin can be applied to different textile substrates like cotton, polyester, and wool. These sericin-treated fabrics have been examined for various properties such as air permeability (Gupta et al., 2014), moisture transfer (El-Newashy et al., 2019), crease retention (Zhang & Hao, 2023), UV protection (El-Sayed et al., 2019), antistatic (Gupta, Chaudhary, & Gupta, 2015a, 2015b), antioxidant (Miguel & Álvarez-López, 2020), and antibacterial characteristics (Rajendran et al., 2012). An overview of the use of sericin in the textile industry is shown in Fig. 15.1.

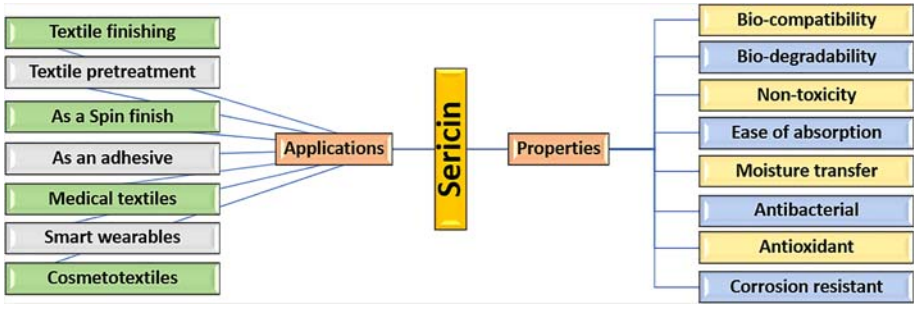


Figure 15.1 Properties and applications of sericin in textile industry.

Science and Technology of Silkworm Sericin. https://doi.org/10.1016/B978-0-443-21736-4.00015-5
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Sericin has been used as a finishing agent on various textile substrates, that is, cotton, polyester, wool, etc. to impart various functional properties. Among all natural fibers, cotton is the most prominent and popular choice of consumers. Sericin can be used to give a durable finish to cotton for sports and medical wear. The sericin-treated cotton substrate shows reduced electrical resistance (Kongdee et al., 2005) while enhancement in air permeability (Gupta et al., 2014), wicking, crease retention, and moisture vapor transmission rate (Nagarajan et al., 2017). In addition, it exhibits outstanding antimicrobial activity (Rajendran et al., 2012). Polyethylene terephthalate (PET) is a highly utilized synthetic fiber for textile applications. It is inert, nonpolar, and hydrophobic in nature. Sericin can be functionalized onto polyester fabrics in a variety of ways to improve their hydrophilicity (Khalifa et al., 2016; Umam & Fitria, 2018). Improved vertical wicking and moisture recovery can be achieved from modified polyesters. In addition, they demonstrated enhanced antistatic, protection against UV radiations, and radical scavenging abilities (Gupta et al., 2015a, 2015b). Sericin-treated wool fabrics can be explored for improved multiple functionalities (Khalifa et al., 2012) such as touch, handle, increased water absorption, and antibacterial properties. It can also be used for felt proofing of wool fibers (Allam et al., 2009).

Sericin has also been explored as a pretreatment for textile substrates to enhance their affinity toward dyeing and printing. Textiles do not directly bind to sericin. To fabricate new biodegradable materials with enhanced properties, sericin can be copolymerized, cross-linked, or combined with other polymers (Zhu et al., 2022). It has an affinity for wool but not for cotton (Khalifa et al., 2012). The ionization of the hydroxyl groups inherent in the structure of cellulosic fibers including cotton exhibits a negative charge when in contact with water. The low affinity of natural dyes for cotton is caused by this negative zeta potential. Therefore, different metallic mordants such as copper, chromium, and other salts must be employed to enhance dye absorption. These unused mordants, however, are detrimental to the environment. Therefore, natural mordants are desirable. Sericin has been investigated as a potential natural mordant that can provide aid in solving environmental problems such as water pollution. Cotton reacts more readily to natural dyes attributed to the functional groups NH_2, $-COOH$, and OH- that are inherent in sericin's structure (Bhandari et al., 2018; Kongdee & Chinthawan, 2007). Wool fabric pretreated with silk sericin followed by dyeing with reactive dye at lower temperature (85°C) results in high color strength and fastness performance as compared to wool fabric dyed at higher temperature (95°C) (Eser & Yavas, 2021). The printing of woolen textiles with acidic, reactive, and basic dyes can also be effectively improved by using sericin (Haggag et al., 2009). Although polyester is typically dyed with hydrophobic dyes like disperse dyes, it can also be dyed with hydrophilic dyes like reactive dyes. To accomplish this, the fabric surface can be modified by applying sericin. Amino acids of sericin will form ionic interactions with the reactive dyes that impart color to the polyester substrates (Umam & Fitria, 2018; Hakeim et al., 2022; Chaudhary et al., 2017). According to the literature available, adding amino compounds to jute before dyeing could promote reactive dye

exhaustion into these modified fibers even in the absence of salt. Silk sericin has been employed as a natural modifying agent to increase the reactive dyeability of jute in the presence of an esterification catalyst (Das et al., 2018).

Even though sericin has several advantageous traits, its use as a spin finish in the textile industry has not been explored much. Sericin is a biopolymer and biocompatible substance that is used as a spin finish in the production of synthetic fibers. It provides a lubricated surface to the fibers and filaments to improve fiber cohesion leading to more flexible, moist, hydrophilic, and antistatic yarns because decreasing friction leads to decreased tension in the yarn. Sericin as a spin finish on PET yarn can improve basic dye uptake due to the presence of strong polar side chains (Zare, 2023).

Moreover, silk sericin has been used as an adhesive for textile-based strain sensors employed in smart wearables. By using sericin as a natural adhesive, acetate fabrics coated with carbon nanotubes have effectively been developed via a simple and environmentally benign method. It binds nickel metal and carbon nanotubes (CNTs) without using any extra fillers. With the help of silk sericin, the material can absorb a significant amount of metal nickel on the surface of CNTs (Duan & Lu, 2021). By employing the outstanding binding property of sericin, silk nonwoven fabric can be successfully fabricated with enhanced mechanical properties without yellowing (Lee et al., 2018). Other applications include medical textiles, cosmetotextiles, etc. (Rajalakshmi et al., 2018, Rangi & Jajpura, 2015).

This chapter covers the wide aspects of the methodology for the preparation of sericin hybrids, various approaches to impart sericin-based hybrids to textile substrates, and their potential applications in textile industries.

2. Structural and functional properties of sericin

As a hydrophilic protein, sericin is composed of 18 types of amino acids mostly serine and aspartic acid. It has been used for various textile substrates in order to impart multiple functional properties such as moisture absorption, handle, antibacterial, antioxidant, UV protection, crosslinking, and so on. Table 15.1 lists the potential improvement in various properties for different textile substrates treated with sericin.

Here, the function of sericin for improving various properties is discussed in detail.

2.1 Antimicrobial activity

Textile materials, which often consist of natural fibers, provide a great environment for microbial growth because of their high surface area and capacity to hold moisture. The growth of fungi, bacteria, and the transit of germs from one place to another is very often in textiles. As consumers pay more attention to their health and cleanliness, the need for antibacterial textiles and functional textiles is rising. To control the spread of microbes and cross-contamination, many antimicrobial

Table 15.1 Review of various substrates treated with sericin for improvement in various properties.

Material used	Substrate used	Properties improvement	References
Sericin	Wool fabrics	• Increased fabric water absorption up to 5% (w/w) • Increased fabric softness (4 points on scale) • Improved antibacterial activity	Khalifa et al. (2012)
Sericin + glutaraldehyde (crosslinking agent)	Cotton fabrics	• Improved air permeability • Decreased wicking property and improved water repellency	Nagarajan et al. (2017)
Sericin + citric acid (crosslinking agent)	Drawn textured PET yarns	• Improved moisture regain and vertical wicking • Improved dye uptake and 32%−42% improvement in ultraviolet protection	Zare (2023)
Sericin + formaldehyde, glutaraldehyde, and modified DMDHEU (cross-linking agent)	Polyester fabrics	• Improved hydrophilicity • Reduced accumulated electrostatic charges	Bhat et al. (2010)
Sericin + glutaraldehyde (crosslinking agent)	Polyester knitted fabrics	• Decreased air permeability and increased water absorption • Increased thermal conductivity and electrical conductivity	El-Newashy et al. (2019)
Sericin	PET fabric	• Significant reduction in the bacterial and fungal attack	Joshi et al. (2009)
Sericin	Cotton fabric	• Increased antibacterial activity	Rajendran et al. (2012)
Sericin + DMDHEU (crosslinking agent)	Cotton fabrics	• Decreased electrical and increased water retention	Kongdee et al. (2005)
Sericin + DMDHEU, DMeDHEU, and ECH (crosslinking agent)	Wool fabrics	• Improved felting resistance	Allam et al. (2009)
H_2O_2/Na_2SO_3/sericin	Wool fabrics	• Enhanced printability with acid, reactive, and basic dyes with improved fastness properties • Increased resistance to felting and pilling	Haggag et al. (2009)
Sericin + citric acid or epichlorohydrin	Polyamide 6 fabric	• Excellent UV protection • Improved dyeability	El-Sayed et al. (2019)

finishing techniques for textiles have been investigated. Antimicrobial textile materials could be employed, especially in medical textiles to minimize microbial illnesses brought on by textile products. To reduce the microbial burden in the wound area, prevent wound infections, and treat wounds, functionalized textiles can be utilized in wound management.

Sericin has extensively been studied for its antibacterial effects (Rajalakshmi et al., 2018; Aramwit et al., 2009; Jassim & Alsaree, 2010), either in its natural state or when combined with other substances like silver. One of the mechanisms is illustrated in Fig. 15.2. The mechanism of antibacterial activity of sericin is related to the physiological function of bacterial cells. When sericin encounters bacterial cells, it causes shrinkage and extreme roughening of the cell surface, which further affects the process of cell division. Sericin exhibits cationic character in acidic conditions because of the amine groups (NH_2) in its structure. Amine groups enable contact with negatively charged bacterial wall membranes. As a result, it prevents the bacteria's regular physiological processes, stunts their growth, and even kills them. The sericin-coated fabric showed a high degree of bactericidal activity against test organisms like Gram-position bacteria (*Staphylococcus aureus*) and Gram-negative bacteria (*Escherichia coli*) (Rajendran et al., 2012).



Figure 15.2 Fabrication and antimicrobial test of the AgNPs/SS/agar film.
From Wang, Y., Cai, R., Tao, G., Wang, P., Zuo, H., Zhao, P., Umar, A., & He, H. (2018). A novel AgNPs/sericin/agar film with enhanced mechanical property and antibacterial capability. *Molecules, 23*(7), 1821. https://doi.org/10.3390/molecules23071821

2.2 Antioxidant activity

Sericin's ability to scavenge ROS, prevent lipid peroxidation, and inhibit tyrosinase and elastase activity are all factors that contribute to its antioxidant characteristics (Chlapanidas et al., 2013). The high levels of serine and threonine, which give hydroxyl groups to chelate ions (such as copper and iron), are also associated with antioxidant properties. Additionally, one of the factors that give sericin its antioxidant and antityrosinase activity may be the pigment molecules (such as flavonoids and carotenoids) that accumulate in sericin layers. Notably, the cocoon strains and extraction techniques have an impact on the antioxidant capabilities of sericin (Miguel & Álvarez-López, 2020; Mohammadi et al., 2019).

2.3 UV protection

Overexposure to UV radiation can cause the degradation of fibers and polymers by producing ROS. Sericin is an organic compound that provides ultraviolet protection by absorbing UV rays of UVA and UVB wavelengths. Fig. 15.3 displays the UV-vis absorbance spectrum for silk sericin.

Due to $\pi \rightarrow \pi^*$ transitions, the aromatic amino acids such as tryptophan, tyrosine, phenylalanine, etc. that are present in silk sericin can absorb UV light between 260 and 290 nm (Wang et al., 2023). Consequently, the presence of sericin may transform the energy of electrical excitation into thermal energy, which is then dissipated and reflected at longer wavelengths of radiation, reducing the production of free radicals.

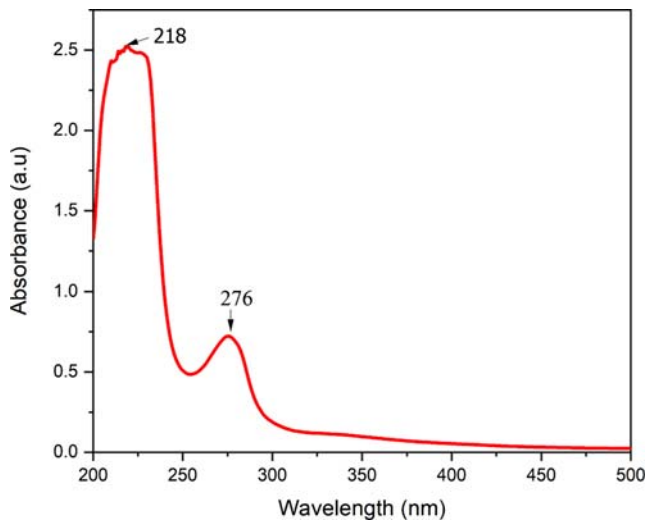


Figure 15.3 UV absorbance spectrum of sericin at 218 and 276 nm.
From Karthick, S. A., Manjari, K., & Devi, M. G. (2023). Biocompatible and bioactive PVA/sericin/chitosan nanofibrous wound dressing matrix. *Applied Surface Science Advances, 13*. https://doi.org/10.1016/j.apsadv.2022.100362

Because sericin contains significant amounts of serine and threonine, which have hydroxyl groups that function as chelating agents for trace ions like copper and iron, it may have an antioxidant action that contributes to its UV protection. Glucose-crosslinked sericin has also shown improved UV blocking and antioxidant properties as illustrated in Fig. 15.4a.

Sericin protects against oxidative stress damage brought on by extremely low temperatures in addition to UV exposure. Pristine PET and PET/viscose textiles have a UPF of 7, which means they provide minimal UVA and UVB protection (around 75%). The UV-protection factor (UPF) mean value of the pigment-dyed PET and PET/viscose fabrics treated with sericin using the pad-dry-cure procedure can be 21−25 (Hakeim et al., 2022).

UV rays can degrade nylon, which is another vulnerability. UV rays penetrate nylon, causing photo-oxidation which leads to decrease in the fabric's elasticity and tensile strength. In the presence or absence of crosslinking agents, fabrics made of polyamide 6 were modified using a green substance (sericin). This outcome could possibly be explained by the polyamide fabrics having enough sericin to act as a protective layer, blocking UV rays from penetrating the garment and damaging the skin (El-Sayed et al., 2019). A similar improvement in the UPF mean value of silk and silk treated with sericin was discovered, rising from 5.2 to 22.5 (Chitichotpanya et al., 2019).

2.4 Moisture absorption and comfort properties

Sericin-treated fabrics are known to provide thermo-physiological comfort characteristics, including water vapor transfer, heat conductivity, resistivity, air and water permeability, and electrostatic charge release. Sericin is made up of 18 amino acids, the majority of which having significant polar side chains such as hydroxyl, carboxyl, and amino groups (Khalifa & Ladhari, 2021). Its high concentration of serine (33.4%) and aspartic acids (16.7%), both of which contain a lot of hydroxyl groups, essentially provides its hydrophilicity (Wu et al., 2007). If comfort is sought, perspiration that

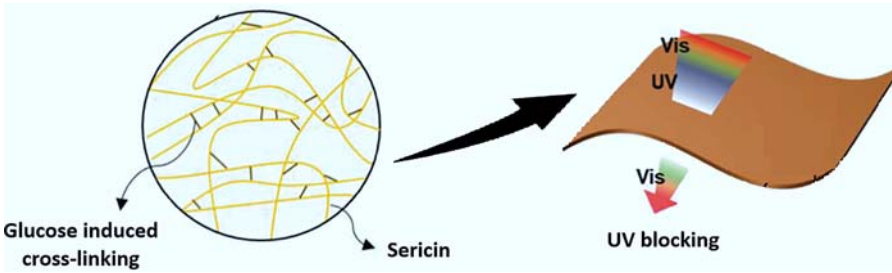


Figure 15.4 Illustration of UV blocking property of glucose crosslinked sericin. Reproduced from Oh, S., Park, J., Nam, J., Hyun, Y., Jin, H.J., & Kwak, H.W. (2021). Antioxidant and UV-blocking glucose-crosslinked sericin films with enhanced structural integrity. *Reactive and Functional Polymers, 165*. https://doi.org/10.1016/j.reactfunctpolym.2021.104942

collects at the surface of the head and neck should be rapidly removed. Sweat can be carried to the outside surface via evaporation in fabrics with vulnerable water absorption and wicking qualities, which is important for the release of body heat. The reduced insulation of sericin-treated fabrics is reflected in their decreased thermal resistance. This would result in greater heat transfer from the body to the environment through the materials (Li, 2001).

Sericin-treated polyester surfaces can have increased moisture recovery as sericin contains polar groups, which have a unique role in enhancing moisture absorption (Khalifa et al., 2012; Chaudhary et al., 2017). Sericin, a biopolymer that can absorb moisture, gives PET hydrophilicity when it is covalently attached to the polymer macromolecules in the presence of a crosslinking agent (El-Newashy et al., 2019). Also, sericin-/MXene-treated fabric shows multifunctional properties viz. breathability, flame retardancy, active electrical heating, and passive radiative heating as shown in Fig. 15.5.

3. Methodology for preparation of sericin hybrids

3.1 In-situ preparation of sericin composites

3.1.1 Sericin silver

In aqueous alkaline media, sericin−Ag nanocomposites can be produced. $AgNO_3$ is a silver precursor that can be employed. The reducing agents for converting silver ions into colloidal silver include NaOH and $NaBH_4$. To avoid particle aggregation, sericin can be employed to stabilize silver nanoparticles. The solubility of sericin is sensitive

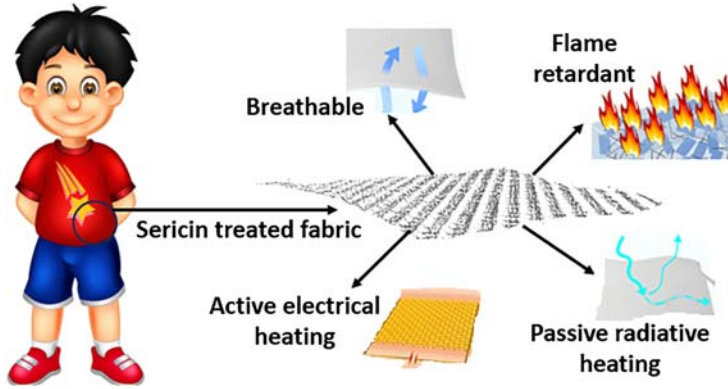


Figure 15.5 Sericin-/MXene-treated apparel showing multifunctional properties. Reproduced from Yang, H., Cheng, L., Yang, Q., Farooq, A., Ying, L., Wang, P., & Wang, Z. (2023). Multifunctional and durable thermal management coating from sericin-MXene biohybrid on silk fabric micro-etched by deep eutectic solvent. *Applied Surface Science, 623*. https://doi.org/10.1016/j.apsusc.2023.156962

to the pH of the solution. Sericin-dissolving time depends on the type of reducing agent. To produce a sericin/Ag nanocomposite, $AgNO_3$ solution is added dropwise into a reducing agent/sericin solution. The solution is then stirred for about half an hour. Impurities are subsequently removed using the centrifugation method (Yavuz Gokce et al., 2020; Yue et al., 2014).

It is also possible to form sericin−Ag nanocomposites using a one-pot, green synthesis method. Sericin is crucial in controlling the synthesis of Ag nanocomposites because of the disulfide bonds and free cystine. In the process of producing sericin, Ag ions are initially added to the solution, where some of them interact with the thiol groups to create functional Ag thiolate intermediates. Following reduction, the protein's spatial structure is further disintegrated from its alkaline state, releasing more thiol sites. Finally, the resultant Ag atoms join to form Ag clusters that are supported by the sericin's NH groups as shown in Fig. 15.6 (Mehdi et al., 2021).

3.1.2 Sericin graphene

Sericin molecules can be adsorbed on graphene sheets in water, resulting in the development of a uniform sericin−graphene dispersion in water devoid of any further additives. The sericin−graphene hybrid is formed by exfoliating graphene in water in a single step with the help of sericin resulting in a homogeneous graphene−sericin dispersion. Sericin exhibits amphiphilicity and is made up of many amino acid residues.

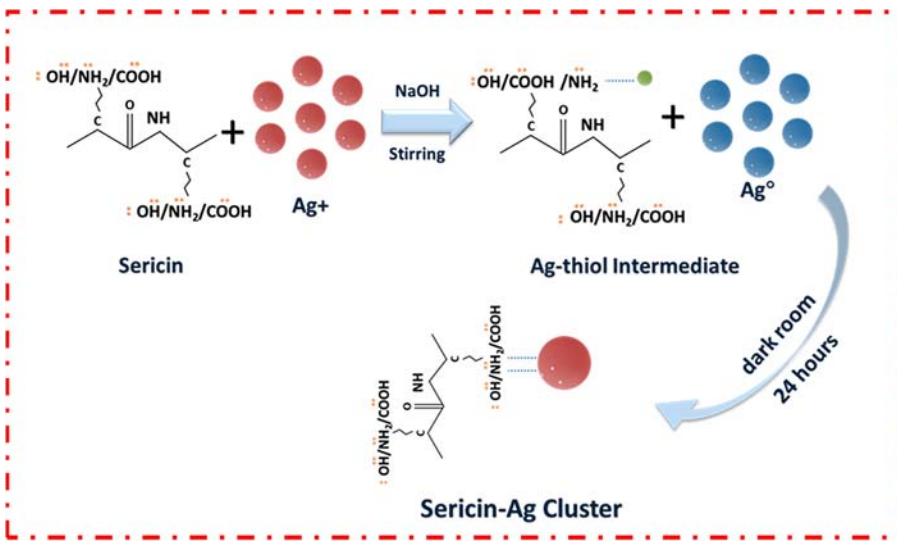


Figure 15.6 Typical illustration of synthesized sericin−Ag NCs.
From Mehdi, M., Qiu, H., Dai, B., Qureshi, R.F., Hussain, S., Yousif, M., Gao, P. & Khatri, Z. (2021). Green synthesis and incorporation of sericin silver nanoclusters into electrospun ultrafine cellulose acetate fibers for anti-bacterial applications. *Polymers, 13*(9). https://doi.org/10.3390/polym13091411

Sericin is highly soluble in water because most of its residues include hydrophilic sidechain groups, particularly serine (35%) and threonine (10%). On the other hand, sericin may establish persistent contact with hydrophobic surfaces and contain a significant number of residues containing aromatic groups (Liang et al., 2022).

3.1.3 Sericin MXenes

MXenes are susceptible to oxygen. Co-assembling with natural sericin is a surface modification technique for MXene nanosheets that protect from oxygen and water and improves oxidative stability.

Chemical etching of the Ti_3AlC_2 MAX powder can be used to create $Ti_3C_2T_x$ MXene nanosheets. In the teflon container, LiF and HCl are introduced while being stirred for 30 min. Then, Ti_3AlC_2 MAX powder is gradually added to the LiF−HCl solution to react for 24 h at 35°C. The products are then repeatedly centrifuged. The $Ti_3C_2T_x$ MXene dispersion is agitated for 30 min before the silk sericin powder is added to create the sericin−MXene dispersion as described in Fig. 15.7 (Yang et al., 2023).

3.1.4 Sericin−TiO_2 nanocomposites

By using the aqueous dispersion process, sericin−TiO_2 nanocomposites can be synthesized. Initially, distilled water solution with an appropriate dispersion agent is used to create a suspension of nano-TiO_2 particles. This solution can be ultrasonicated for around 30−40 min to create a stable dispersion and further homogenize it. The extracted sericin is then heated with steam until it dissolves, and it is then cooled to room temperature. Nano-TiO_2 colloidal suspension is gradually added to the sericin solution for nanocomposite dispersion. The mixture is stirred continuously for 15 min at room temperature. As a result, sericin−TiO_2 nanocomposites can be developed (Doakhan et al., 2013).



Figure 15.7 Schematic illustration of surface modification of MXene with silk sericin. From Yang, H., Cheng, L., Yang, Q., Farooq, A., Ying, L., Wang, P., & Wang, Z. (2023). Multifunctional and durable thermal management coating from sericin-MXene biohybrid on silk fabric micro-etched by deep eutectic solvent. *Applied Surface Science, 623*. https://doi.org/10.1016/j.apsusc.2023.156962

3.1.5 Sericin copper

The main function of the use of sericin is to prevent the particles of copper from aggregation. The Cu^{2+} and sericin initially formed a complex, which is then reduced to nanoparticles by the addition of ascorbic acid to the mixture. The amide, hydroxyl, and carboxyl groups of the sericin, which serve as a capping agent, get arranged around the Cu nanoparticles. It also prevents the production of CuO or Cu_2O and provides stability and homogeneous distribution. Sericin helps counteract the van der Waals forces between the crystals of the individual atoms (Chitichotpanya et al., 2019).

These sericin hybrids have enhanced multifunctional properties such as antibacterial, UV protection, flame retardancy, thermal management, etc., and show potential applications for medical textile products such as aprons, linens, medical bandages, and for packaging purposes.

3.2 Sericin-based electrospun fibers

Nanofibers are a particular type of nanomaterials that are often produced using an electrospinning approach. By using this technique, which involves applying a strong electric field to a polymeric material solution, continuous nanofibers of various sizes are formed. These could be utilized to create functional fabrics. Sericin alone lacks the appropriate mechanical properties due to its delicate nature, needed to create nanofibers. So, one of the best ways to enhance sericin's mechanical characteristics and increase the range of applications for it is to combine it with other polymers. Trifluoroacetic acid, or TFA, can be used as a solvent to electrospun sericin alone into nanofibers. These nanofibers have poor mechanical characteristics; hence, additional natural and synthetic polymers such as gelatin, chitosan, silk fibroin, polyvinyl alcohol (PVA), polycaprolactone (PCL), etc. have been combined with sericin.

3.2.1 Sericin/silk fibroin nanofibers

Electrospinning can be used to combine silk fibroin with silk sericin, which is helpful for biomedical textiles (Lin & Zuo, 2021; Y. Wang et al., 2020). Silk fibroin is hydrophobic in nature, while silk sericin exhibits excellent hydrophilicity. Thus, a blend can be employed to alleviate the hydrophobicity issue. The dissolving of sericin and silk fibroin in formic acid can be used to develop an electro-spinnable mix solution.

3.2.2 Sericin/PCL nanofibers

Synthetic polymer polycaprolactone (PCL) has many distinctive characteristics, including stable chemical properties, biocompatibility, and high film-forming capacity (Li et al., 2015). Polycaprolactone can be dissolved in dimethylformamide (DMF) to obtain a polymer solution followed by the addition of ferulic acid. A solution of silk sericin is then added to polymeric solutions and constantly agitated at room temperature to create a homogeneous dispersion, which is then used to create an electrospinning solution. Therefore, this technique is beneficial to create silk sericin nanofibers loaded with ferulic acid (Anand et al., 2022).

3.2.3 Sericin/PVA nanofibers

Sericin/PVA nanofibers have been utilized in the removal of carcinogenic dyes from the wastewater of dye houses and in medical textiles such as wound dressing, scaffolds, etc.

Due to the presence of polar groups in sericin, such as the −OH, −COOH, and $-NH_2$ groups, these nanofibers have a high efficiency to absorb dyes. Sericin/PVA can be cross-linked with other molecules such as β-cyclodextrin at high temperatures in the presence of citric acid as illustrated in Fig. 15.8 (Zhao et al., 2015). These can be also crosslinked with clay (Purwar et al., 2016) and chitosan (Hadipour-Goudarzi et al., 2014) to impart antimicrobial characteristics.

4. Approaches to impart sericin hybrids to textile substrates

The prepared sericin hybrid can be incorporated into textile substrates by several methods. It can be designed in such a way that sericin hybrid can be integrated into fiber or applied to textile material via coating or finishing technology. There are other ways such as the formation of nanofiber including sericin with other base materials.

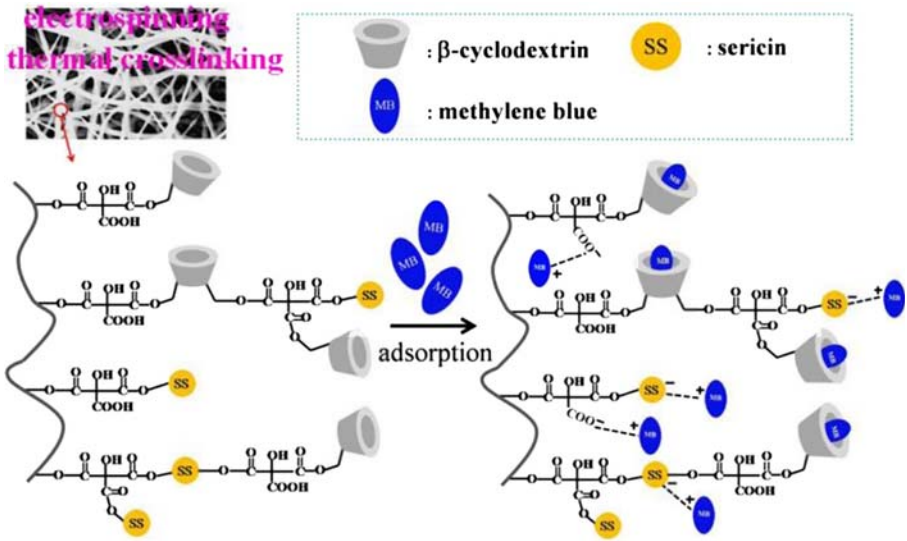


Figure 15.8 The structures of crosslinked sericin/β-cyclodextrin/PVA composite nanofibers and their adsorption mechanism toward methylene blue dye.
From Zhao, R., Wang, Y., Li, X., Sun, B., Jiang, Z., & Wang, C. (2015). Water-insoluble sericin/β-cyclodextrin/PVA composite electrospun nanofibers as effective adsorbents toward methylene blue. *Colloids and Surfaces B: Biointerfaces, 136*, 375−382. https://doi.org/10.1016/j.colsurfb.2015.09.038

Even textile composite can be prepared with the presence of sericin hybrid material. The following ways to apply/incorporate sericin or sericin hybrid to textile materials are:

4.1 Incorporation of sericin or sericin hybrids into fibers

The preparation of nanofibers with sericin or sericin hybrid can be done using electrospinning method. This technique is also used to develop a combination of chitosan and polyvinyl alcohol nanofiber with the incorporation of sericin/tetracycline into it. The prepared nanofibers have diameters in the range of 305–425 nm. Additionally, flexibility and swelling capacity get increase with an increase in sericin content. In contrast, mechanical strength gets reduced with an increase in sericin content in the nanofiber. The preparation method of nanofibers is represented in Fig. 15.9 (Bakhsheshi-Rad et al., 2020). In another study, sericin is modified into a sericin multifunctional crosslinker by modifying its carboxylic group using allyl glycidyl ether. Simultaneously, polylactic acid macromonomer is synthesized by condensation polymerization of lactic acid followed by functionalizing it with allyl glycidyl ether. Finally, nanogel of polylactic monomer and sericin crosslinker is developed in water–oil emulsion system by free radical polymerization. This prepared nanogel is embedded into poly(lactide-co-glycolide) electrospun nanofiber, which is

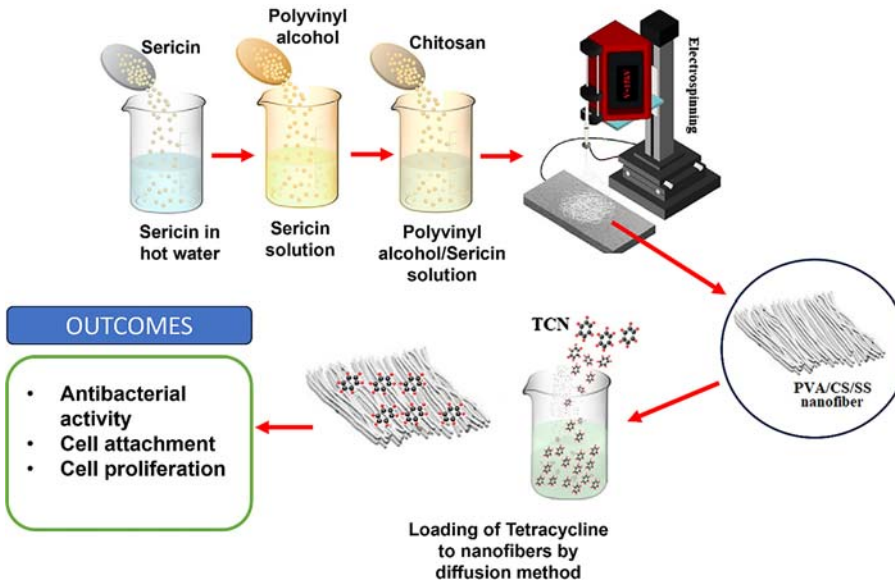


Figure 15.9 Preparation method of polyvinyl alcohol/chitosan/sericin nanofibers with tetracycline loading.
From Bakhsheshi-Rad, H.R., Ismail, A.F., Aziz, M., Akbari, M., Hadisi, Z., Omidi, M., & Chen, X. (2020). Development of the PVA/CS nanofibers containing silk protein sericin as a wound dressing: In vitro and in vivo assessment. *International Journal of Biological Macromolecules, 149*, 513–521. https://doi.org/10.1016/j.ijbiomac.2020.01.139

prepared by the electrospinning technique (Kongprayoon et al., 2022). Sericin is also used to develop core-shell electrospun nanofiber where sericin is present in the core in combination with polyvinyl alcohol and poly(lactide-co-glycolide) is used for the shell. In this case, the core is hydrophilic and the shell is hydrophobic. Core−sheath nanofibers are prepared by coaxial electrospinning method, and the final electrospun nanofibers are accumulated on aluminum foil (Tuancharoensri et al., 2022).

4.2 Application of sericin or sericin hybrids on fabrics

Sericin or sericin hybrid material can be applied to textile substrates via coating or finishing processes. In finishing processes, sericin can be applied to textiles by exhaustion process or pad-dry-cure method.

4.2.1 Exhaustion method

The exhaustion process is mostly applicable to textile substrates having an affinity with sericin or sericin hybrid materials. In a study, it is explored that extracted sericin has an affinity to wool fabric and optimum conditions have been found out for fixing of sericin on wool fiber via the exhaustion method. The same extracted sericin has no affinity to cotton fabric and sericin finishing is not suitable for cotton fabric by exhaustion process. The sericin concentration of 2.5% (w/w) shows an exhaustion rate of 48% for wool fabric. This is the given condition of sericin finishing to wool fabric (Khalifa et al., 2012). However, sericin can be applied to the cotton fabric by pad-dry-cure method.

4.2.2 Pad-dry-cure method

The pad-dry-cure method is the most widely used technique for sericin or sericin hybrid application on fabric especially where crosslinking agents are additionally used and curing is necessary. Sericin or functionalized sericin can be applied by this method onto various textile substrates where curing temperature is a critical parameter that depends on the type of substrate and the cross-linking agent used. Sericin is applied to the cotton fabric by immersing it in sericin solution, then passing it through padding mangle followed by the dryer, and finally, curing it for 5 min at 70°C. Although cotton fabric can be treated using sericin without any additional crosslinking agent but washing durability may compromised (Rajendran et al., 2012). Additional crosslinking agents are applied with sericin to increase the durability of the textile materials. The incorporation of sericin hybrid can enhance the functional properties of textile fabrics better as compared to sericin individually. Sericin can be combined with nanoparticles such as TiO_2, Ag, etc. Sericin−TiO_2 nanocomposite is applied onto cotton fabric by using crosslinking agents, that is, 1,2,3,4-butane tetracarboxylic acid or citric acid (Doakhan et al., 2013). Similarly, cotton fabric is treated with sericin-silver nanocomposite using different commercial crosslinking agents, that is, RUCO-COAT VA, RUCO-PLAST PMN, and AC-249 at acidic pH of 5. Initially, untreated cotton fabric is immersed in a nanocomposite solution and then dried (at 100°C

for 5 min) followed by a curing process (150°C for 3 min). The crosslinker helps in better washing durability of the treated fabric as well as for enhancement of mechanical strength. The incorporation of nanocomposite on cotton fabric is identified from the SEM image illustrated in Fig. 15.10 (Gokce et al., 2020). Sericin can be applied to

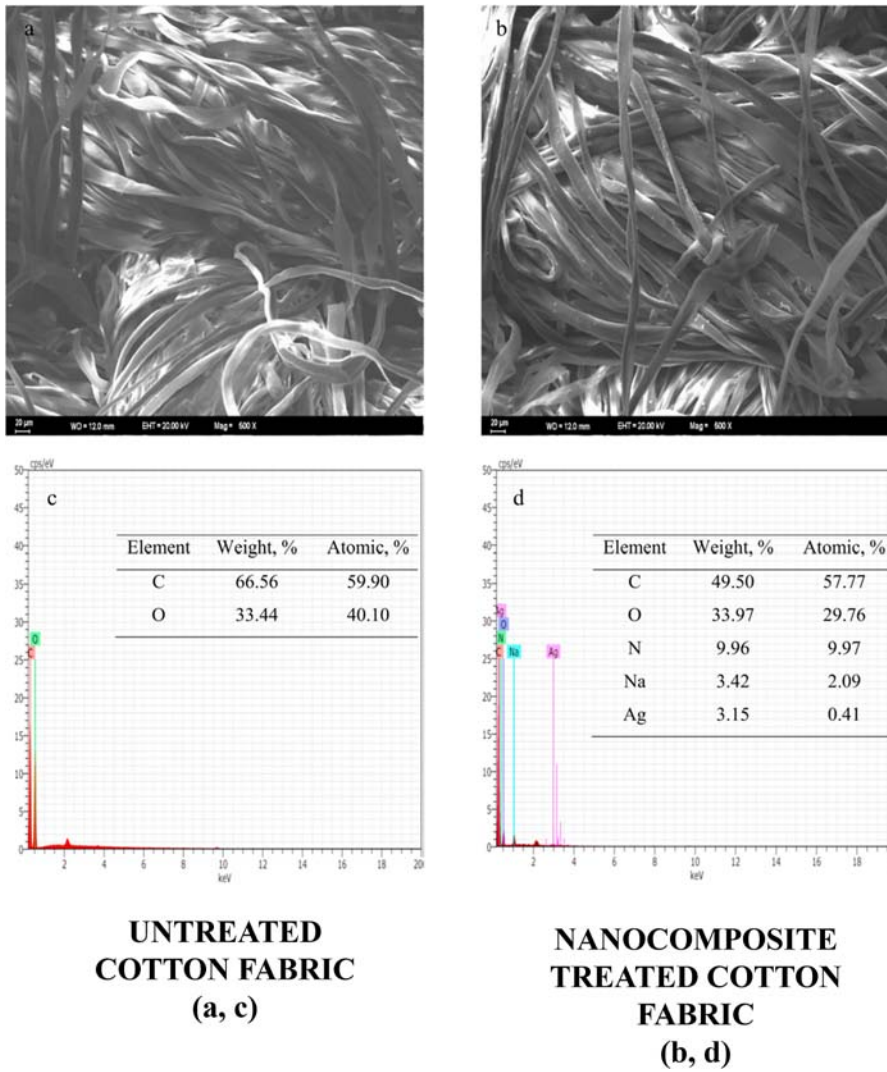


Figure 15.10 SEM images with EDS results of (a,c) untreated cotton fabric, and (b,d) cotton fabric treated with waste sericin−silver nanocomposite.
From Gokce, Y., Aktas, Z., Capar, G., Kutlu, E. & Anis, P. (2020). Improved antibacterial property of cotton fabrics coated with waste sericin/silver nanocomposite. *Materials Chemistry and Physics, 254*. https://doi.org/10.1016/j.matchemphys.2020.123508

other types of textile substrates such as polyester by pad-dry-cure method where polyester is initially treated with sodium hydroxide (NaOH) to activate end groups in polyester. The pretreated polyester fabric is immersed in a sericin solution with acetic acid, magnesium chloride, and glutaraldehyde then passed through padding mangle and finally dried followed by curing. Glutaraldehyde is used as a crosslinking agent in this treatment process (Gulrajani et al., 2008). Polyester can also be finished with sericin by pretreating polyester with UV rays for surface modifications. Furthermore, the sericin is bound to the modified polyester surface by a crosslinking agent, that is, glutaraldehyde through the pad-dry-cure method. This process results in multifunctional properties along with an increase in dye uptake of basic dyes (Chaudhary et al., 2017).

Sericin can also be modified with other functional groups to improve the functional properties of the treated fabric. It is modified with an active acryloyl group and applied to the cotton fabric to add functional properties. This modification of sericin is carried out by an amidation reaction between sericin and acryloyl chloride. The modified sericin is finished to cotton fabric by using 1,3,5-triacroylaminohexahydro-striazine as a crosslinking agent in an alkaline condition via padding (1 dip-1 nip procedure) followed by drying (80°C for 1 min) and curing (150°C for 3 min) (Zhang & Hao, 2023). Other than cotton and polyester fabric, sericin finishing on microdenier cotton and polyester blend fabric is also studied. Blended fabric samples can be pretreated with sericin with oxygen plasma and then finished with sericin and crosslinked using glutaraldehyde using pad dry cure technique (Rajalakshmi et al., 2022). Nowadays, sericin-based hydrogels are being used to treat textile substrates to enhance their functional properties. A hydrogel comprises several elements such as silver nanoparticles, sericin, and poly (N-isopropylacrylamide) is applied to aminated-modified polyester fabric using citric acid as a crosslinking agent. The modified polyester fabric is immersed in hydrogel solution and then passed through two dip-two nip padding method followed by drying at 80°C for 15 min and curing at 160°C for 5 min (Liu et al., 2020).

4.2.3 Coating technique

Sericin hybrid is applied to textile substrate also by coating technique besides other processes such as exhaustion and pad-dry-cure method. According to Yang et al., degummed silk fabric is pretreated with the choline chloride/oxalic acid deep eutectic solvent to prepare etched silk fabric. It is then dipped in sericin−MXene solution several times at room temperature, followed by drying at 40°C. A strong bonding is established between fibers and sericin−MXene by the pretreatment as the combined effect of mechanical bonding and hydrogen bonding plays a vital role. The complete coating process required for the preparation of sericin-MXene-coated silk fabric is explained in Fig. 15.11 (Yang et al., 2023).

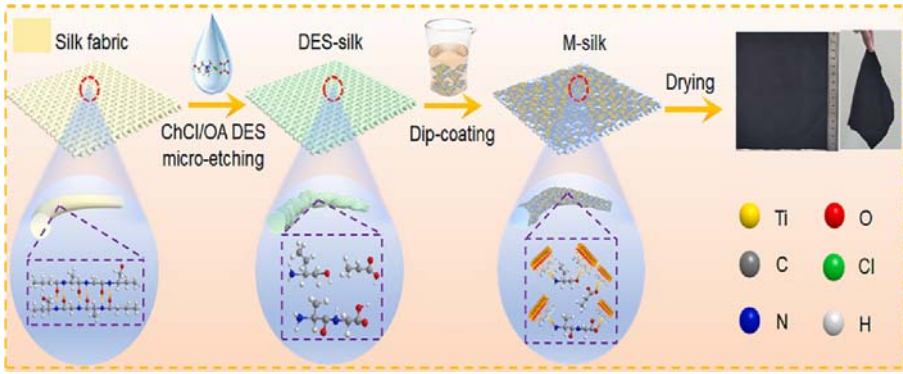


Figure 15.11 Application of sericin−MXene to silk fabric by dip-coating method. From Yang, H., Cheng, L., Yang, Q., Farooq, A., Ying, L., Wang, P., & Wang, Z. (2023). Multifunctional and durable thermal management coating from sericin-MXene biohybrid on silk fabric micro-etched by deep eutectic solvent. *Applied Surface Science, 623*. https://doi.org/10.1016/j.apsusc.2023.156962

5. Potential applications of sericin hybrid textile substrates

Sericin inherits many efficient functional properties like antioxidant (Fan et al., 2009), antibacterial (Senakoon et al., 2009), high moisture absorption (Gupta et al., 2015a, 2015b), resistance to ultraviolet rays (Saha et al., 2023), biocompatibility (Fatahian et al., 2021), and wound healing (Gupta et al., 2015a, 2015b), which can be further improved by developing sericin hybrid materials. These immense numbers of functional properties of sericin/sericin hybrids result in potential application in various sectors including the textile industry. Its ecofriendly and biodegradable nature makes it more valuable and demandable.

5.1 Air and water filtration

Sericin can be employed in fabric-based filters for air filtration. The sericin/PVA/clay nanofibrous mat is used as an air filtration mask having several properties such as antibacterial and higher filtration efficiency having filtering capability of size range from 1 μm to 10 μm. To fabricate these mats, a spinning dope solution is prepared by combining sericin, polyvinyl alcohol (PVA), and clay, which is used to develop nanofibers that finally turn out to be nanofibrous mat (Purwar et al., 2016). In some studies, it is also used for water filtration where it is used as an antifouling agent. This property is enhanced in polypropylene hollow fiber microfiltration membrane by coating it with sericin. Initially, the membrane is preconditioned with sulfuric acid and hydrogen peroxide solution that activates the hydroxyl groups on the membrane surface. Then, the pretreated polypropylene membrane is coated by passing it through a sericin solution. The sericin is temporarily adhered to the polypropylene membrane via

hydrogen bonding and finally crosslinked using glutaraldehyde followed by curing at 40°C. This sericin-coated membrane shows high resistance to foul in both the case of synthetic gray water and collected water. The volume of water filtered is more in the case of sericin-coated one compared to the untreated membrane. Overall, it can be concluded that sericin-coated membrane shows good fouling-resistant properties with significant purification efficiency (Verma & Subbiah, 2019).

5.2 Medical textiles

Sericin-based textiles can be widely used in the medical sector. It can be used for medical linens, wound healing purposes, and drug delivery. Sericin-finished polyester fabric has been used for wound dressing and to heal skin diseases as it shows high vertical wicking properties, good moisture retention properties, enhanced antioxidant properties, resistance to ultraviolet rays, and also a significant increase in antistatic properties. This type of functional textile substrate is prepared using sericin finishing on polyester fabric. First, surface modification is done on polyester fabric using ultraviolet rays, which are then passed through a padding mangle containing 10 g/L sericin solution and crosslinked with glutaraldehyde by curing and drying at the end (Gupta et al., 2015a, 2015b). Porous nanofibers prepared from tetracycline, sericin, chitosan, and polyvinyl alcohol with diameters around 305−425 nm show bactericidal properties in both stains, that is, Gram-positive and Gram-negative bacteria due to the synergetic effect of both sericin and tetracycline. This prepared nanostructure shows good capability for wound dressing application in the case of both in-vivo and in-vitro. This application is possible as it has sufficient capability to absorb moisture and water through swelling and make the wound area dry. The hydrophilic property and elongation at break increase with decrease in fiber diameter. However, mechanical strength declines with an increase in sericin concentration. In the case of in vivo application, it shows enhanced wound healing properties compared to traditional gauze (Bakhsheshi-Rad et al., 2020). Sericin is also demandable for drug delivery purposes. Sericin crosslinker and polylactic acid are used to synthesize nanogels. The final prepared nanogels are embedded in nanofibers prepared from polylactide-co-glycolide. These synthesized nanogels are used for drug release purposes. The drug release mechanism also depends on the diameter of the nanogel and the concentration of sericin crosslinker. This nanostructure has the potential for tissue regeneration as well as drug delivery application as the toxicity level is negligible to normal human skin fibroblast cell lines. This also results in enhanced cell proliferation with enzymatic degradability (Kongprayoon et al., 2022).

5.3 Multifunctional textiles

Sericin-finished cotton fabric shows multiple functional properties such as good moisture retention capability, a decrease in electrical resistivity, and antibacterial activity. Cotton fabric finished with sericin using DMDHEU (dimethylol dihydroxy ethylene urea), 60% acetic acid, and magnesium chloride has shown high color depth, increased moisture retention property, and lesser electrical resistivity. There is no growth of

Klebsiella pneumoniae for treated and washed fabrics. However, there is the presence of partial growth and full growth of *Staphylococcus aureus* in the case of both unwashed and washed sericin-DMDHEU-treated fabrics. The increase of functional properties with less amount of free formaldehyde results in a suitable form of textile with lesser irritation to the skin (Kongdee et al., 2005). It is reported that sericin finishing on wool via exhaustion method shows significant water absorption properties as well as enhanced antibacterial properties with attractive brown shade (Khalifa et al., 2012). Cotton fabric is finished with modified sericin containing acryloyl group where 1,3,5-triacroylaminohexahydro-striazine has been used as crosslinker. The antiwrinkle property and wrinkle recovery get enhanced with the rise in the concentration of modified sericin. This finishing improved the dyeability property by increasing color depth. The resistance to ultraviolet rays can also get increase with an increase in modified sericin content (Zhang & Hao, 2023).

5.4 Antimicrobial textiles

The antimicrobial property of sericin also depends on the type of silk from which sericin is extracted. Sericin is a good antibacterial agent but sericin with other agents shows improved antibacterial properties as it acts synergistically. Sericin with nano-TiO_2 as a finishing agent to cotton fabric via pad-dry-cure method using citric acid or 1,2,3,4-butane tetracarboxylic acid shows enhanced functional properties. The cotton fabrics treated with only nano-TiO_2 do not show significant antibacterial effects against Gram-positive and Gram-negative strains at lower concentrations. However, fabric treated with a higher concentration of nano-TiO_2 shows some antibacterial effects, which can be further improved by using a combination of sericin and nano-TiO_2 due to their synergistic effect. The physical property, that is, breaking strength gets reduced for the fabrics individually treated with nano-TiO_2 due to free oxygen radicals that initiate degradation reactions, whereas fabrics individually treated with sericin show no change in breaking strength. Furthermore, fabric treated with nanocomposites shows no significant changes in the breaking strength (Doakhan et al., 2013). Nanocomposites prepared using discarded sericin, silver, and three different crosslinkers show antibacterial properties against both Gram-positive and Gram-negative bacteria, that is, *Staphylococcus aureus* and *Escherichia coli* with washing durability. Even after 20 cycles of laundering, the antibacterial properties of the prepared nanocomposites show good performance (Gokce et al., 2020). Rajalakshmi et al. studied the antimicrobial properties of sericin-treated cotton fabric, sericin-treated micropolyester fabric, and sericin-treated blend of cotton-micro denier polyester. The sericin-treated cotton fabric shows high performance of the antibacterial properties as well as antifungal properties. Among all types of treated fabrics, sericin-finished cotton/micropolyester shows outstanding bactericidal and fungicidal properties (Rajalakshmi et al., 2018). According to Gün Gök et al., the mixture of sericin and polyvinyl alcohol is used to produce nanostructure with incorporation of gelatin-silver nanoparticles. First, gelatin−silver nanoparticle is synthesized, and then it is added to the polyvinyl−sericin mixture. This combination is electrospun to form nanofibers via electrospinning. The prepared sample shows excellent growth

inhibition of both Gram-positive and Gram-negative bacteria with significant thermal stability (Gün Gök, 2022).

5.5 UV-resistant textiles

The silk fabric is finished with modified sericin to achieve functional properties such as UV protection and antibacterial properties. In situ synthesis of copper nanoparticles is carried out and then embedded in sericin. Then, final sericin−copper nanoparticle functionalized fabric is developed. This prepared fabric shows very effective UV protection as compared to only sericin-finished silk fabric. The synergistic effect of copper nanoparticle and sericin shows bacterial reduction properties against both Gram-negative (*E. coli*) and Gram-positive (*S. aureus*). These properties are sustained in the treated fabric even after 20 laundering cycles (Chitichotpanya et al., 2019). A similar experiment is also carried out using silver nanoparticles on silk fabric. Chitichotpanya et al. synthesized silver nanoparticles and embedded them in sericin to functionalize silk fabric. The functionalized silk fabric exhibits high resistance to UV rays and bacterial reduction even after 20 washing cycles. The changes in UPF values with different washing cycles are reported in Table 15.2. Fig. 15.12 shows the schematic representation of modified sericin using silver nanoparticles (Chitichotpanya & Chitichotpanya, 2017).

Sericin is also used for modification of nylon 6 fabric to impart functional properties where citric acid and epichlorohydrin can be used as crosslinkers. The sericin-treated nylon fabric leads to a lower yellowness index and increased moisture content. The dye uptake capability also increased after treating it with sericin as the number of amino groups increased. The ultraviolet protection factor gets significantly increased after treating nylon 6 with sericin (El-Sayed et al., 2019). The combination of polyvinyl alcohol and sericin, which is prepared in film form, shows high flexibility, high elasticity, and transparency. This film can have a high capability of absorbing ultraviolet radiation, that is, phonons. The absorbed phonons are transformed into harmless fluorescence light, and the produced heat is transmitted. This prepared film can be incorporated onto the surface of textile substrates to get enhanced functional properties. The given Fig. 15.13 illustrates the preparation of sericin film with polyvinyl alcohol (Vinutha et al., 2021).

Table 15.2 Ultraviolet resistance property of different untreated and treated fabrics.

Type of samples	No. of washing cycles	Ultraviolet protection factor
Untreated	0	5.1
Treated	0	42.8
	10	39.4
	20	35.6

From Chitichotpanya, P., & Chitichotpanya, C. (2017). In vitro assessment of sericin-silver functionalized silk fabrics for enhanced UV protection and antibacterial properties using experimental design. *Coatings, 7*(9). https://doi.org/10.3390/coatings7090145

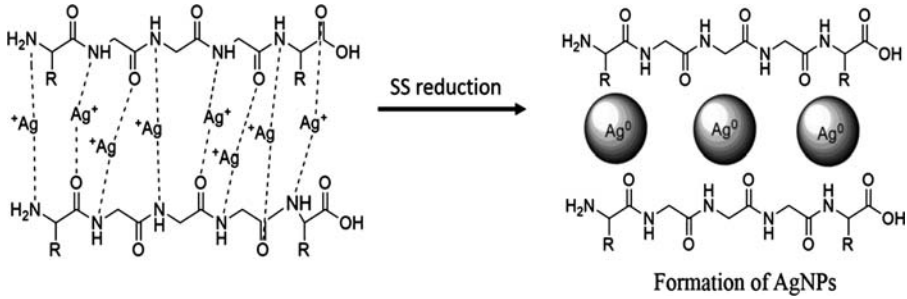


Figure 15.12 Schematic representation of modified sericin using silver nanoparticles.
From Chitichotpanya, P., & Chitichotpanya, C. (2017). In vitro assessment of sericin-silver functionalized silk fabrics for enhanced UV protection and antibacterial properties using experimental design. *Coatings, 7*(9). https://doi.org/10.3390/coatings7090145

5.6 Sericin as spin finish

Sericin is used as a spin finish and applied on the drawn textured polyester yarn. Sericin solution is applied to polyester yarn by pad-dry-cure method. Polyester yarn is impregnated in sericin solution, which additionally contains citric acid as a cross-linking agent and sodium hypophosphite as a catalyst followed by passing it through 2 dip-2 nip padding mangle. Finally, the treated yarns are dried and cured. The treatment with sericin leads to an increase in smoothness, water retention property,

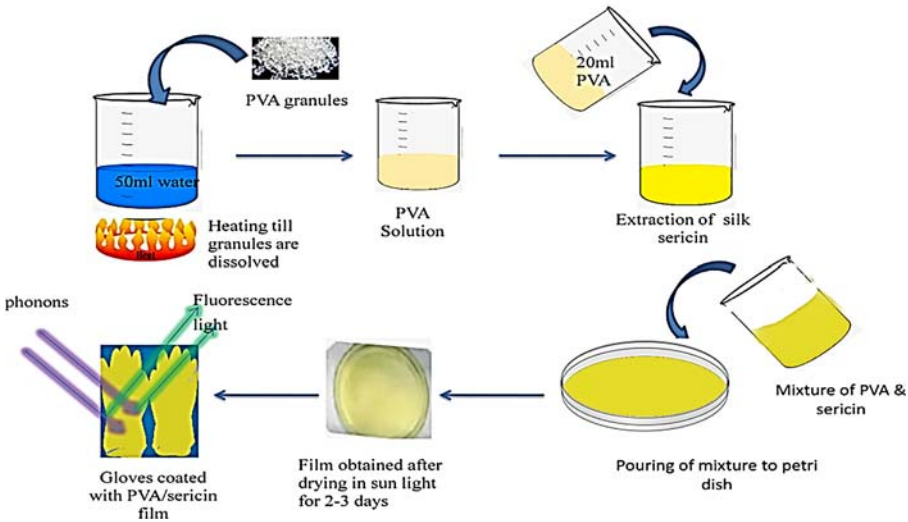


Figure 15.13 Preparation of polyvinyl−sericin film and its applications.
From Vinutha, P., Divakar, H. N., Subbaiah, K. M., & Savitha, M. (2021). Preparation and characterization of temperature regulating silk cocoon extract (sericin)/PVA based smart fabric. *IOP Conference Series: Materials Science and Engineering, 1189*(1). https://doi.org/10.1088/1757-899x/1189/1/012011

improvement in antistatic property, and increase in dye uptake due to an increase in stronger polar side chains (Zare, 2023).

6. Conclusions

It can be concluded from this chapter that sericin is a new frontier material and is a promising candidate for successful implementation in textile segments. Sericin is also getting gigantic attention due to its biocompatibility and biodegradability to achieve sustainable and greener approaches to impart various functional properties into textile substrates. The introduction of sericin to textiles leads to the addition of functional properties (such as UV resistance, moisture absorption, antioxidants, etc.) to traditional textiles as well. The functionalities also get more improved when act synergistically with other materials. Sericin hybrid textile substrates can potentially be used in medical textiles, apparel, home textiles, water and air filtration, sensors, and lots of other niche applications.

7. Future thrusts and challenges

Sericin being a greener solution represents ecofriendly and sustainable approaches in the textile sector. The numerous functional properties of sericin will lead to the development of multifunctional textile substrates. Despite of enormous number of functionalities of sericin applied to textiles, it lacks efficiency for some functional properties such as antibacterial properties. It is reported in a few studies that antibacterial properties are negligible for only sericin-treated textiles. As mentioned, this is due to the degradation of a silk protein called seroin (during the degumming or extraction process), which is responsible for antibacterial properties (Gupta et al., 2015a, 2015b). These selective functional properties are inferior to the sericin obtained from cultivated silk, that is, mulberry silk. However, these functional properties are magnified in the case of sericin obtained from wild silk such as Tasar silk, Muga silk, Eri silk, etc. There are challenges to obtain sericin from wild silk as there can be inconsistency of sericin color, molecular weight, composition % in sericin, and functional properties. The primary challenge is the overall increased cost of wild silk as it cannot be cultivated abundantly. The sericin hybrid textile substrates would get its value and more attention after exploration of its other new functional properties and enhancement of existing properties.

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Sericin application in personal care and cosmetic products: An approach toward upcycling waste

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Sourav Banerjee [1], *S. Wazed Ali* [1,2] *and S.N. Naik* [1,3]
[1]School of Interdisciplinary Research (SIRe), Indian Institute of Technology Delhi, New Delhi, India; [2]Department of Textile and Fibre Engineering, Indian Institute of Technology Delhi, New Delhi, India; [3]Centre for Rural Development and Technology, Indian Institute of Technology Delhi, New Delhi, India

1. Introduction

The word cosmetics is derived from the Greek "kosmetikē," meaning "technique of dress and ornament." Cosmetics have been used since ancient times, with historical evidence of their use in ancient Egypt and the Indus Valley. Cosmetic products are intricate systems comprising multiple ingredients, each serving a specific function in the final formulation and, therefore, being essential (McMullen & Dell'Acqua, 2023). A considerable number of basic elements have been found in different types of cosmetic products. Water is the main ingredient of many lotions, creams, cleansers, shampoos, and deodorants, as it is one of the safest and most common solvents that help dissolve most of the other ingredients used in cosmetics. Various emulsifiers are used to mix some of the immiscible ingredients together. Some common emulsifiers are Laureth-4, polysorbates, and potassium cetyl sulfate, which help maintain homogeneity and consistency in the product. Sometimes, the mixture of ingredients deteriorates the product quality over time. Here, preservatives play a crucial role in extending the shelf life of products, as these materials have antimicrobial properties to prevent microbial growth in products. Parabens, benzyl alcohol, salicylic acid, formaldehyde, and tetrasodium EDTA (ethylenediamine tetra-acetic acid) are typical examples of preservatives used in cosmetic products (Uter et al., 2023; Bialas & Zelent-Kraciuk, 2023).

Furthermore, these ingredients are frequently petroleum-based and are sometimes suspected to be potential endocrine disruptors, such as specific anti-UV agents or preservatives, with possible adverse effects on the environment and users. The cosmetic industry is actively seeking competitive multifunctional ingredients. On the one hand, the goal is to restructure ingredient lists, and on the other hand, there is a push for biobased ingredients to offer more natural-based solutions. Various research endeavors are exploring biobased materials such as ferulic acid, essential oils, and vitamins to understand how they can enhance properties without introducing hazardous elements. Sericin is one such material that has been used for many decades. In the 1960s, China

Science and Technology of Silkworm Sericin. https://doi.org/10.1016/B978-0-443-21736-4.00016-7
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utilized fibroin powder as silk cream, and by the 1980s, Japan had incorporated silk fibroin peptide, a hydrolyzate of lower molecular weight, into beauty products. Sericin, used as a glue similar to animal collagen glue, was preferred for its safety and ease of use over traditional alternatives (Sheng et al., 2013).

The silk filament consists of a double strand of fibroin that binds with a gummy material known as silk gum or silk sericin. Sericin, also called silk glue, is a globular protein constituting 25%−30% of silk proteins. It is composed of 18 amino acids, most of which possess strong polar side chains such as hydroxyl, carboxyl, and amino groups. Its high hydrophilicity is attributed to the elevated serine and aspartic acid content, accounting for approximately 33.4% and 16.7% of sericin, respectively (Li et al., 2023).

In 1951, Shaw and Smith (Shaw & Smith, 1951) researched the amino acids in silk sericin, categorizing it into three types based on solubility in hot water, alkali, and acid: sericin A, sericin B, and sericin C. The nomenclature indicates the outer side to the inner side in sericin. Fig. 16.1 summarizes the detailed properties and amino acid content. Sericin is a partially soluble protein in hot water, with the solubility correlated with the amorphous and crystalline zones of silk sericin. The amorphous region, characterized by a random coil structure, represents the main molecular form of easily soluble sericin, while the crystalline region containing β sheets is more resistant to dissolution (Hazeri et al., 2012).

Any materials suitable for cosmetic applications must possess several vital properties to ensure their efficacy and safety. First and foremost, they should exhibit compatibility with the skin, avoiding irritation or adverse reactions. Additionally, cosmetic materials must have appropriate texture, spreadability, and adherence to facilitate easy application. Stability and resistance to degradation over time are crucial to maintain the product's integrity. Furthermore, the material should be biocompatible, promoting skin health without causing harm. Other desirable features include a pleasant esthetic appearance, the absence of odor, and the ability to blend seamlessly

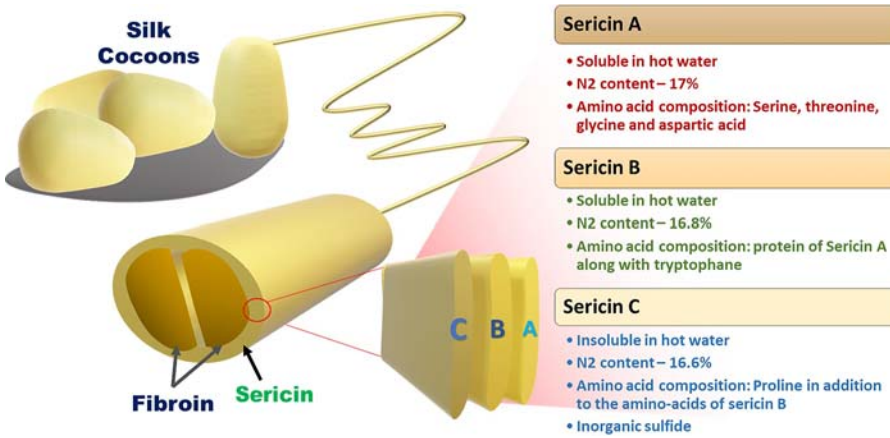


Figure 16.1 Types of sericin and its properties (self-drawn). This figure will help to elaborate different types of sericin with composition.

with other cosmetic ingredients (Pellevoisin et al., 2018, pp. 3−37; Pistollato et al., 2021).

Moreover, the material's origin, whether natural or synthetic, may be a consideration in meeting consumer preferences for sustainable and environmentally friendly choices. In summary, a successful cosmetic material combines sensory, functional, and safety attributes to enhance the overall user experience. Now, two questions are crucial before a detailed discussion about the application of sericin in cosmetics.

First, why can sericin be an appropriate solution for cosmetic applications?

Sericin formulations with low molecular weight, especially between 10 and 20 kDa, satisfy the requirements for skin and hair care products concerning qualities like skin permeability, natural source-based, easily soluble in formulations, and compatibility. Furthermore, sericin exhibits inherent properties beneficial for cosmetic use, including antibacterial, antityrosinase, and antielastase effects, as well as capabilities for scavenging free radicals and inhibiting glutathione-S-transferase (Park et al., 2018).

Second, why can it be recovered from textile wastewater and used efficiently?

The first step to obtain useable dry sericin involves the removal of water. However, this process necessitates additional energy and technology, such as ultrafiltration, lyophilization, and spray drying, ultimately increasing production costs. Following the traditional degumming process in the silk industry, a higher degree of degradation is observed in the recovered sericin. Consequently, its effectiveness diminishes when used in cosmetics, with fragmented sericin yielding lower results. Sericin is moisture-sensitive, and in aqueous solutions, it promotes microbial growth while reducing protein stability over time. Therefore, proper drying and sterilization are essential to address these issues.

The word "upcycling" involves the transformation of by-products, waste materials, or unwanted products into new materials or products perceived to have more significant benefits and environmental value (Wegener, 2016, pp. 181−188, Ali et al., 2024; Bridgens et al., 2018; Jehanno et al., 2022). Silk sericin, once considered an underutilized protein by-product in the textile industry, generates tons of residues annually. However, significant efforts have been dedicated to its recovery, driven by its association with various biological properties, including antioxidant, antibacterial, anticoagulation, and regenerative activities. Various researchers have explored extraction and recovery techniques for sericin, comparing different properties with virgin sericin. Isolation methods include extraction with heat, enzymatic reactions, and precipitation from aqueous solutions. Other chapters in this book detail the merits and demerits of these processes and the properties of the extracted material. Worldwide, around 400,000 tons of cocoons are produced annually, with reeling mills generating 50,000 tons of sericin, discharged into water, causing significant environmental pollution due to its higher oxygen demand for microbial degradation. The recovery and upcycling of waste silk sericin reduce the ecological impact in the silk industry and hold economic and social benefits for various pharmaceutical and cosmetic applications (Vaithanomsat & Kitpreechavanich, 2008).

The global market size of cosmetic products was estimated around USD 262 billion in 2022 and is predicted to expand with a 4.2% compound annual growth rate from 2023 to 2030. Similarly, India captured around USD 1.35 billion market share of

cosmetic products in 2023 and is predicted to increase up to USD 2.27 million by 2028 (Cosmetic Industry in India Size & Share Analysis—Growth Trends & Forecasts (2024−2029), 2024). The industry's current state underscores the critical importance of material requirements for the supply chain of cosmetic products. Bio-based ingredients, such as sericin and other natural compounds, are emerging as potential sources for their economic aspects and environmental values. These ingredients align with the industry's growing emphasis on sustainability, offering an eco-friendly alternative to conventional, often petroleum-based components. The utilization of biobased materials not only addresses economic considerations but also contributes to the broader goal of promoting environmentally conscious practices within the cosmetic industry.

The use of bio-based materials is not always associated with safety. The toxicity of any material depends on its interaction with the human body (Almeida et al., 2017). In certain instances, biomolecules found in cosmetic products, particularly macromolecules, may play a crucial role in preventing immune responses on the skin or reactions to cosmetic ingredients, some of which can lead to allergic reactions. However, various studies have suggested that sericin represents a safer alternative in addressing this concern.

This chapter aims to elucidate the potential mechanisms that render sericin suitable for cosmetic applications, providing a comprehensive review of recent research papers on the subject.

2. Recent work on sericin-based cosmetic and personal care products

Ancient civilizations discovered that boiling silk cocoons yielded silk fibers, and the residual extract, rich in various amino acids, benefited the human body. Sericin, possessing a microstructure akin to human skin cells, has demonstrated the ability to stimulate skin cell reproduction and exhibits antiaging and antihyperpigmentation properties. However, sericin obtained from silk industries often contains impurities, and its protein percentage is too low, necessitating significant dilution and alkali treatment. This makes it unsuitable for cosmetics, especially in the production of medical-related products. Despite these challenges, sericin has applications in wound healing and scar treatment, particularly in bandages (Bandyopadhyay et al., 2019). Researchers have explored enzymatic techniques to enhance sericin yield. Numerous studies have showcased the diverse product types derived from sericin and their applications, summarized in Table 16.1, additionally, provides an overview of leading cosmetic industries and their respective product types (Table 16.2).

The experts for cosmetic constituent protection conducted a review regarding the safety of hydrolyzed sericin and other sericin protein components, primarily serving as skin and hair conditioning agents and bulking agents in cosmetic products (Omar et al., 2022). The conclusion reached was that sericin, a water-soluble globular protein, is one of the eight silk protein ingredients deemed harmless for cosmetics manufacturing. Sericin's amino acid composition, notably rich in serine, aspartic acid, glutamic acid, lysine, and arginine, functions as beneficial nutrients for the

Table 16.1 Sericin-based product list and its application.

Genre of commodities	Achievable properties
Moisturizer	Hydration to the skin, leaving it soft and supple
Facial creams	Nourishment and help in improving skin texture
Antiaging creams	Antioxidant properties contribute to antiaging formulations and reduce the appearance of fine lines and wrinkles
Sunscreen cream	Shielding the skin from harmful UV rays
Hair care product	Conditioning and cleansing properties and repair damaged strands
Nail care product	Prevent chapping, brittleness, and impart inherent gloss
Oil	Skin hydration and proper absorption of sericin through oil (coconut oil)

From Kundu, S. C., Dash, B. C., Dash, R. & Kaplan, D. L. (2008). Natural protective glue protein, sericin bioengineered by silkworms: Potential for biomedical and biotechnological applications. *Progress in Polymer Science (Oxford), 33*(10), 998−1012. https://doi.org/10.1016/j.progpolymsci.2008.08.002.

Table 16.2 List of companies and their sericin related products.

Company name	Product types
Elmiplant Romania, Romania	Cosmetics
SINOSILK, China	
Dr. Temt, Austria	
Seiren Co., Ltd., Japan	
Plank, USA	
Comfort Zone, Italy	
Acca Kappa, Italy	Hair care
Aurora Silk, USA	
SINOSILK, China	
The Hair Care Company, USA	
Silk Biochemical Co., Ltd., China	Sericin powder
Huzhou Longs Biochem Co., Ltd., China	
Xian Tianyi Biotechnology Co., Ltd., China	Silk peptide sericin
Shaanxi Seyon Industry Co., Ltd., China	
Wako, USA	Pure sericin

From Kundu, S. C., Dash, B. C., Dash, R. & Kaplan, D. L. (2008). Natural protective glue protein, sericin bioengineered by silkworms: Potential for biomedical and biotechnological applications. *Progress in Polymer Science (Oxford), 33*(10), 998−1012. https://doi.org/10.1016/j.progpolymsci.2008.08.002.

skin. The skin can readily absorb these nutrients through the epidermal gaps and glands, leading to enhanced skin nutrition, increased vitality, and improved elasticity of skin cells. Moreover, sericin facilitates the metabolism of epidermal cells (Matsumoto et al., 2020). A key distinction from fibroin lies in the fact that fibroin, being

water-insoluble, cannot be absorbed by the skin. Consequently, the prolonged use of cosmetics incorporating sericin provides essential nutrients for sustaining skin beauty (Padamwar & Pawar, 2004).

The skin's outer layer, the stratum corneum, contains a natural moisturizing factor (NMF) that retains moisture, and the sebum membrane prevents moisture evaporation. These elements play a vital role in skin hydration, ensuring an optimal moisture level for enhanced elasticity, smoothness, and softness. Sericin, with its amino acid composition closely resembling the skin's NMF, exhibits polar groups on the surface of its polypeptide chains. This allows sericin to transfer water from the body to the skin's stratum corneum, maintaining essential skin moisture. Research has shown that the NMF value of sericin is approximately 29.34, which closely matches the NMF value of human skin, which is 30. This similarity is the reason why sericin is more compatible with the skin (Sheng et al., 2013). Remarkably, sericin has demonstrated an equivalent hygroscopic rate even at 20 times lower concentration than standard glycerol. The underlying mechanism involves the hydrophilic groups within the loosely structured polypeptide chain on the molecule's surface, facilitating water retention in the stratum corneum. This study has explained the effective moisturizing and hygroscopic properties of sericin, suggesting that a small amount can be incorporated into cosmetics with positive results. The research also indicated that sericin protein exhibits favorable characteristics for penetrating the cell membrane and being effectively absorbed by the skin due to its small molecular weight (Kunz, 2016).

Additionally, it demonstrates a specific impact in reducing the visibility of localized fine wrinkles on the skin. Sericin has been investigated for its ability to inhibit melanin production, a process that plays a role in whitening human skin. Melanocytes in the cortical layer contribute to this process but can also produce melanin, leading to skin darkening. The mechanism involves tyrosine in melanocytes oxidizing the tyrosine present in the keratin protein fraction of the skin to form melanin. Additionally, exposure to UV radiation can enhance this oxidation reaction, resulting in darkening, especially with frequent sunlight exposure in the summer. The study revealed that adding 1% sericin reduced tyrosine activity by over half, leading to a 52.39% inhibition rate of melanin. Therefore, skincare cosmetics incorporating sericin can contribute to maintaining fair and flawless skin. The experimental findings have additionally indicated that sericin exhibits effective adsorption properties in hair, enhancing hair flexibility by 87% (Sheng et al., 2013). Due to its strong affinity and interaction with hair, sericin can create a transparent film on the hair's surface, effectively preventing hair damage and facilitating the repair of damaged hair.

Padamwar and colleagues (Padamwar et al., 2005) conducted a study on the moisturizing properties of sericin, identifying two main factors responsible for dry skin: alterations in the normal hydration gradient of the stratum corneum and physiochemical changes in the skin. Apart from internal hydration, external water is essential for replenishing the skin. The distinctive transformation of α-random coil sericin to a β-sheet structure results in the gelation of sericin (Jo & Park, 2015). The evaluation of sericin gel's moisturizing properties involved skin impedance measurement, hydroxyproline content analysis, assessment of transepidermal water loss, and scanning electron microscopy (SEM). Sericin likely enables the skin to retain more water and lose less through evaporation, leading to softer and more supple skin. SEM images of skin replicas treated with sericin gels exhibited smoother characteristics than those

treated with pluronic and carbopol, indicating enhanced hydration of the upper stratum corneum layer (Fig. 16.2). The increase in hydroxyproline content in sericin-treated skin, compared to normal and dry skin, is associated with restoring amino acids. The plausible mechanism underlying its moisturizing property involves the hydroxy group of hydroxyproline stabilizing collagen through direct interchain hydrogen bonding and, in some instances, via a water molecule between the neighboring chains'

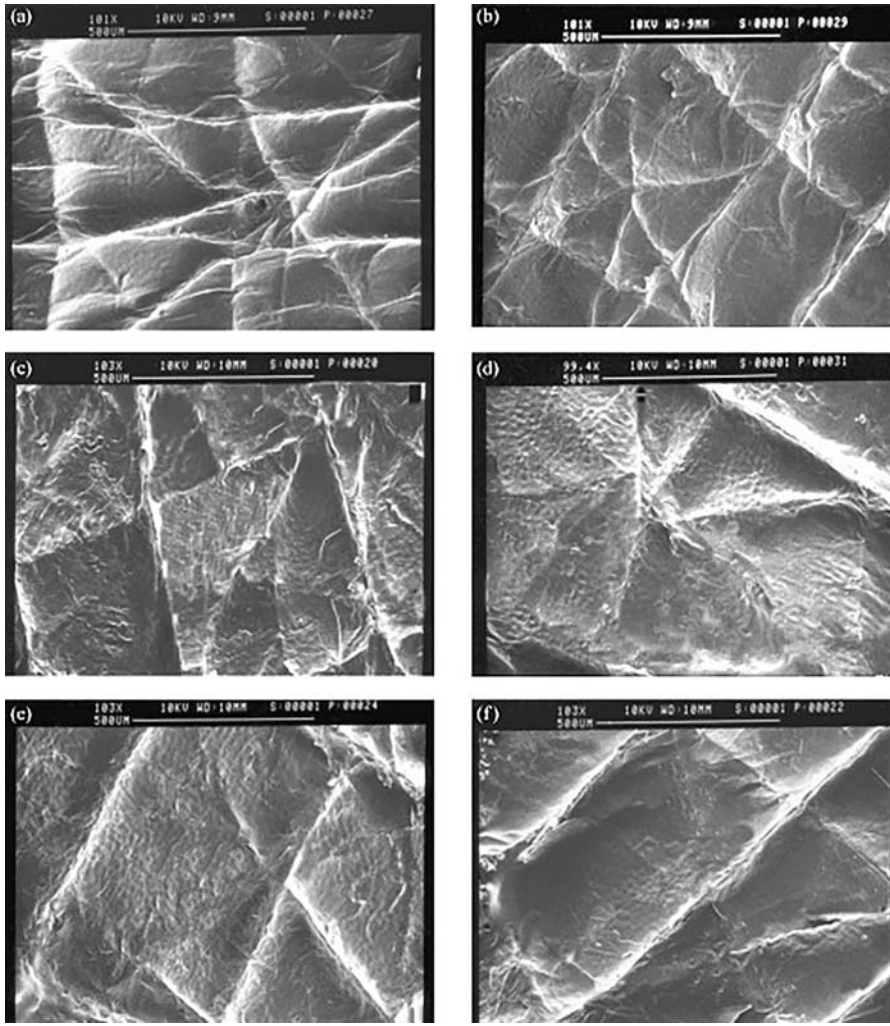


Figure 16.2 Scanning electron microscopy captured images of (a) dehydrated skin, (b) healthy skin, (c) skin subjected to 1.5% sericin treatment, (d) skin exposed to 2% sericin treatment, (e) skin treated with a combination of 2% sericin and 5% pluronic, and (f) skin treated with a combination of 2% sericin and 0.2% carbopol. Sericin application effects on skin.
From Padamwar, M. N., Pawar, A. P., Daithankar, A. V. & Mahadik, K. R. (2005). Silk sericin as a moisturizer: an in vivo study. *Journal of Cosmetic Dermatology, 4*(4), 250−257. https://doi.org/10.1111/j.1473-2165.2005.00200.x.

backbone. This forms an additional hydrogen bond between the hydroxyproline chain and the water molecule.

Kundu et al. (2008) have reviewed the potential applications of sericin in various biomedical and biotechnological contexts. Studies have demonstrated that sericin treatments can effectively manage skin issues such as dermatitis. The inclusion of sericin in nail cosmetics has proven to prevent nail brittleness and enhance nail gloss. Additionally, when incorporated into hair cosmetics and bath preparations containing olive oil and fatty acids, sericin can minimize damage to the hair surface by binding to the hair. Various research findings suggest that sericin hydrolysates with low molecular weights are commonly utilized as skin and hair conditioners. The diverse range of cosmetic applications extends to sericin powder, lotions with moisturizing and conditioning effects, creams with enhanced cleansing properties, and cosmetics designed to absorb sweat and sebum.

The degradation of healthy skin with time has led to the development of various antiaging products to rejuvenate its condition. Kitisin and his team (Kitisin et al., 2013) assessed silk sericin properties, exploring potential correlations with collagen type I stimulation, antioxidation, and antiapoptosis in an in-vitro fibroblast cell culture model. The levels of methionine and cysteine in silk sericin were identified as significant factors promoting cell growth and collagen synthesis. The findings further suggested that silk sericin could function as an antiapoptotic agent, triggering the antiapoptosis signal bcl-2 by mitigating fibroblast oxidative stress. This study underscores the potential of silk sericin as an effective antiaging agent, with potential benefits for both the pharmaceutical and cosmeceutical industries.

Shankar and colleagues (Shankar et al., 2023) have conducted a study on synthesizing hybrid nanoparticles comprising sericin protein conjugated with magnesium oxide (MgO). The findings of the study indicated that these hybrid nanoparticles exhibit potential applications as antibacterial, antiaging, and anticancer agents. Specifically, tyrosine, an enzyme linked to melanogenesis and the formation of dark spots, was targeted. Additionally, increased hyaluronidase activity contributed to the breakdown of hyaluronic acid and the appearance of fine wrinkles on the face (Wang et al., 2020). Comparative analysis with sericin alone revealed that the hybrid nanoparticles demonstrated enhanced activity against elastase, hyaluronidase, collagenase, and tyrosinase (Fig. 16.3).

Zhu et al. have presented a straightforward, eco-friendly, sustainable approach involving the development of innovative primary zein nanoparticles embedded with curcumin and coated with silk sericin (ZHSCs) (Zhu et al., 2022). This strategy aims to facilitate the topical delivery of curcumin, allowing it to penetrate the dermis and exhibit antidermatitis effects on lesions with minimal side effects. Imaging studies indicated that ZHSCs enhance the penetration of curcumin through the epidermal layer of the skin (Fig. 16.4). Sericin demonstrates synergistic benefits on keratinocytes and fibroblasts, promoting proliferation and mitotic effects. Additionally, the antityrosinase property of sericin positions it as a valuable treatment for hyperpigmentation, a skin condition resulting from excessive melanin production. In a cell model of dermatitis induced by TNF-α/IFN-γ costimulation, ZHSCs nanoparticles noticeably downregulated the generation of inflammatory chemokines in keratinocytes, exerting an antidermatitis effect, when compared to free curcumin. Consequently, this optimized external preparation enhances curcumin's percutaneous bioavailability, making it a

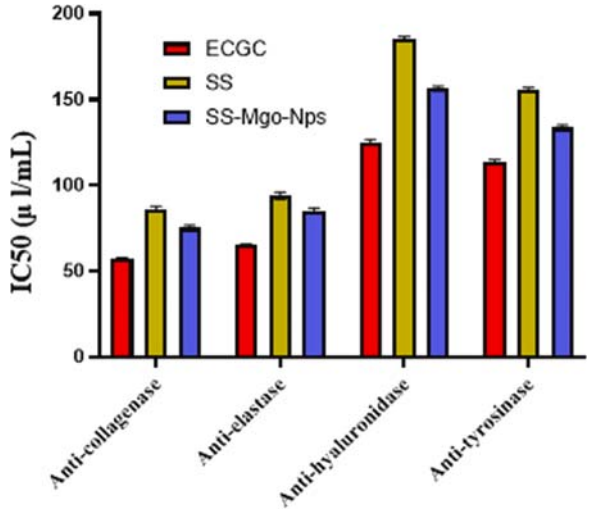


Figure 16.3 The antiaging effectiveness of sericin-MgO-NPs was demonstrated by its IC50 value, which was comparable to that of epigallocatechin-3-gallate (EGCG). Antiaging effect of sericin.
From Shankar, S., Murthy, A. N., Rachitha, P., Raghavendra, V. B., Sunayana, N., Chinnathambi, A., Alharbi, S. A., Basavegowda, N., Brindhadevi, K. & Pugazhendhi, A. (2023). Silk sericin conjugated magnesium oxide nanoparticles for its antioxidant, anti-aging, and anti-biofilm activities. *Environmental Research, 223*. https://doi.org/10.1016/j.envres.2023.115421.

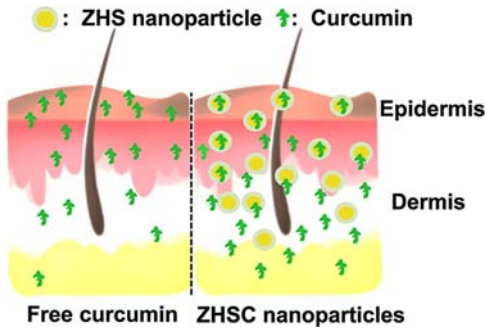


Figure 16.4 Potential mechanism of free curcumin and ZHSC nanoparticle skin penetration. Skin penetration of sericin nanoparticle.
From Zhu, J., Tang, C., Luo, F., Yin, S. & Chemistry, X. Y. (2022). Topical application of zein-silk sericin nanoparticles loaded with curcumin for improved therapy of dermatitis. *Elsevier*.

promising topical delivery system or a conveniently incorporated ingredient in cosmeceutical products.

Cherdchom and colleagues (Cherdchom et al., 2024) have investigated the urea-based extraction method for sericin. Their research revealed that sericin extracted with low concentrations of urea effectively reduces melanin production by suppressing tyrosinase activity, showcasing its antimelanogenesis effectiveness. Furthermore, the

inhibitory impact of urea-extracted sericin on melanogenesis is associated with increased production of intracellular reactive oxygen species (ROS). Urea-extracted sericin demonstrates favorable effects by activating the Nrf2 pathway, triggering the expression of antioxidant-related genes like HO-1, NQO1, and GCLC. Notably, serine, abundant in the hydroxyl group present in all types of sericin extraction, contributes to the diverse functionalities of sericin.

Sericin, renowned for its role in healing damaged cuticles, restoring shine, and enhancing texture, has found application in various hair care products such as conditioners and hair dyes. Formulations containing minimal sericin were employed to assess its effectiveness in coloring hair strands. Comprehensive data analysis unequivocally demonstrated the successful restoration of damaged hair to a healthier appearance postapplication of sericin nanoparticles. A research group (Jena et al., 2018) delved into sericin's chemical characterization and cosmeceutical properties derived from diverse tasar cocoon species. While sericin's biological and cosmetic benefits make it appealing for use in the beauty industry, definitive conclusions about its appropriateness for the intended purpose can only be drawn through in vivo research. The study highlighted serine, aspartic acid, and glycine (55.68%−59.61%) in sericin from various ecoraces. Additionally, the research identified antityrosinase, antielastase activities, inhibition of glutathione-S-transferase activity, free radical scavenging potential, and inhibition of lipid peroxidation in sericin from ecoraces.

3. Sericin properties favorable for cosmetic applications

Sericin has various properties perfect for beauty products (Fig. 16.5). This discussion will examine some essential features that make sericin a significant cosmetic ingredient. From keeping the skin moist to having antioxidants and benefits for the skin, sericin's special qualities make it useful in different beauty products. Understanding

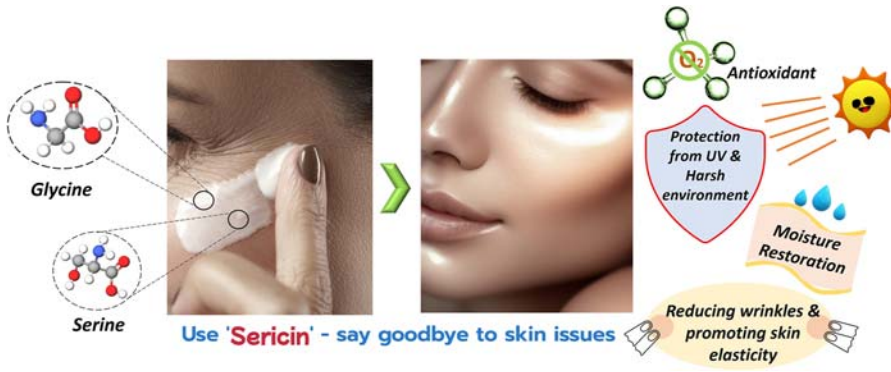


Figure 16.5 Potential properties of sericin for cosmetic applications (self-drawn). Multifunctional sericin in cosmetic world.

these properties becomes pivotal in harnessing the full potential of sericin for enhancing skincare and beauty products.

3.1 Biocompatibility and immunoreactivity

Ensuring the absence of adverse effects, particularly immune responses, is crucial when utilizing any material on the human body. Additionally, for a product to be effectively formulated, sericin must possess the property of not reacting with other ingredients, thereby preserving its inherent properties. Numerous studies have established that sericin is an immunologically inert material. Initially, concerns arose that silk application might lead to various adverse effects, including inflammation, allergenicity, and immunogenicity, with sericin being considered a potential cause. However, extensive research has clarified that sericin itself does not elicit a significant immune response. Instead, it is suggested that a combination of sericin and fibroin proteins may induce chronic immune responses with unclear mechanisms. When sericin is introduced into the culture media of various cell lines, it exhibits no cytotoxic effects. Some studies have indicated that sericin does not trigger macrophage activation. A particular investigation observed that both sericin and sericin-based membranes caused a mild increase in tumor necrosis factor-alpha (TNF-α) levels and interleukin-1 beta (IL-1β) in murine macrophages. Immunological responses were studied in both laboratory-bred mice and rabbits. The study extracted degraded and intact sericin from wild-type and fibroin-deficient mutant silkworm cocoons (*B. mori*). Inflammatory responses were monitored for 3−17 days, during which intact sericin-based hydrogel was internally inoculated in mice. This did not lead to increased infiltration of macrophages or neutrophils in the tissue at the hydrogel-embedded location compared to alginate hydrogel and fibroin hydrogel. Furthermore, the sericin proteins exhibited a minimal increase in immunoglobulin G and immunoglobulin E levels compared to fibrinogen, underscoring sericin's low immunogenicity and allergenicity. Elevated levels of immunoglobulin E in mammalian blood can trigger allergic reactions. The inflammatory response induced by a sericin-based cream was evaluated on wounds caused in rats. After 7 days of cream application, the quantification of interleukin 1 beta (IL1β), a lymphocyte-activating factor, and TNFα (an inflammatory cytokine) were performed. The results revealed a significant decrease in the release of these cytokines. Similar effects were observed in studies by other researchers, indicating that sericin reduces the levels of cytokines produced by macrophages and monocytes. These findings suggest that sericin is a nontoxic and nonallergenic natural protein suitable for skin applications (Hu et al., 2018; Silva et al., 2022; Wray et al., 2011).

3.2 Antioxidant

Reactive oxygen species are generated during normal cellular metabolism but can become harmful in high concentrations, leading to cell or tissue injury and contributing to various diseases (such as cancer, cirrhosis, and ischemic reperfusion). Sericin is renowned for its robust antioxidant activity. Several studies have elucidated that sericin's antioxidant properties arise from its ability to scavenge free radicals, inhibit lipid

peroxidation, and exhibit antityrosinase and antielastase activities. Additionally, research suggests that sericin may enhance the activity of antioxidant enzymes like superoxide dismutase, catalase, and glutathione peroxidase. The antioxidant effects of sericin are linked to its high content of serine (32.16%), glycine (16.43%), and threonine (8.04%), whose hydroxyl groups function as metal chelators, particularly for metals like copper and iron. Conversely, the presence of pigment molecules (such as flavonoids and carotenoids) in sericin layers could contribute to its antioxidant properties and antityrosinase activity. Sericin also exhibits photoprotective capabilities by efficiently absorbing ultraviolet radiation and preventing oxidative damage, thereby maintaining redox balance. In addition to UV irradiation, sericin protects against oxidative stress caused by ultra-low temperatures, such as cryopreservation. Ultra-low temperature freezing induces oxidative stress on cells, tissues, and organs, reducing their survival rate and biological function. Leveraging the benefits of sericin in cell culture and its antioxidant capacity, sericin-based cryoprotectants have been developed and applied to safeguard mammalian cells, buffalo semen, human sperm, etc. Sericin emerges as a cost-effective solution for preserving biological materials under such environmentally challenging conditions (Fan et al., 2009; Liu et al., 2022).

3.3 Antimicrobial

An antimicrobial biomaterial is characterized by its ability to eliminate or hinder the growth and multiplication of microbes. This quality is crucial not only for applications on skin, hair, or other body parts but also for ensuring the prolonged durability of both the material itself and the cosmetic products in which it is used. In wound care, preventing infections is paramount, as microbial presence at the wound site can impede natural healing, leading to more severe complications. Therefore, integrating biomaterials with antibacterial properties holds promise for developing pharmaceutical and health-oriented cosmetic products. A variety of literature indicates that sericin's antimicrobial activity may be linked to the presence of cysteine, an uncharged polar amino acid containing sulfhydryl groups. These groups form weak hydrogen bonds with oxygen or nitrogen, creating a highly reactive compound that influences microorganisms' enzymatic reactions and metabolic functions. Sericin has demonstrated antimicrobial effectiveness against both Gram-positive and Gram-negative bacteria, including *S. aureus* and *E. coli*, as well as fungi like *Candida albicans* and *Aspergillus flavus*. Studies indicate that increasing sericin concentration between 10 and 20 mg/mL enhances its inhibitory effects on *S. pneumoniae*, *P. aeruginosa*, and *E. coli* growth. The diverse amino acids present in sericin play a vital role in disrupting microbial cell membranes, contributing to its overall antimicrobial effects. By incorporating sericin, cosmetic products enhance esthetics and provide additional health benefits by inhibiting microbial growth on the skin. This aligns with the increasing demand for multifunctional cosmetic ingredients (Silva et al., 2022).

3.4 Anti-inflammatory

In the healing process, inflammation plays a pivotal role by facilitating the phagocytosis of necrotic tissues and potential contaminants at the wound site. Inflammatory cells release cytokines and growth factors during this stage, attracting cells essential for tissue regeneration. Proper regulation of this phase is crucial, as an uncontrolled and excessive expression of inflammatory cytokines can activate metalloproteinases, causing the breakdown of the extracellular matrix (Rahimpour et al., 2023). Biomaterials created for treating wounds should possess the capability to efficiently control the inflammatory process. The evaluation of antiinflammatory activity often involves examining the release of cytokines like interleukin 1 (IL-1) and tumor necrosis factor-alpha (TNF-α). Sericin has undergone scrutiny in both laboratory and live testing, showcasing its ability to regulate the release of inflammatory cytokines, including IL-1β and TNF-α. This characteristic could prove advantageous in developing cosmetic products aimed at alleviating inflammation, particularly in cases related to skin disorders or supporting wound healing (Silva et al., 2022).

4. Challenges and toxicity of sericin-based material

While sericin exhibits numerous properties and holds vast potential for cosmetic applications, it has encountered challenges during the recovery and product manufacturing processes (Fig. 16.6).

4.1 Solubility

Similar to fibroin, which is insoluble in water, sericin exhibits restricted solubility under normal conditions and is not readily water-soluble unless it undergoes degradation. Higher temperatures are required for partial dissolution during the degumming process. The restricted solubility of sericin inhibits its seamless integration into formulations, limiting its applicability in specific cosmetic uses. The limited solubility of sericin is attributed to its complex structure and the presence of hydrophobic amino acids (Jo, 2015). Manufacturers and researchers have addressed these solubility limitations through innovative formulation techniques or exploring alternative processing methods to unlock the full potential of sericin in the cosmetic industry, such as enzymatic hydrolysis and the addition of surfactants. From a different perspective, the higher hygroscopic nature of sericin poses a potential challenge in cosmetic applications, leading to the absorption of moisture from the air and causing the product to become sticky or clumpy. To address this issue, researchers have been investigating diverse methods to mitigate sericin's hygroscopicity. These approaches include cross-linking sericin with other polymers or incorporating it into blends with other materials (Sabu Mathew et al., 2023).

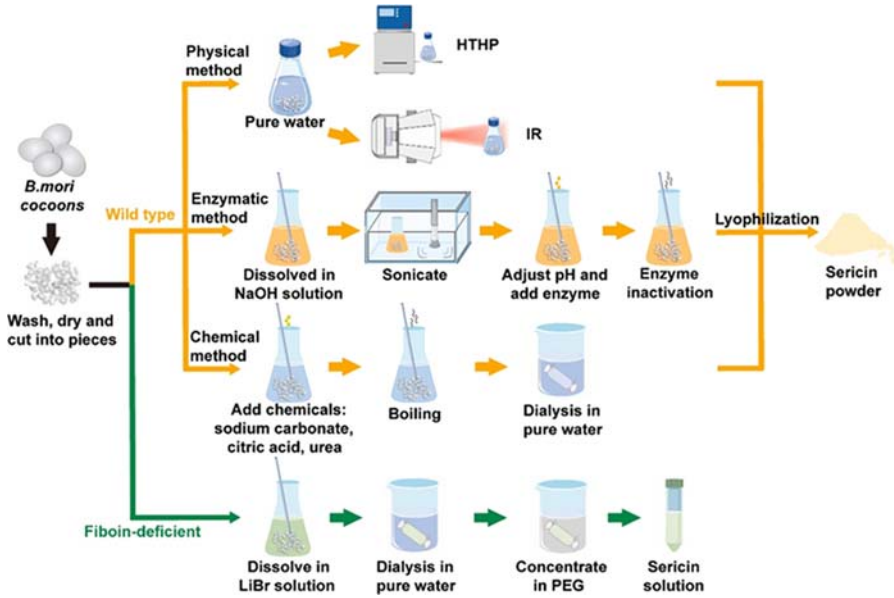


Figure 16.6 Different routes of sericin recovery. Sericin recovery via different methods. From Sabu Mathew, S., Maria, H. J., Allardyce, B. J., Rajkhowa, R. & Thomas, S. (2023). Waste to wealth: Exploring the versatile prospects of discarded silk sericin. *ACS Sustainable Chemistry and Engineering*. https://doi.org/10.1021/acssuschemeng.3c04264.

4.2 Allergenicity

Numerous studies have indicated that sericin is generally nontoxic and nonallergenic to the skin. Nonetheless, some studies have suggested that it may lead to allergic reactions on the skin due to the presence of antigens from an insect of the genus Anthrenus in the silk material. Individual sensitivities can differ; specific individuals might still exhibit an allergic response. Conducting a patch test before using any product containing sericin or a related product is crucial to ascertain skin compatibility. In the event of experiencing allergic reactions after using sericin-containing products, it is recommended to discontinue use and seek advice from a dermatologist (Aramwit, 2014; Jiao et al., 2017).

4.3 Environmental impact

Sericin is safe and has good biodegradability and biocompatibility, with no toxicity concerns. However, it is essential to delve deeper into its environmental impact during recovery or upcycling on a global scale. Recovery scenarios were found to have significantly higher environmental impacts compared to the base situation. Regarding kg CO_2 equivalence, the effect on climate change in the recovery scenarios was

approximately 2000−2650 times higher than the base scenario. Research indicates that the endpoint impact score for climate change was 50%, followed by 34% for natural resources and 15% for human health impacts for recovery purposes. The linear economy model in industrial production is not sustainable, contributing to the environmental effects through resource depletion and greenhouse gas emissions. In such cases, adopting a circular economy model, especially in resource recovery from wastewater, has gained prominence in the last decade. The recovery and recycling of waste silk sericin reduces environmental impact in the silk industry and offers significant economic and social benefits for various pharmaceutical and cosmetic applications. Furthermore, conducting a life cycle analysis (LCA) as a decision support tool would provide more insights into the environmental impacts of proposed sericin upcycling processes (Capar & Pilevneli, 2024; Shitole et al., 2020).

4.4 Cost

The cost of sericin is relatively high, and it varies based on its physical properties and purity. The average price for edible or cosmetic grade (ISO9001 certified) sericin is $65/kg, while it can go up to $215/g for cell culture grade sericin (Source: Sigma−Aldrich). In a research study, the estimated cost of sericin recovery was investigated in a silk degumming facility that implemented membrane hybrid processes at the pilot scale. This estimation was based on optimized processes at the laboratory scale, as selecting the most optimal processes is a crucial aspect of economic analyses. The study revealed that the cost of sericin recovery in the laboratory and pilot studies at the silk degumming facility was significantly higher than commercially available sericin. The total cost of sericin recovery for a plant lifetime of 15 years varied considerably between $150,000 and $2,830,000. Depending on the chosen recovery method, the unit costs of sericin recovery alternatives ranged from $95 to $1450 per kg of dry sericin. Further research on alternative silk degumming processes is needed, aiming to reduce sericin recovery costs and ultimately lower overall production costs (Capar & Pilevneli, 2024).

5. Future potentials

The future prospects of sericin as a cosmetic ingredient hold immense promise, propelled by its distinctive properties and its potential advantages for skincare, hair care, and various cosmetic applications. As research and technology continue to make strides, sericin is poised to assume a pivotal role in shaping the landscape of the cosmetics industry. In the forthcoming years, sericin holds the potential to be integrated into diverse cosmetic formulations, alongside other natural constituents, for the creation of moisturizers, serums, and masks. These products could seamlessly collaborate to deliver profound and enduring hydration to the skin, working together synergistically. One of the remarkable abilities of sericin is its capacity to stimulate collagen synthesis. As technology advances, formulations centered around sericin

could emerge as pivotal constituents in serums, creams, and treatments designed to address fine lines, wrinkles, and skin sagging. Several studies have also demonstrated its ability to enhance the skin's natural barrier function. Cosmetic products could use sericin to bolster the skin's protective barrier, thereby preventing the loss of moisture and the entry of external irritants. Hair loss has emerged as a significant concern today, influenced by factors such as pollution, environmental conditions, and lifestyle shifts that directly impact our bodies. Sericin's attraction to hair proteins could pave the way for its incorporation into hair care products and leave-in treatments. Introducing sericin alongside other proteins might enhance hair texture, minimize frizz, and facilitate the mending of damage. Continuous research endeavors have the potential to unveil innovative strategies for harnessing sericin's structure to facilitate the effective delivery of various bioactive substances, including antioxidants, vitamins, and peptides, directly into the skin via cosmetic products. Research collaboration and advanced technology can potentially address the concern of sericin-sensitive skin. Prospective formulations could prioritize soothing irritated skin, mitigating redness, and easing discomfort arising from a range of skin conditions. An additional method for effectively addressing skin-specific concerns will involve personalized cosmetics. As advances in personalized skincare continue, sericin could be integrated into customized formulations that are based on an individual's skin type, concerns, and unique needs.

Looking ahead, the collaboration among cosmetic scientists, dermatologists, and experts in the silk industry is poised to yield fresh insights into the properties and applications of sericin in advanced cosmetic formulations. As consumer demand for natural, effective, and sustainable ingredients continues to grow, sericin has the potential to emerge as a highly sought-after component within the cosmetics industry.

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Challenges and toxicity assessment of sericin materials in bio-based applications

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Kerim Emre Öksüz [1,2]
[1]Sivas Cumhuriyet University, Faculty of Engineering, Department of Metallurgical and Materials Engineering, Sivas, Turkey; [2]Institute of Science and Technology, Department of Bioengineering, Sivas Cumhuriyet University, Sivas, Turkey

1. Introduction

Nature exhibits a wide array of organisms boasting distinctive protective mechanisms. Notably, various lepidopteran and other insect species have developed intricate physical structures, serving as defenses against potential predators (Johnson et al., 2001; Kauffman & Kennedy, 1989). The remarkable efficacy of these structures beckons further investigation into the intricate interplay between their properties, compositions, and functions (Zhao et al., 2007). Illustratively, silkworms offer a compelling illustration of this phenomenon, as they skillfully weave protective cocoons to serve as sanctuaries during the transformative journey from larval to adult stages (Kundu et al., 2008). This intricate interplay between organisms and their protective adaptations underscores the rich tapestry of strategies that the natural world has evolved to ensure survival and thrive in diverse ecological niches. Fig. 17.1 illustrates the five stages of the silkworm's metamorphosis within its life cycle, accompanied by detailed explanations (Chand et al., 2022; Sonthisombat et al., 2004). The cocoon serves as the origin of commercial silk, a coveted material employed in crafting exquisite, high-grade textiles. In the realm of nature, evolution significantly shapes the variety of silk structures and functions, contingent upon the environment and the requirements of the organisms responsible for their production. Silk, a naturally derived polymer, is synthesized by a diverse array of insects and spiders (Hudson et al., 1995; Vollrath & Knight, 2001; Öksüz et al., 2021). The commonly found *Bombyx mori* yields the highest fiber production and the finest grade of raw silk, deriving its sustenance from the leaves of the *Morus* spp., or mulberry plant (Li et al., 2005). Sericin, a prominent component found not only in the silk produced by mulberry silkworms but also in that of nonmulberry silkworms, holds promising potential across diverse fields, including pharmacology, cosmetics, and biotechnology. Presently, sericin is being recognized for its versatile applications. Specifically, thorough examinations of bioactive and cytotoxic properties will contribute to enhancing the value of sericins, particularly within the cosmetics industry. This

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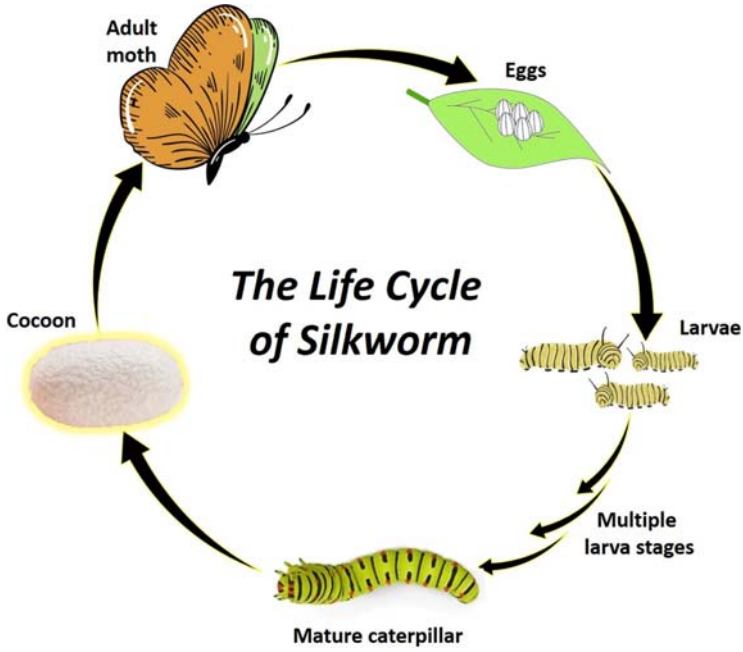


Figure 17.1 The life cycle of silkworm.

comprehensive book chapter will be dedicated to an in-depth examination of these aspects, offering a thorough exploration and analysis of sericins various roles and impacts in these specific contexts. Furthermore, this chapter reviews recent developments in the use of this protein for biomedical, medical and pharmaceutical applications in relation to its structural and chemical properties. It focuses on the development of new biomaterials combined with the safe sericin protein and the reported clinical studies using sericin-based materials for tissue engineering as well as the active mechanisms of sericin in vivo and in vitro.

Egg Stage (I): After the female silk moths lay their eggs, often in groups on surfaces like leaves or twigs, these eggs, small in size at 1−2 mm, display hues of yellow or white. Enveloped in a safeguarding layer known as sericin, they await optimal conditions for hatching. The incubation span typically ranges from 10 to 14 days, contingent upon temperature and humidity. *Larva Stage (II):* When the eggs hatch, they give rise to minute silkworm larvae or caterpillars, identifiable by their distinct features - a small head, supple body, and an abundance of fine hairs covering their skin. These voracious eaters eagerly consume mulberry leaves, their main sustenance, and undergo multiple molting cycles to accommodate their expanding forms. *Pupa Stage (III):* Following their last instar, silkworms transition into the pupal phase, a period of rest and transformation. During this phase, the silkworm expertly crafts a safeguarding cocoon from silk threads secreted by specialized head glands. This cocoon acts as both a shield and a secure haven, facilitating the pupas metamorphic journey.

Cocoon Stage (IV): Within a brief span, the silkworm finalizes its cocoon formation. Shaped like an oval, the cocoon is crafted from an unbroken strand of silk, astonishingly stretching up to 900 m. This remarkable filament comprises two key proteins: fibroin, granting strength to the thread, and sericin, an adhesive substance amalgamating the fibers. These silk fibers, produced by the silkworm, serve as the essential resource for silk manufacturing. *Moth Stage (V):* Within the cocoon, the pupa undergoes full metamorphosis, maturing into an adult silk moth. Once this transformation concludes, the adult moth secretes a unique enzyme that dissolves a section of the cocoon, forming an exit orifice. Its adult phase lasts briefly, spanning 5−10 days, with reproduction as its primary objective (Liu et al., 2009; Sonthisombat & Speakman, 2003).

2. Meta-analysis update on sericin based studies

Some scientific studies on sericin protein date back to the 1920s (Kodama, 1926). According to the Springer Link database, approximately 2330 manuscripts have been published between 2004 and 2024 (https://link.springer.com/search?new-search=true&query=sericin&date=custom&dateFrom=2004&dateTo=2024). Among these, 1137 are research articles, 697 are book chapters, 270 are review articles, 146 are reference work entries, 58 are conference papers, 16 are protocols, and six are other related publications (Fig. 17.2a). Similarly, since 2004, approximately 4500 publications on sericin have been reported in the Science Direct database. Among them, 2516 are research articles, 866 are review articles, 727 are book chapters, 64 are encyclopedia entries, 25 are conference abstracts, 73 are short communications, and 229 are other related publications (Fig. 17.2b) (https://www.sciencedirect.com/search?qs=sericin&date=2004-2024). It is reported that out of all published articles, 2785 were published in the last 5 years (2019−24) (https://www.sciencedirect.com/search?qs=sericin&date=2019-2024), of which 1627 were published in the last 2 years (2022−24) (https://www.sciencedirect.com/search?qs=sericin&date=2022-2024), and 1105 were published in the last year alone (2023−24) (Fig. 17.2c) (https://www.sciencedirect.com/search?qs=sericin&date=2023-2024).

Furthermore, considering only the publications related to the in vivo properties of sericin and its applications in biomaterials, 1050 articles were published from 2004 to 2024 according to the Springer Link database. Among these, 184 were review articles, with very few details presented on sericin, particularly clinical trials (Fig. 17.3a) (https://link.springer.com/search?new-search=true&query=sericin+in+vivo&date=custom&dateFrom=2004&dateTo=2024). Similarly, the Science Direct database shows that only 2282 articles were published on this topic from 2004 to 2024 (Fig. 17.3b) (https://www.sciencedirect.com/search?date=2004-2024&qs=sericin%20in%20vivo).

Interestingly, according to these meta-analysis reports, the literature on sericin-related biomaterials predominantly comprises research articles, book chapters, and reviews, with a notable lack of clinical trials. In the Springer Link and Science Direct databases, when the keyword "sericin" is changed to "human trials," the total number

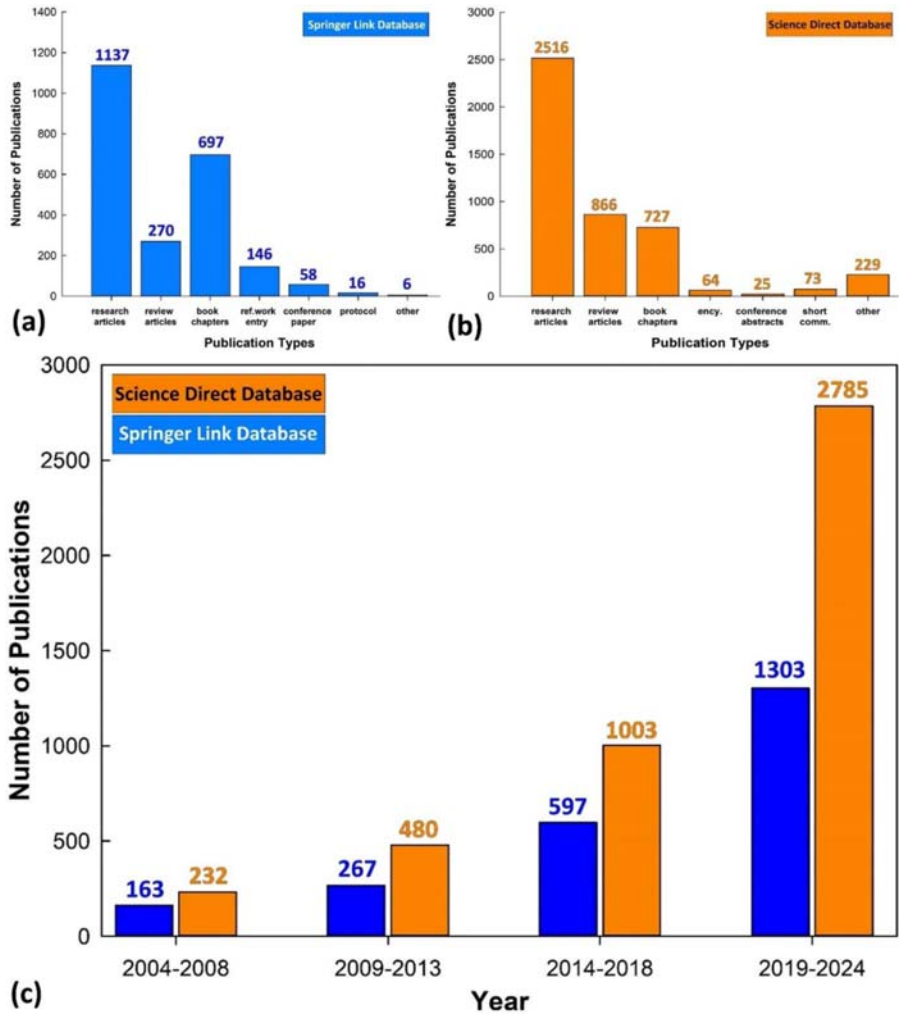


Figure 17.2 (a) Types of publications as per the Springer Link databases and (b) types of publications as per the Science Direct databases, (c) meta-analysis of publications on sericin from 20 years ago to date as per the Springer Link and Science Direct databases (*keyword: sericin*).

of studies conducted in the last 20 years is 274 (https://link.springer.com/search?new-search=true&query=sericin+trials+on+human&date=custom&dateFrom=2004&dateTo=2024) and 751 (https://www.sciencedirect.com/search?date=2004-2024&qs=sericin%20trials%20on%20human), respectively. Additionally, most of these studies involve in vivo tests, and few include clinical studies on humans for sericin-based biomaterials. Therefore, it is recommended that further clinical studies be conducted to support the efficacy levels and claims in humans.

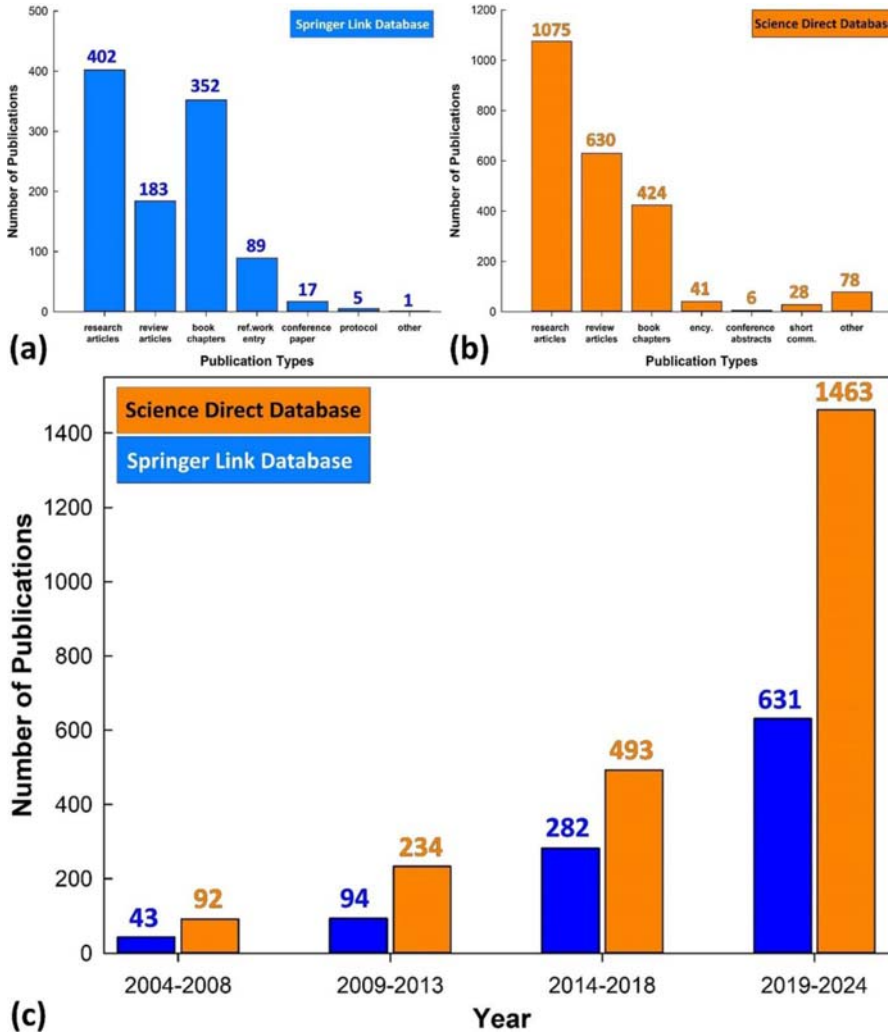


Figure 17.3 (a) Types of publications as per the Springer Link databases and (b) types of publications as per the Science Direct databases, (c) meta-analysis of publications on sericin from 20 years ago to date as per the Springer Link and Science Direct databases (*keyword: sericin* in vivo).

3. Structure, properties and applications of silk fibers

3.1 Silk "the queen of fibers" proteins

The cocoons of the mulberry silkworm *B. mori* are made up of two primary categories of proteins: fibroins and sericin (Tosun et al., 2023). Fibroin, the main protein, makes up more than 70% of the cocoon and fibroin is a hydrophobic glycoprotein released from the posterior section of the silk gland (PSG) (Couble et al., 1983; Zafar et al.,

2015). Fibroin is a heterodimeric protein consisting of a heavy chain (395 kDa) and two small subunits, namely P25 and L-chain, each weighing 25 kDa (Tanaka et al., 1999; Zhou, 2000). The expression of the fibroin and P25 genes is regulated at the transcriptional level during the larval development of both *B. mori* and *A. mylitta*. Fibroin exhibits semicrystalline properties, comprising of two phases: one is the well-known highly crystalline β-sheeted phase, while the other is a less crystalline or noncrystalline phase (Couble et al., 1983; Kaplan, 1998).

3.2 Molecular structure of fibroin

Fibroins, which are intricate and sizable proteins, possess distinct structural attributes in various silk varieties; nevertheless, they share certain fundamental characteristics. Within the silk composition, two recurring domains are present across all fibroins. The initial domain is defined by its amorphous nature, often referred to as flexible and disorderly segments, while the second domain, represented by the boxes, exhibits a well-structured, repetitive pattern reminiscent of crystals. The depiction of the fibroin N-terminal domains (FibNT) asymmetric unit can be observed in Fig. 17.4. The primary constituents of silk fibroin in *B. mori* are predominantly glycine (43%), alanine (30%), and serine (12%). Various polymorphic forms of silk exist, encompassing the glandular state preceding crystallization (silk I), the spun silk state characterized by β-sheet secondary structure (silk II), and an air-water interfaced assembly (silk III, displaying a helical arrangement) (Jin & Kaplan, 2003; Kaplan, 1998). The silk I configuration (soluble in water) readily transitions to a silk II arrangement when subjected to heat or mechanical spinning. In addition, exposure to CH_3OH or KCL results in the transformation of silk I into a β-sheet configuration (Huemmerich et al., 2006). The asymmetry in β-sheet structures arises from the occupancy of hydrogen side chains from glycine and methyl side chains from alanine. The creation of intersheet stacking within the crystals arises due to the interaction between the methyl groups and hydrogen groups located on opposing sheets. This interaction gives rise to a thermodynamically stable structure through the influence of robust hydrogen bonds and Van der Waals forces. In the region perpendicular to the axis of the chains and the fiber, a network of inter- and intra-chain hydrogen bonding is established, contributing to the structural stability (He et al., 2012; Kaplan, 1998).

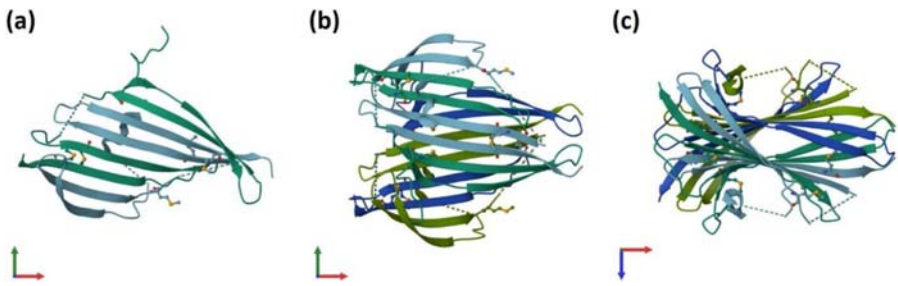


Figure 17.4 Overall structure of FibNT. (a) Two fibroin heavy chains structure, subunit A (*greenish-blue*), and subunit B (*green*) are shown in cartoon representation, (b) front view of the tetramer. (c) side view of the tetramer (four fibroin heavy chains).

4. Molecular structure and biochemical properties of sericin

Sericins, recognized as adhesive (glue) proteins, constitute 20%−30% of the cocoons composition. These stable fibroin-sericin components are hot water-soluble glycoproteins responsible for binding the fibers (fibroin) together, resulting in the formation of a composite cocoon structure (Jin & Kaplan, 2003; Vollrath & Knight, 2001). Sericin is produced in the intermediate section of the silk gland and comprises various polypeptides with weights ranging from 24 to 400 kDa. It is notable for its substantial glycine content (16%) and elevated serine content (40%) (Michaille et al., 1986). Three major sericin fractions, with molecular weights of 150, 250, and 400 kDa, have been isolated from silkworm cocoons (Takasu et al., 2002). Sericin maintains a partially unfolded structure, with 35% in β-sheet conformation, 63% in a random coil, and no α-helical content (Zhang et al., 2012). In addition to the major silk proteins, fibroin, and sericin, cocoons also encompass a water-soluble, low molecular weight protein called seroin. This seroin protein, arising from a distinct gene expressed exclusively in the middle and posterior portions of the silk gland, contributes to the cocoons composition (Zurovec et al., 1998). Various sections of the middle silk gland (MSG) of *B. mori* have yielded five distinct sericin polypeptides: s-1, s-2, s-3, s-4, and s-5. Among these, s-1, s-2, and s-3 stand out as the primary constituents. Histological examinations have revealed that s-1, s-2, and s-3 are respectively secreted from the posterior, middle, and middle-to-anterior segments of the MSG. SDS-polyacrylamide gel electrophoresis (SDS-PAGE) analysis under acidic conditions confirmed the secretion of the three major (s-1, s-2, and s-3) and two minor (s-4 and s-5) sericin polypeptides from various sections of the middle gland. These polypeptides exhibited molecular weights ranging from 80 to 310 kDa. Notably, these polypeptides boasted a notable presence of serine, glycine, and aspartic acid in their composition (Kunz et al., 2016; Tokutake, 1980). The primary structure of sericin in fibroin, depicted as (Gly-Ser-Gly-Ala-Gly-Ala)*n*, is shown in Fig. 17.5a and b. Additionally, a 3D illustration of the fibroin chemical structure and the structural alignment of proteins like *Ser1* and *Ser3* are also presented in Fig. 17.5c and d.

5. Biodegradable materials in biomedical applications

Within the scholarly literature, high-strength implants produced from metal alloys (Simsir et al., 2021; Akkan et al., 2017; Şahin & Öksüz, 2013), bioceramic biomaterials designed in both powder and bulk forms (Öksüz et al., 2019; Özer & Öksüz, 2019; Öksüz & Özer, 2017; Erasmus et al., 2017; Öksüz, 2023), and notably advanced biopolymer-biocomposite materials (Ateş et al., 2023; Bohórquez-Moreno et al., 2023; Öksüz et al., 2023; Öksüz, 2024), have emerged as extensively explored focal points in the realm of tissue engineering. However, biomaterials derived from nonautologous sources inevitably elicit biological responses to varying extents. Core elements of tissue reactions to biomaterials encompass the continuum of tissue response, which commences upon the interaction or implantation of a biomaterial within living tissue. This

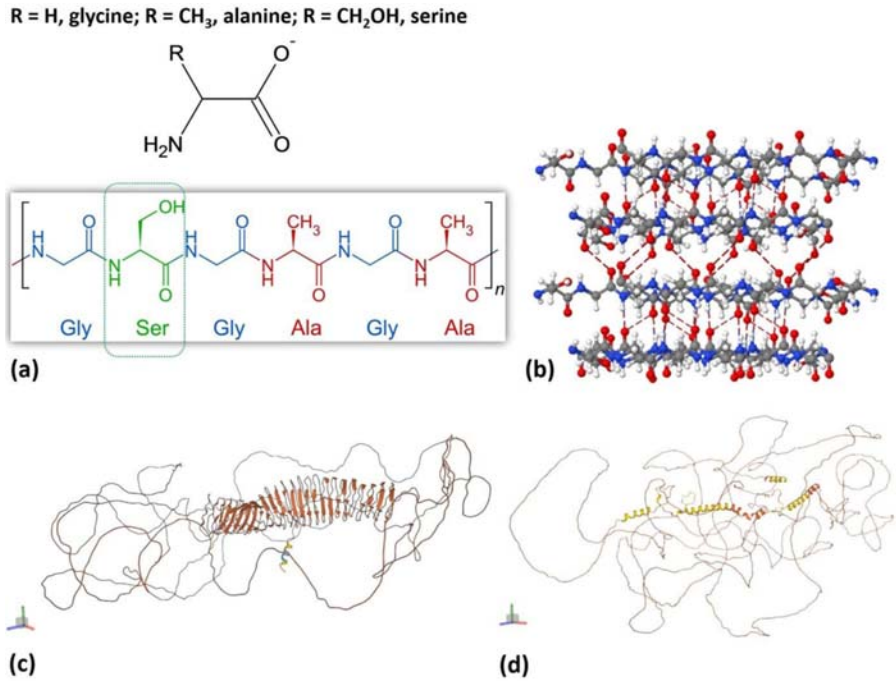


Figure 17.5 (a, b) Primary structure of fibroin (Gly-Ser-Gly-Ala-Gly-Ala)n, The silk produced by silkworms comprises two primary proteins, namely sericin and fibroin, each playing distinct roles in the composition and properties of the silk thread. Among these, fibroin takes on the pivotal role as the structural core of the silk, forming a robust framework. On the other hand, sericin functions as an adhesive substance that encapsulates the fibroin, providing a protective and cohesive layer around it. The fibroin protein is predominantly composed of a sequence of amino acids, including Gly-**Ser**-Gly-Ala-Gly-Ala, which undergoes an intricate folding process resulting in the formation of β-pleated sheets referred to as β-keratin. This folding is stabilized by the establishment of hydrogen bonds between the protein chains, further reinforced by the arrangement of side chains both above and below the plane of the hydrogen bond network. This interplay of molecular interactions contributes to the silks distinctive structural integrity and remarkable properties (c, d). The visualization of molecular structure of *Ser1* and *Ser3* proteins respectively. *Ser1* and *Ser3* proteins are the primary sericins in cocoon silk, while *Ser2* and *Ser4* proteins are predominantly found in noncocoon silk (Guo et al., 2022).

continuous tissue response is comprised of reactions ignited both by the implantation process and the presence of biomaterials (Anderson, 2001). Metallic, ceramic, and polymeric implants have demonstrated successful integration into living tissues, adeptly addressing the demands of contemporary medical practices.

The in vivo evaluation of tissue reactions to biomaterials serves as a means to assess their biocompatibility. Biocompatibility is generally defined as the ability of a biomaterial to elicit an appropriate host response within a given application. The chemical and physical attributes of biomaterials introduced into tissue are crucial factors governing biodegradation levels, influenced by interactions with bodily fluids. The

emergence of environmentally friendly, biodegradable polymers has garnered significant attention, thanks to their applicability in diverse biomedical applications. Subsequent to the implantation process, regarded as one of the most invasive introductions of biomaterials into tissue, host reactions can give rise to undesirable outcomes such as tissue injury, blood-material interactions, transient matrix formation, as well as acute and chronic inflammation. This can lead to the formation of granulation tissue, foreign body reactions, and the development of fibrous capsules. To counter these challenges, meticulous biomaterial design incorporating diverse components is pursued to enhance biocompatibility. The using of silk sericin, a natural polymer produced by silkworms and combined with polymer materials, has expanded its applicability owing to its pronounced clinical advantages in the fields of tissue and bioengineering.

6. Biological challenges and cytotoxicity of sericin

In recent years, the utilization of silk biomaterials in biomedical fields has been accompanied by various biological responses, with a notable focus on allergic reactions, particularly in relation to sericin. Studies conducted in 1984 documented significant reactions when pure silk sutures were employed in cataract surgery for 12 patients (Soong & Kenyon, 1984). These reactions encompassed nodular episcleritis, peripheral corneal ulceration, occasional instances of endophthalmitis, and wound necrosis. Moreover, Type I allergic responses and up-regulated levels of specific IgE were identified in patients undergoing repeated surgical procedures (Kurosaki et al., 1999; Rossitch et al., 1987). Nevertheless, upon the removal of sericin protein from fibroin, purified silk fibroin fibers and films demonstrated comparable biocompatibility to other widely used biomaterials. Also, hypersensitivity reactions to silk have been documented by several researchers, manifesting as respiratory issues like asthma (Celedón et al., 2001). In a study by Wen et al. (1990), the extracted sericin was identified as the trigger for a T-cell mediated allergic response, as demonstrated through skin tests involving 64 asthma children. These findings have led to the attribution of immune responses to sericin rather than the core fibroin protein (Zaoming et al., 1996), resulting in the avoidance of silk sericin in clinical applications. Uff et al. (1995) further observed that soluble factors generated by sonication of native silkworm fibers induced the production of proinflammatory cytokines and enhanced phagocytosis. Nevertheless, subsequent to the elimination of the sericin protein, purified silk fibroin fibers and films displayed a level of biocompatibility akin to that observed in relation to other frequently employed materials. Moreover, they retained many of the inherent qualities inherent to native silk fibers (Santin et al., 1999; Setzen & Williams, 1997). Even polymer based materials-coated silks failed to induce sensitization responses in human subjects (Kurosaki et al., 1999; Soong & Kenyon, 1984). While sericin remains a plausible instigator of these responses, it is plausible that degradation products of fibroin could also potentially contribute to unfavorable biological reactions. Consequently, the utilization of silk sericin, along with other biomaterials, has diminished in the past few decades due to the proliferation of commonly used synthetic materials. Nonetheless, uncertainty persists regarding whether sericin, a water-soluble

protein, truly underpins these biological reactions in humans. Given the prior reports of allergic responses in certain patients potentially linked to silk sericin, comprehensive investigations are imperative to ascertain the safety of this protein.

To address concerns about its reliability as a biomaterial, the production stages of sericin must be thoroughly understood. It has been reported that the amino acid composition in sericin depends on the method used for its synthesis or extraction (Veiga et al., 2020). Apart from glycine, all amino acids exist as two mirror-image structures known as D-(right-handed) and L-(left-handed) enantiomers. While amino acids primarily play roles in protein synthesis and metabolism, D-amino acids have distinct and specific functions across different organisms (Marcone et al., 2019). Research has demonstrated that D-sericin exhibits significant nephrotoxicity in rats, leading to polyuria, diabetes, proteinuria, creatinine accumulation, and histopathological changes in the kidneys, whereas L-sericin at the same doses does not induce nephrotoxicity (Hasegawa et al., 2019). As discussed in the literature, prior studies have indicated that silk may have allergenic effects that can lead to sensitization in humans. Sensitization to silk has been identified as a significant factor in childhood asthma in rural China (Celedón et al., 2001). Additionally, other studies have reported a high prevalence of sensitization to silk allergens and occupational asthma among silk yarn workers (Gowda et al., 2014, 2016). In vivo, eosinophils (EO) are recognized as crucial cells in the immune response and allergic reaction processes. In a recent study Qin et al. (2020) aimed at more rigorously determining the adverse allergic effects of sericin on living organisms, the safety of water-extract sericin obtained from silkworm (*Bombyx mori*) cocoons was tested on Sprague−Dawley rats. Different model approaches were used, including a contact allergy test in guinea pigs, a series of genotoxicity studies, and a 90-day subchronic toxicity study. The results indicated that the eosinophil count in the treatment groups was not significantly different from that of the negative control group in the 90-day subchronic toxicity test, demonstrating that the water-extract sericin had little sensitizing effect on the rats. It was also reported that the water-extract sericin was neither mutagenic nor genotoxic both in vitro and in vivo, and that it exhibited low toxicity under the experimental conditions of the present study.

In recent studies supporting this work, it was suggested that inappropriate referencing has contributed to the perception of adverse biological reactions to sericin and has partially contributed to the misconception regarding sericin's biosafety. In their in vivo experiments, they found that sericin accumulated inflammatory cells at a low level, similar to alginate and fibroin, but much less than chitosan. They reported scientific findings indicating that sericin can actually recruit cells that promote regeneration, such as vascular endothelial (progenitor) cells, and does not trigger an allergic reaction. Sericin demonstrated low and acceptable immunogenicity, leading them to believe that this ancient, natural protein is a bio-safe biomaterial suitable for biomedical applications (Jiao et al., 2017). Meanwhile, the current study by Chen et al. (2021) described a wound dressing formulation utilizing Gold-loaded Dextran/Silk Sericin nanoparticles. The antibacterial efficacy of both Dextran/Silk Sericin and Gold-loaded Dextran/Silk Sericin nanoparticles was evaluated against Gram-positive and Gram-negative microorganisms. Additionally, in vivo wound healing was observed in a mice model over a 16-day period. Compared to untreated wounds, those treated

with Gold-loaded Dextran/Silk Sericin nanoparticles healed more quickly with fewer injuries. These results indicated that Gold-loaded Dextran/Silk Sericin nanoparticle-based dressing material could be a groundbreaking nanomaterial with potential for wound repair and implantations, as demonstrated in an animal model.

Lately, numerous scientists have endeavored to create innovative biomaterials utilizing sericin. This includes applications like wound dressing, tissue engineering, regenerative medicine, and cosmetic products, primarily due to sericins ability to promote collagen (Aramwit, Kanokpanont, De-Eknamkul, Kamei, & Srichana, 2009; Aramwit et al., 2010; Kaewkorn et al., 2012; National Center for Biotechnology Information, 2024a). Sericin boasts a range of favorable traits for biomedical uses, such as being biodegradable, possessing strong moisture absorption, and showing minimal immunogenicity. Yet, beyond these attributes, sericin also displays intriguing bioactive characteristics such as antioxidant properties, pH responsiveness, and the ability to stimulate the growth of mammalian cells, suggesting potential roles in the realm of regenerative medicine.

Sericin-based biomaterials such as hydrogels, biosponges, biocomposites, and films achieved through crosslinking or blending with other polymers or inorganic elements has found utility in tasks like dermal reconstruction and wound dressing for skin tissue repair, bone tissue engineering, and drug delivery systems (Kundu & Kundu, 2012; National Center for Biotechnology Information, 2024b). Given its delicate and gel-like characteristics, it could find increased relevance in dermal or neural contexts. The occurrence of optimal wound healing necessitates a well-coordinated and intricate sequence of cellular and biochemical processes. Effective wound repair hinges on continuous communication among the involved tissues. Within this dynamic environment, cytokines and growth factors assume multifaceted roles that can trigger and shape the wound healing process. Due to sericin proteins role in dermal care, these cytokines and growth factors have been extensively explored in both in vitro and in vivo settings as cellular responses to silk sericin (Kundu & Kundu, 2012; Tosun et al., 2023). Studies of biocompatibility and antioxidant-antibacterial potential, both in vitro and in vivo, have demonstrated that sericin is immunologically inert and have proven the safety and open wide possibility of applications of sericin in biomedicine and tissue engineering.

7. In vitro and in vivo studies on biological responses to silk sericin

In order to explore the biological responses of silk sericin in vitro and in vivo, numerous experiments have been performed in the literature regarding sericin, considering its numerous biological applications such as antimicrobial, UV-protective, anti-aging, antioxidant, hepatoprotective, antiinflammatory, anticancer, antiviral, and wound healing, among others. Additionally, sericin has potential for use in conjunction with high performance engineered nanoparticles for advanced therapeutic applications (Das et al., 2021).

Silk sericin obtained from *B.mori* and combined with hydroxyapatite nanoparticles was investigated for its biocompatibility with human osteogenic sarcoma cell line (SaOS-2). It was also observed that the produced biomaterials increased osteoblast cell proliferation and cytoskeletal organization significantly. Examinations into biocompatibility and antioxidant capabilities, conducted both in vitro and in vivo, have conclusively revealed sericins immunological neutrality. This has firmly established the safety and vast potential for sericins application in the fields of biomedicine and tissue engineering. To examine into the reactions of silk sericin within a controlled environment, numerous experiments have been undertaken across various cell lines in vitro. For instance, sericin extracted from *B.mori*, when combined with hydroxyapatite nanoparticles, underwent scrutiny for its compatibility with the human osteogenic sarcoma cell line (SaOS-2) (Tosun et al., 2023). Furthermore, these investigations revealed a notable enhancement in osteoblast cell proliferation and the substantial organization of the cellular cytoskeleton upon exposure to the produced biomaterials. Additionally, sericin has demonstrated the ability to inhibit lipid peroxidation and tyrosinase activity in vitro (Kato et al., 1998). This effect could potentially be attributed to its notably elevated proportion of hydroxyl amino acids (approximately 40%), particularly serine and threonine, which may facilitate antioxidant actions through the chelation of trace elements like copper and iron. Likewise, research indicates that sericin powder exhibits antioxidative properties and inhibits the activity of tyrosinase (Wu et al., 2007). Substituting the culture medium with a sericin solution derived from the cocoon of the mulberry silkworm *B. mori* led to a substantial increase in cell proliferation percentages within the mouse L929 fibroblastic cell line, particularly notable at higher sericin concentrations (Aramwit, Kanokpanont, De-Eknamkul, & Srichana, 2009). Additionally, the introduction of sericin at concentrations ranging from 0.2 to 1.0 mg/mL into the culture media for alveolar macrophage NR8383 and mouse J774.2 monocyte cell lines resulted in negligible releases of TNF-1α and IL-1β.

The antibacterial activity of sericin-conjugated silver (Ag) engineered nanoparticles (ENPs) on the pathogens *Escherichia coli*, *Staphylococcus aureus*, and *Klebsiella pneumoniae* was evaluated by Tahir et al. (2020). It was reported that sericin-conjugated Ag ENPs significantly reduced the growth of these bacteria. They also demonstrated that the synthesized sericin-conjugated Ag ENPs were stable at different temperatures and pH levels, and were effective against bacteria, suggesting their potential for wide-ranging applications as an economical and stable antimicrobial agent. In a similar study, Lv et al. (2018) synthesized sericin-conjugated Ag ENPs and showed that they have the potential to kill *E. coli* and *S. aureus*. They reported that these conjugated nanoparticles could be a promising antimicrobial agent against sexually transmitted infections. Gentamicin sulfate-conjugated Poly (L-lactic acid)-Sericin hybrid scaffolds were prepared by Pankongadisak et al. (2018). It was reported that these scaffolds were highly effective against *S. aureus TISTR 1466* and *E. coli TISTR 780* pathogens. These sericin-doped biomaterial scaffolds were nontoxic in MC3T3-E1 cell lines (with cell viability ranging between $\sim$84% and $\sim$125%) and could be used as a potential candidate for bone tissue engineering applications.

Shah et al. (2019) developed a novel moxifloxacin-loaded, in situ silver nanoparticle-chitosan-sericin composite dressing using the solvent casting method. In vivo evaluation using a burn-injured rat model showed that the nanocomposite films promoted faster wound healing. Histological analysis revealed enhanced blood vessel formation, epidermal regeneration, and collagen deposition, indicating their effectiveness as wound care materials. Treated groups with sericin exhibited minimal inflammation, fibrosis, fibroblast differentiation into myofibroblasts, neovascularization, and collagen deposition. The inhibitory effects of sericin on UV-induced melanogenesis were investigated by Kumar & Mandal (2019) through the assessment of tyrosinase activity, intracellular melanin content, and ROS levels in mouse melanoma cells. Sericin was found to significantly reduce ROS production and melanin content in UV-irradiated melanocyte cells compared to controls. A skincare formulation incorporating Sericin was prepared, and it was found that sericin did not affect the formulation's flow properties. Sericin was thus identified as an antioxidant with potential applications in skincare cosmetics.

In addition to the aforementioned studies, sericin-based therapeutics are considered a viable treatment option due to sericin's accessibility, low cost, biocompatibility, and biodegradability. Sericin has potential clinical applications in various biomedical fields. Its chemical reactivity and pH-sensitive properties enable the formation of engineered structures such as nanoparticles, hydrogels, and micelles, thereby enhancing drug and cell bioactivity. Sericin-based nanoparticles can be effectively used as carriers for controlled drug or cell release, as they degrade into nontoxic, absorbable products like amino acids and peptides. Due to these properties, sericin has been approved for use in numerous pharmaceutical applications, including solubility enhancers, release regulators, and stabilizing agents as a pure drug carrier (Mathew et al., 2024; Şahin et al., 2023; Shin et al., 2022; Lamboni et al., 2015). In addition to drug and cell delivery, sericin can serve as a contrast agent by being conjugated with specific targeting ligands or imaging probes. This allows for targeted imaging in tissue engineering and other therapeutic applications (Das et al., 2021; Kumar & Abrahamse, 2022).

Sericin-alginate gels were produced by Zhang et al. (2015) that not only delivered myoblast cells but also enhanced their proliferation, migration, and viability. Sericin/dextran hydrogels were used by Liu et al. (2016) to track the breakdown of drug-loaded hydrogels in real-time, utilizing sericin's natural photoluminescence. Drugs were effectively encapsulated in a pH-responsive system by composite metal-organic networks containing sericin microparticles. When doxorubicin-loaded sericin particles were delivered using this method, sustained release in the lungs for several days was achieved, the spread of nodules and lung mass was reduced, and overall mouse health was preserved, suggesting its potential for treating lung metastatic cancer (Liu et al., 2021). This suggests that sericin presence did not induce significant cellular damage. The literature findings validate that sericin exhibits no toxic effects when used as a biomaterial both in vitro and in vivo. Furthermore, these findings underscore the numerous advantages that sericin provides in comparison to other natural or synthetic materials.

8. Immunological response and action mechanisms of sericin in bone grafting

Biocompatibility is a fundamental requirement for any biomedical material. When in contact with the human body, a biomaterial should not cause adverse effects such as an immune response (Cacopardo et al., 2022). Sericin, being an immunologically inert protein, has demonstrated biocompatibility in various studies. The addition of sericin to different cell culture media has shown that it does not promote cytotoxicity, proving it to be a safe biomaterial. Additionally, sericin does not induce immunological responses (Terada et al., 2005).

In the study conducted by Gil et al. (2012), it was demonstrated that sericin does not activate macrophages. Additionally, Chlapanidas et al. (2013) examined the effects of sericin derived from various silkworm strains on peripheral blood mononuclear cells. Their results indicated that sericin from some strains did not alter the secretion levels of tumor necrosis factor-alpha (TNF-α) and interleukin 10 (IL10), but it did reduce the secretion of interferon-gamma (IFN-γ) in vitro. Similarly, Aramwit, Kanokpanont, De-Eknamkul, and Srichana (2009) evaluated the inflammatory response to a sericin-based cream applied to wounds in rats and observed a significant decrease in interleukin 1 beta (IL-1β) and TNF-α levels after 7 days. These findings collectively support the conclusion that sericin is a biocompatible material that does not elicit severe immune responses.

Silk mats produced from the silkworm cocoon of *Bombyx mori* and designed as biomaterials contain various proteins, including sericin. When these sericin-containing silk mats were used as membranes for bone regeneration, they exhibited new bone formation comparable to that of collagen membranes (Jo et al., 2017). When the silk mat was immersed in phosphate buffered saline (PBS), soluble fragments were released into the solution. After determining the protein concentration, this solution was applied to macrophages, and cDNA microarray analysis was used to examine differentially expressed genes (Kim et al., 2018). Among the genes analyzed, bone morphogenetic protein-2 (BMP-2) expression was increased by the application of the sericin-containing silk mat-derived solution (Kim et al., 2018). BMP-2 is a potent osteogenic protein (Han et al., 2021), and it is hypothesized that a protein present in this solution may stimulate macrophages to secrete BMP-2. The graphical illustration of this hypothesis is shown in Fig. 17.6.

Isolating this protein could potentially be advantageous for bone regeneration therapy. By applying different degumming temperatures, it is possible to obtain various protein profiles from silk cocoons (Jo et al., 2021). Based on their molecular weights, these proteins can be classified into specific groups (Jo et al., 2021). Through this process, the protein in silk that induces BMP-2 was identified as sericin (Jo et al., 2021). Sericin, an insect-derived protein, is regarded as a foreign protein by mammals (Kim, 2021). Foreign proteins typically trigger immune responses when immune cells detect them through pattern-recognizing receptors, such as Toll-like receptors (TLRs). When sericin is applied to macrophages, it is recognized by the TLRs on these immune cells (Jo et al., 2021; Kim, 2021).

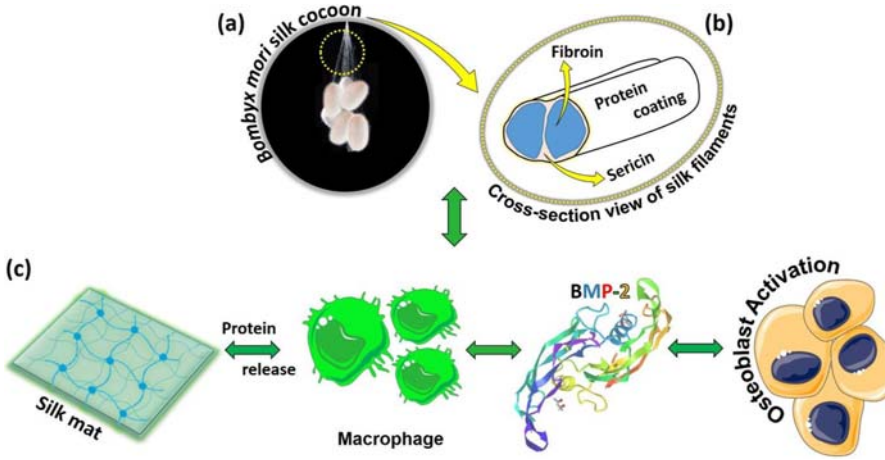


Figure 17.6 (a) Real photographs of *Bombyx mori* cocoon silk, (b) schematic illustration of the structure of the raw silk fiber. The silkworm cocoon is composed of a long filament of silk, consisting of fibroin encased in a thin layer of sericin. (c) Schematic illustration of the mechanism of sericin action in an in vivo environment. The silk mat, containing natural protein compositions derived from the silkworm cocoon, releases a soluble protein fraction when immersed in PBS. The sericin protein present in the solution triggers the release of BMP-2 from macrophages, which stimulates osteoblasts. This process enhances bone regeneration, thereby accelerating new tissue formation.

As a result, the BMP-2-inducing effect of sericin is facilitated by the TLRs present on macrophages (Kim, 2021). It is significant to recognize that TLRs are pattern-recognition receptors; thus, the structural conformation of sericin protein might influence the expression levels of BMP-2 (Jo et al., 2021; Lee et al., 2022). The potential role of sericin in inducing BMP-2 expression is significant in elucidating its capability for new bone tissue formation (Kim et al., 2018). Understanding the interaction between sericin protein and TLRs will pave the way for novel approaches in biomedical applications.

The degumming process significantly affects the conformation of sericin, a protein derived from silk. It has been observed that degumming at temperatures below 65°C results in a greater abundance of β-sheet structures compared to temperatures above 100°C (Jo et al., 2021). This β-sheet conformation enhances sericin's ability to induce BMP-2 expression in macrophages. However, low-temperature degumming yields less sericin than high-temperature methods. To overcome this, alternative degumming solutions such as 70% ethanol, formic acid, and 2% 4-hexylresorcinol have been found effective in producing sericin with a high content of β-sheet structures (Jo & Um, 2015). These solutions stabilize the protein at high temperatures, promoting the formation of β-sheets, which are crucial for the mechanical properties and stability of sericin-based materials (Lee et al., 2022).

Immunomodulation, a tissue engineering technique, uses molecules to direct the immune response. In bone tissue regeneration, macrophages within bone tissue are

essential (Weivoda & Bradley, 2023). Sericin, a protein from silk, has been observed to induce BMP-2 expression in macrophages, which in turn stimulates and activates resting osteoblasts. Co-culture experiments demonstrated that sericin activates osteoblasts when administered to macrophages (Jo et al., 2021). Additionally, implanting a sericin-incorporated gelatin sponge into a bone defect resulted in higher new bone formation and increased BMP-2 expression compared to using a gelatin sponge alone (Jo et al., 2021; Lee et al., 2022).

These studies and findings underscore the importance of understanding the complex structure and mechanisms of action of sericin in biological environments, particularly in its application as a bone graft material. Further research is needed to elucidate the fundamental mechanisms responsible for BMP-2 expression among *B. mori* subspecies.

9. Conclusions

Sericin, a natural polymer silk protein, exhibits a range of biological characteristics evident both in vitro and in vivo. These attributes encompass compelling antioxidant, antityrosinase, and antiinflammatory effects. Additionally, sericin demonstrates the remarkable capability to stimulate and enhance the proliferation of cells, promoting tissue growth and regeneration. Sericin impacts several biological processes, including cell adhesion and proliferation, tissue repair (such as for skin, bones, and joints), and exhibits antioxidant, antiinflammatory, antimicrobial, and antitumor properties, among others. The effectiveness of these actions relies on various factors, including the protein's structural characteristics (such as molecular weight range, chemical structure, and purity) and the production and release of signaling molecules. Previous research suggests a potential connection between silk sericin and excessive sensitivity reactions observed in humans when exposed to silk-based materials. This intriguing connection continues to stimulate exploration and investigation into the complex interactions between sericin and human biological systems. In summary, the literature review indicates that the early studies suggesting adverse biological reactions to sericin were later cited as primary references to substantiate claims of sericin's harmful effects. This improper referencing has, in part, contributed to the misunderstanding about sericin's biosafety. As highlighted in this book chapter, sericin possesses distinctive properties that render it highly suitable for various biomedical and pharmaceutical applications. One of the most investigated strategies involves incorporating sericin into drug delivery systems such as films, nanoparticles, foams, hydrogels, fibers, biocomposites, wound dressings, and other biomaterials. Sericin has also been extensively utilized in tissue engineering, particularly for bone tissue engineering, wound healing, tissue repair, and skin re-epithelialization. Overall, sericin supports the design and development of cost-effective, biocompatible, and biodegradable products. Additionally, sericin offers significant advantages over other natural biomaterials due to its ease of functionalization with other biomaterials. This book chapter provides insights synthesized from in vitro, in vivo, and clinical investigations, collectively indicating that silk sericin possesses a nonallergenic nature and can be

considered safe for use as a biomaterial within biomedical applications. However, caution is advised when employing sericin in conjunction with fibroin, a fibrous protein found in silk cocoons, due to the potential generation of biological reactions that could pose a threat to human cells.

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Enrichment of silk sericin and its carbonized derivatives for wastewater treatment

18

Xiaoning Zhang and Can Huang
State Key Laboratory of Resource Insects, College of Sericulture, Textile and Biomass Sciences, Southwest University, Chongqing, China

1. Introduction

Silk sericin (SS) is a globular protein that encases silk fibers, accounting for approximately 15%−35% of the total cocoon weight. In the commercial silk industry, cocoons must be degummed to produce soft silk filaments, resulting in the release of unutilized sericin into wastewater (Wang et al., 2024). Annually, around 400,000 tons of dried cocoons are produced worldwide, leading to at least 50,000 tons (12.5%) of degumming wastewater containing sericin. Discarding SS without proper treatment can cause significant environmental and ecological issues, primarily due to its low molecular weight and high solubility in water, which make its enrichment challenging (Ji et al., 2022). Therefore, finding an effective method to enrich SS from wastewater holds substantial economic and social benefits.

Recently, the rapid growth of manufacturing and textile industries has brought attention to water pollution from dyeing processes. Effluent containing organic dyes and heavy metal ions, if not properly treated, can severely contaminate water resources, harm aquatic life, and pose risks to human health. Various techniques, such as adsorption, membrane separation, electrocoagulation, chemical precipitation, microbial treatment, and photocatalytic degradation, have been employed to remove dyes and heavy metals from wastewater (Ahmed et al., 2022; Qasem et al., 2021; Velusamy et al., 2021). Among these, adsorption is favored for its simplicity and cost-effectiveness.

Several studies have explored the use of discarded SS for removing organic dyes and heavy metals from water. For instance, researchers fabricated hierarchical biohybrid structures from sericin and hydroxyapatite (HAP), which exhibited excellent adsorption capabilities for toxic metals like Pb(II), Cd(II), and Hg(II), and the dye Congo red, due to their large surface area and the chemical properties of sericin and HAP (Koley et al., 2016). Another study by Arnusch and colleagues used a sericin−chitosan conjugate to remove hexavalent chromium (Cr(VI)) and methyl orange (MO) from aqueous solutions. The adsorbent, created by crosslinking sericin with chitosan using glutaraldehyde, showed high adsorption capacities of 139 mg/g for Cr(VI)

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and 385 mg/g for MO, demonstrating its potential as an efficient and eco-friendly solution for industrial wastewater treatment (Singh et al., 2018).

Utilizing SS as a source for adsorbent fabrication presents a sustainable and cost-effective solution for water pollution. Since sericin is a by-product of the silk industry and is typically considered waste, repurposing it into valuable adsorbents not only addresses waste management issues but also reduces the cost associated with producing adsorbents.

However, despite these promising applications, the high water solubility of SS remains a significant challenge. This solubility can cause sericin to dissolve during the adsorption process, reducing its effectiveness. Addressing this issue is crucial for the practical and sustainable use of SS-derived adsorbents. Silva and colleagues investigated particles made from SS and alginate blends for copper and zinc removal. They found that thermal drying improved the cross-linking process, reducing water solubility and increasing adsorption capacity (da Silva et al., 2016; Dusi et al., 2022).

Carbonization, an intense thermal treatment, offers a potential solution by increasing the stability of SS in water. During carbonization, high-temperature pyrolysis removes volatile components, leaving a carbon-rich solid residue. These carbon-based materials typically have high surface areas, porous structures, and enhanced chemical stability, making them less likely to dissolve in water (Soffian et al., 2022).

Jin and colleagues explored the use of sericin-derived activated carbon (S-AC) embedded in alginate beads for methylene blue (MB) removal from water. The S-AC, prepared through thermal carbonization with NaOH activation, had a high surface area of 2150.1 m^2/g. The S-AC/alginate beads maintained a significant surface area and demonstrated high adsorption capacity, removing 502.5 mg/g of MB. These beads exhibited robust reusability, retaining 90.1% of their adsorption efficiency after five cycles (Kwak et al., 2018).

Kwak and colleagues developed a nitrogen-rich magnetic bioactivated carbon from SS for effective anionic dye removal. Using a one-step chemical activation and carbonization process, they produced N-doped activated carbon with a high surface area of 3289.1 m^2/g. The addition of magnetic nanoparticles enhanced the separation efficiency and adsorption capacity for methyl orange, achieving 869.57 mg/g with a faster removal rate compared to nonmagnetic counterparts (Hong et al., 2020).

Although it aligns with several sustainable development goals (SDGs), including responsible consumption and production (SDG 12) and clean water and sanitation (SDG 6) (United Nations, 2024), the application of carbonization to convert SS into carbon-based materials for environmental applications is not widely reported. Additionally, it should be noted that none of above studies address the enrichment of SS from aqueous solutions. Our research team has recently reported a method to enrich SS from aqueous solutions, converting the SS-based composite into carbonaceous materials for water pollution treatment. The chapter will not only discusses the preparation and application of sericin-derived materials but also addresses the challenges of enriching sericin from wastewater. It is our hope that the comprehensive approach provides a thorough understanding of the entire process, from raw material sourcing to final application, which is beneficial for both academic and industrial readers.

2. Silk sericin enrichment through electrodeposition

20 g of silkworm cocoons were stirred with 500 mL of deionized water at 100 rpm for 2 hours. The mixture was then autoclaved at 120°C for 1 hours and allowed to cool to room temperature. After filtration and freezing, the solution was lyophilized to obtain SS powder.

The pH of the CMCS solution was adjusted to 12 using a 5 M sodium hydroxide solution. The SS solution was then mixed with the CMCS solution for 4 hours at 25°C. As low temperatures promote the formation of hydrogen bonds among the solution components (Li et al., 2024), the prepared SS/CMCS mixture was stored in a refrigerator at 4°C overnight to facilitate hydrogen bond formation between SS and CMCS molecules.

An electrochemical workstation with a three-electrode setup was used to fabricate the SS/CMCS hydrogel. The setup included a graphite electrode (working electrode), an Ag/AgCl electrode (reference electrode), and a platinum electrode (counter electrode).

To fabricate the SS/CMCS hydrogel, the electrodes were immersed in the SS/CMCS aqueous solution containing 0.5% (w/v) NaCl. A direct current (DC) voltage was applied using an amperometric I-t curve method. The formed hydrogel was gently peeled from the graphite electrode and rinsed three times with deionized water for 15 minutes to remove any residuals. The gelation parameters were optimized and are detailed below.

2.1 Determination of CMCS concentration

A 4% (w/v) solution of SS was selected for gel preparation, and the impact of varying CMCS concentrations on gelation was systematically examined. At a CMCS concentration of 0.1% (w/v), a gel-like precipitate was observed floating on the solution surface (Fig. 18.1a). This newly formed hydrogel could not be retained by the electrode due to insufficient electrostatic attraction, attributed to the low concentration of negatively charged CMCS molecules within the gel matrix. Additionally, the hydrophilic nature of SS contributed to the dispersion of the hydrogel into the solution.

When the CMCS concentration was increased to 0.2% (w/v), the hydrogel's outline within the solution became discernible (Fig. 18.1b). Further increases in CMCS concentration resulted in increased hydrogel thickness. Although the hydrogel remained transparent, a progressive darkening in color was noted with higher CMCS concentrations (c-e), indicating the formation of a denser gel structure.

Moreover, it was observed that hydrogels formed at CMCS concentrations ranging from 0.1% to 0.4% (w/v) tended to detach from the graphite electrode upon removal from the SS/CMCS mixture, as illustrated in Fig. 18.1f–i. This detachment was detrimental to the efficient separation of the hydrogel from the liquid phase. Conversely, at a CMCS concentration of 0.5% (w/v), the hydrogel demonstrated strong adhesion to the graphite electrode, facilitating easy separation from the SS/CMCS mixture (Fig. 18.1j). Consequently, a CMCS concentration of 0.5% (w/v) was deemed optimal for the preparation of SS/CMCS hydrogel.

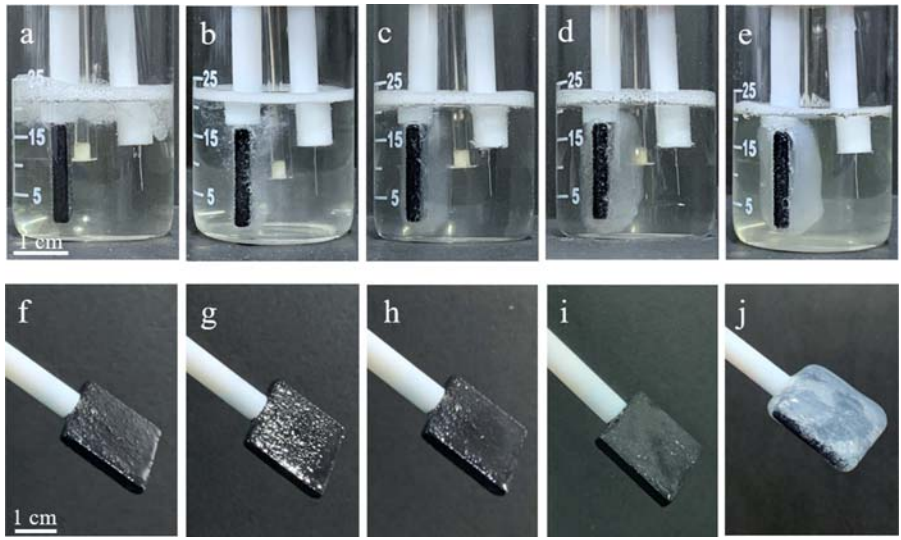


Figure 18.1 The effect of CMCS concentration on the gelation, the concentration of CMCS is (a) 0.1% (w/v), (b) 0.2% (w/v), (c) 0.3% (w/v), (d) 0.4% (w/v), (e) 0.5% (w/v); the electrodes in (f)−(j) corresponds to those in (a)−(e) respectively, and the photos were captured once the electrodes were lifted from the SS/CMCS mixture, after the gelation.
From Ji, Y., Zhang, X., Chen, Z., Xiao, Y., Li, S., Gu, J., Hu, H., & Cheng, G. (2022). Silk sericin enrichment through electrodeposition and carbonous materials for the removal of methylene blue from aqueous solution. *International Journal of Molecular Sciences*, *23*(3). https://doi.org/10.3390/ijms23031668.

2.2 Determination of driving voltage for gelation

The influence of driving voltage on the gelation of a 4% SS/0.5% CMCS solution was systematically investigated. At a driving voltage of 1 V, no hydrogel formation was observed on the graphite electrode surface (Fig. 18.2a). Increasing the driving voltage to 2 V resulted in the formation of a thin hydrogel layer on the electrode surface (Fig. 18.2b). When the driving voltage was further increased to 3 V, a thick and dense hydrogel was observed on the graphite electrode surface (Fig. 18.2c). Based on these observations, a driving voltage of 3 V was selected as the optimal condition for the preparation of SS/CMCS hydrogel.

2.3 Determination of electrodeposition time

The influence of electrodeposition time (1 minutes, 3 minutes, 5 minutes, and 7 minutes) on the gelation process was systematically studied. As depicted in Fig. 18.3, an increase in electrodeposition time resulted in a corresponding increase in the thickness of the SS/CMCS hydrogel. However, when the electrodeposition time was extended to 7 minutes (Fig. 18.3d), the hydrogel formed on the graphite

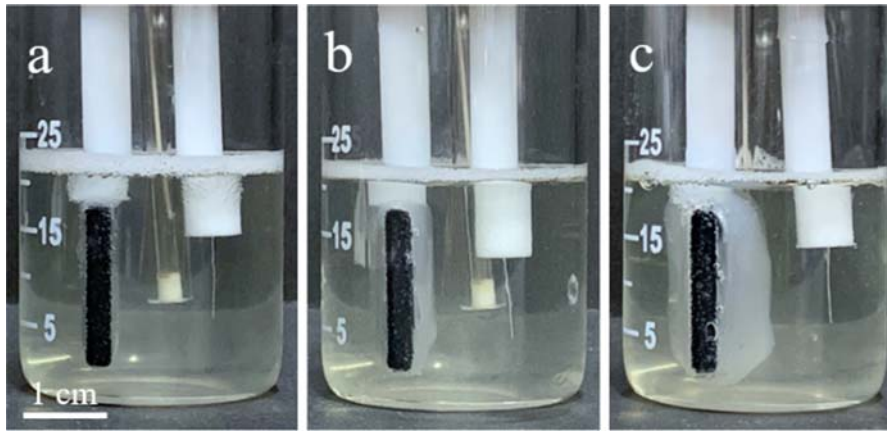


Figure 18.2 The effect of driving voltage on the gelation: (a) 1 V, (b) 2 V, and (c) 3 V.
From Ji, Y., Zhang, X., Chen, Z., Xiao, Y., Li, S., Gu, J., Hu, H., & Cheng, G. (2022). Silk sericin enrichment through electrodeposition and carbonous materials for the removal of methylene blue from aqueous solution. *International Journal of Molecular Sciences*, *23*(3). https://doi.org/10.3390/ijms23031668.

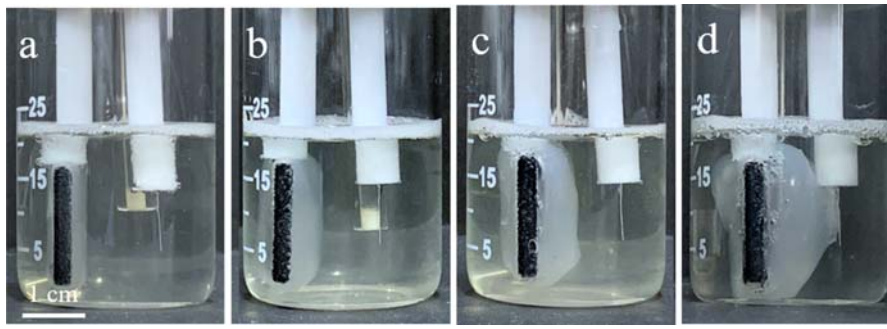


Figure 18.3 The effect of electrodeposition time on the gelation: (a) 1 minutes, (b) 3 minutes, (c) 5 minutes, and (d) 7 minutes.
From Ji, Y., Zhang, X., Chen, Z., Xiao, Y., Li, S., Gu, J., Hu, H., & Cheng, G. (2022). Silk sericin enrichment through electrodeposition and carbonous materials for the removal of methylene blue from aqueous solution. *International Journal of Molecular Sciences*, *23*(3). https://doi.org/10.3390/ijms23031668.

electrode surface made contact with the platinum electrode, potentially compromising the hydrogel's structural integrity and properties. Based on these observations, an optimal electrodeposition time of 5 minutes was selected for the fabrication of SS/CMCS hydrogel.

2.4 Evaluation of SS content in SS/CMCS hydrogel

The mass percentage of SS(n%) in the SS/CMCS hydrogel was quantified using the Bradford assay (Chen et al., 2021). Initially, a 1% CMCS solution was prepared and designated as solution A. From this solution, CMCS hydrogel was synthesized according to the procedures described in Sections 2.1−2.3. The remaining CMCS solution was labeled as solution B. Subsequently, SS solutions with varying concentrations (40%, 20%, 10%, 5%, 2.5%, 1.25%, and 0.625% w/v) were mixed with solutions A and B in a 1:1 volume ratio, respectively. Following an eightfold dilution, 5 μL of each sample was mixed with 250 μL of Brilliant Blue G-250 dye to determine the SS concentration and generate a standard curve for SS in different matrices, both pre- and postgelation (Fig. 18.4). Absorbance measurements were conducted using a microplate reader at 595 nm.

The mass percentage of SS in the SS/CMCS hydrogel was calculated using Eq. (18.1):

$$n\% = \frac{(C_1V_1 - C_2V_2)}{m} \times 100\% \tag{18.1}$$

where C_1 and C_2 represent the concentrations (mg/mL) of SS in the SS/CMCS mixture before and after gelation; V_1 and V_2 are the volumes (mL) of the SS/CMCS mixture before and after gelation, respectively; C_1V_1 and C_2V_2 represent the mass (mg) of SS in

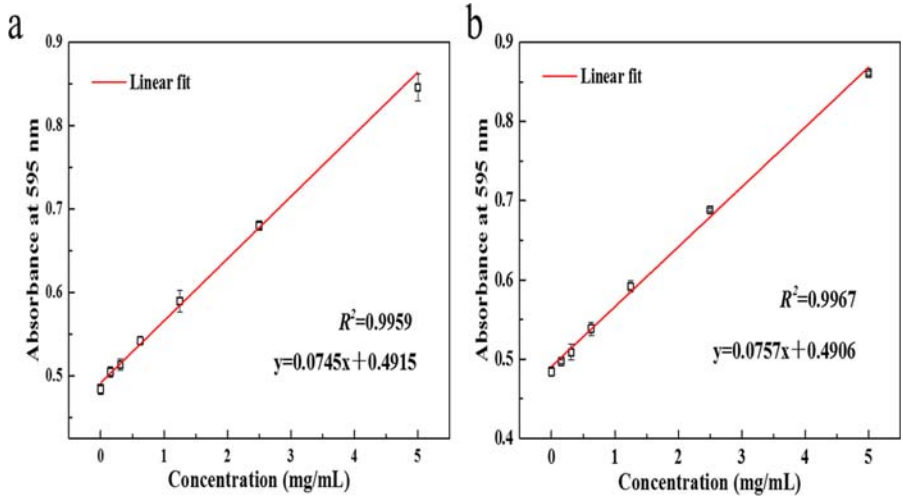


Figure 18.4 The standard curves of SS content in SS/CMCS mixture (a) before and (b) after gelation.
From Ji, Y., Zhang, X., Chen, Z., Xiao, Y., Li, S., Gu, J., Hu, H., & Cheng, G. (2022). Silk sericin enrichment through electrodeposition and carbonous materials for the removal of methylene blue from aqueous solution. *International Journal of Molecular Sciences, 23*(3). https://doi.org/10.3390/ijms23031668.

the SS/CMCS mixture before and after gelation; $(C_1V_1-C_2V_2)$ represents the mass (mg) of SS in the SS/CMCS hydrogel; and m is the mass (mg) of freeze-dried hydrogel.

Table 18.1 illustrates that the SS content in the SS/CMCS hydrogel was quantified as $77.12 \pm 3.48\%$ using the Bradford assay, confirming that SS is the predominant component of the hydrogel.

2.5 Determination of intermolecular interactions in SS/CMCS hydrogel

The viscosities of the 8% SS solution, 1% CMCS solution, and the mixture containing 4% SS and 0.5% CMCS (4% SS/0.5% CMCS) were evaluated using a viscometer with a 48 mm parallel plate at a shear rate of 50 rpm and a temperature of 25°C. All samples were equilibrated in the viscometer for 5 minutes to ensure consistent temperature.

The viscosity measurements aimed to investigate the intermolecular interactions between SS and CMCS molecules. The results are shown in Table 18.2.

The viscosity of the mixture can be theoretically determined by the Arrhenius equation (Chen et al., 2021):

$$\ln \eta_m = \phi_1 \ln \eta_1 + \phi_2 \ln \eta_2 \tag{18.2}$$

where η_m is the theoretical viscosity of the mixture (mpa·s), η_i is the viscosity of the pure component i (mpa·s), and ϕ_i is the volume fraction of component i (v/v).

According to Eq. (18.2), the theoretical viscosity of the SS/CMCS mixture was 3.03 mPa s, which was less than the experimentally obtained value of 3.72 mPa s. This discrepancy suggests interactions between the SS and CMCS molecules in the mixture (Stefanovic et al., 2017). At a pH of 7.48 (the pH of the prepared SS/CMCS solution), the carboxyl groups (pKa = 4.53 [Kalliola et al., 2018]) and amino groups (pKa = 5.93 [Morandim-Giannetti et al., 2019]) of CMCS were deprotonated, resulting in negatively charged CMCS molecules. Additionally, the isoelectric point of SS molecules is around a pH of 4 (Zhang et al., 2019), indicating that SS molecules also carried negative charges. Thus, electrostatic interactions are unlikely to be the primary interaction between SS and CMCS molecules.

However, polar functional groups such as the amino and carboxyl groups of both SS and CMCS may form hydrogen bonds, leading to crosslinking among SS and CMCS molecules. It has been reported that the formation of hydrogen bonds between the components of a mixture can increase viscosity (Li et al., 2024). Therefore, we hypothesize that intermolecular hydrogen bonds form between SS and CMCS molecules, resulting in crosslinking and increased viscosity of the mixture.

The FTIR spectra of freeze-dried SS solution, CMCS hydrogel, and SS/CMCS hydrogel were recorded to elucidate the composition and potential interactions between SS and CMCS molecules within the hydrogel matrix. As illustrated in Fig. 18.5, the SS solution exhibited characteristic absorption peaks at 1655, 1541,

Table 18.1 Measurement of SS content in SS/CMCS hydrogel.

Sample number	Before gelation		After gelation		Weight of hydrogel (mg)	SS content (%)
	SS concentration (mg/mL)	Volume (mL)	SS concentration (mg/mL)	Volume (mL)		
1	38.87	20	36.84	16.20	222.98	80.99
2	38.70	20	37.45	16.10	230.38	74.25
3	38.49	20	37.20	15.80	239.12	76.13
Average	38.69	20	37.16	16.03	230.83	77.12
Standard deviation	0.19	0	0.31	0.21	8.08	3.48

Ji, Y., Zhang, X., Chen, Z., Xiao, Y., Li, S., Gu, J., Hu, H., & Cheng, G. (2022). Silk sericin enrichment through electrodeposition and carbonous materials for the removal of methylene blue from aqueous solution. *International Journal of Molecular Sciences, 23*(3). https://doi.org/10.3390/ijms23031668

Table 18.2 The viscosity of solutions and the mixture.

Samples	Viscosity (mpa·s)
8% SS solution	1.82 ± 0.02
1% CMCS solution	5.04 ± 0.02
4% SS/0.5% CMCS mixture	3.72 ± 0.01

From Ji, Y., Zhang, X., Chen, Z., Xiao, Y., Li, S., Gu, J., Hu, H., & Cheng, G. (2022). Silk sericin enrichment through electrodeposition and carbonous materials for the removal of methylene blue from aqueous solution. *International Journal of Molecular Sciences, 23*(3). https://doi.org/10.3390/ijms23031668

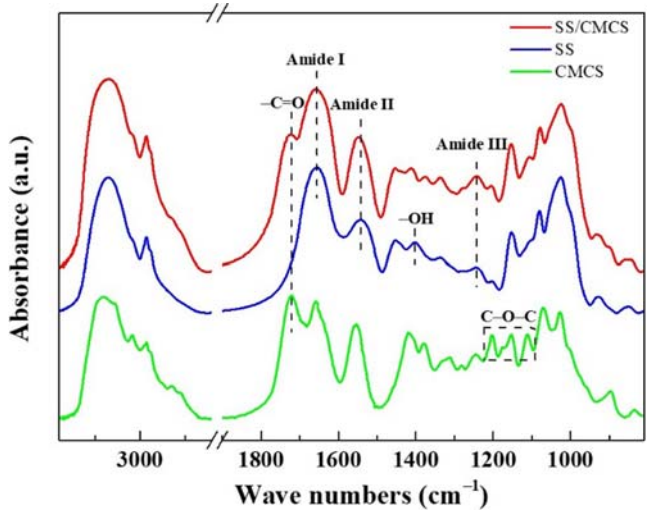


Figure 18.5 The FTIR spectra for freeze-dried SS solution, CMCS hydrogel, and SS/CMCS hydrogel.
From Ji, Ji, Y., Zhang, X., Chen, Z., Xiao, Y., Li, S., Gu, J., Hu, H., & Cheng, G. (2022). Silk sericin enrichment through electrodeposition and carbonous materials for the removal of methylene blue from aqueous solution. *International Journal of Molecular Sciences, 23*(3). https://doi.org/10.3390/ijms23031668.

and 1243 cm^{-1}, corresponding to amide I, amide II, and amide III bands, respectively (Zhang et al., 2017).

The CMCS hydrogel displayed distinct absorption bands at 1723 cm^{-1} (C═O stretching) (Song et al., 2018), 1556 cm^{-1} (N−H bending) (VAGHANI et al., 2012), 1027 cm^{-1} (O−H stretching), and in the range of 1200−1080 cm^{-1} (asymmetric stretching of C−O−C glycosidic linkages) (Dara et al., 2020). The FTIR spectrum of the SS/CMCS hydrogel revealed the presence of characteristic peaks from both SS and CMCS, confirming the incorporation of both components into the hydrogel structure.

Furthermore, a shift to higher wavenumbers was observed for the amide I and amide II bands in the SS/CMCS hydrogel, moving from 1655 to 1659 cm^{-1} and from 1541 to 1548 cm^{-1}, respectively, compared to the SS spectrum. Such shifts in amide band positions indicate the formation of intermolecular hydrogen bonds (Pabboj et al., 2024). Therefore, these observed shifts suggest that hydrogen bonding interactions occur between SS and CMCS molecules within the hydrogel network.

2.6 Evaluation of thermal stability

The thermal degradation behavior of SS, carboxymethyl chitosan (CMCS), and their composite hydrogel (SS/CMCS) was investigated using thermogravimetric analysis (TGA). As illustrated in Fig. 18.6a, the TGA curves for both the freeze-dried SS/CMCS hydrogel and the SS solution exhibit a similar spectral pattern. This resemblance is likely due to the predominant presence of SS in the SS/CMCS hydrogel.

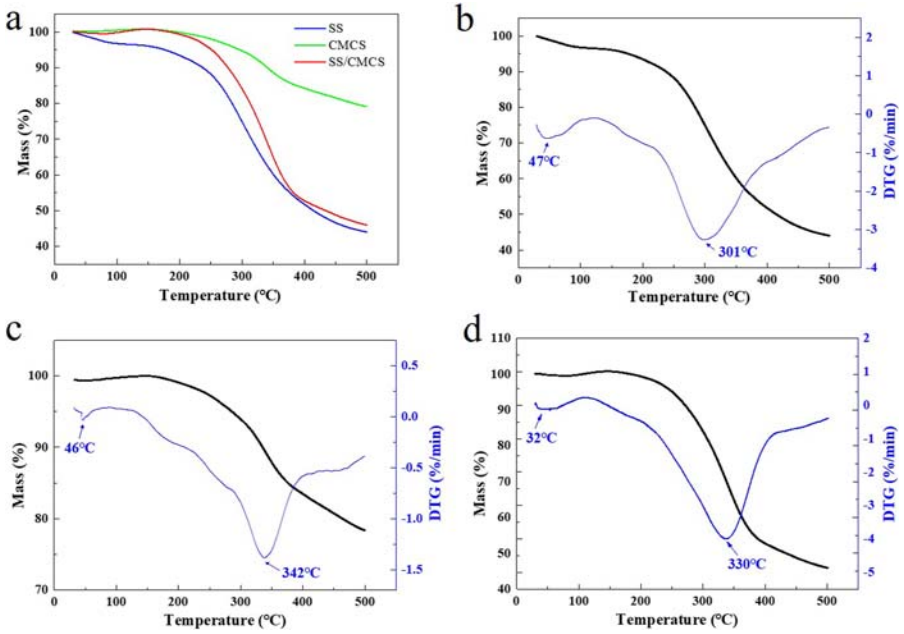


Figure 18.6 (a) TGA curves for the decomposition of freeze-dried SS solution, CMCS hydrogel, and SS/CMCS hydrogel; TGA-DTG profiles for freeze-dried (b) SS solution, (c) CMCS hydrogel, and (d) SS/CMCS hydrogel.
From Ji, Y., Zhang, X., Chen, Z., Xiao, Y., Li, S., Gu, J., Hu, H., & Cheng, G. (2022). Silk sericin enrichment through electrodeposition and carbonous materials for the removal of methylene blue from aqueous solution. *International Journal of Molecular Sciences, 23*(3). https://doi.org/10.3390/ijms23031668.

In Fig. 18.6b–d, the derivative thermogravimetry (DTG) curves reveal an initial mass loss within the temperature range of 30–120°C, attributable to the vaporization of adsorbed moisture. Subsequently, significant and rapid mass losses occur between 120 and 500°C, representing the thermal degradation via pyrolysis of the samples.

The maximum thermal decomposition (DTG_{max}) temperature is a critical parameter that corresponds to the temperature at which the highest rate of thermal degradation occurs, serving as an essential metric for assessing and comparing the thermal stability of the samples (Gairola et al., 2023). The DTG_{max} temperatures for SS and CMCS were determined to be 301 and 342°C, respectively. The DTG_{max} temperature of the SS/CMCS hydrogel was found to be 330°C, indicating that the thermal stability of the SS/CMCS hydrogel is lower than that of CMCS but higher than that of SS. This intermediate DTG_{max} temperature is attributed to the incorporation of SS, which reduces the crystallinity of CMCS.

Based on the findings of this study, it is hypothesized that SS forms crosslinks with CMCS via hydrogen bonding. These crosslinked complexes are then electrodeposited onto the anode, resulting in the formation of the composite hydrogel (Fig. 18.7).

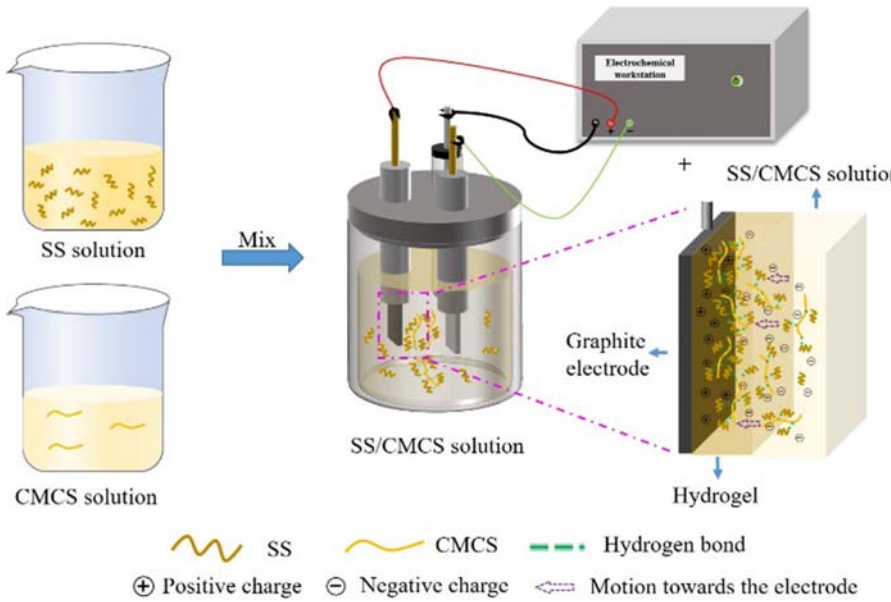


Figure 18.7 The proposed mechanism of the gelation process.
From Ji, Y., Zhang, X., Chen, Z., Xiao, Y., Li, S., Gu, J., Hu, H., & Cheng, G. (2022). Silk sericin enrichment through electrodeposition and carbonous materials for the removal of methylene blue from aqueous solution. *International Journal of Molecular Sciences, 23*(3). https://doi.org/10.3390/ijms23031668.

3. Preparation and characterization of SS-derived carbon

The freeze-dried hydrogel underwent carbonization in a tube furnace following a precise thermal protocol: initially, the samples were heated from ambient temperature to 150°C at a rate of 10°C/minutes and held for 120 minutes under a nitrogen atmosphere to eliminate absorbed moisture. Subsequently, the temperature was increased to 350°C at a rate of 5°C/minutes and maintained for 180 minutes. Further heating ensued, with the temperature raised from 350 to 850, 950, or 1050°C at a rate of 2°C/minutes and held for 120 minutes to facilitate the development of graphitic structures (Wang et al., 2016). Postcarbonization, the samples were rinsed with deionized water heated to 60°C until the rinse water achieved a neutral pH. The samples were then freeze-dried and stored in desiccators for future use. The resulting samples were designated as SCY, where *Y* denotes the final carbonization temperature.

SEM imaging (Fig. 18.8) was employed to examine the morphological evolution of the freeze-dried hydrogel and its carbonized derivatives at various temperatures. The SS/CMCS hydrogel surface (Fig. 18.8a) displayed an irregular, reticular, and porous architecture, indicative of intermolecular crosslinking between CMCS and SS molecules. Fig. 18.8b–f illustrates that increasing pyrolysis temperatures led to a progressively more developed pore structure. As the pyrolysis temperature rose from 450°C to 1050°C, the pore size on the surfaces of SC450, SC650, SC850, and SC1050

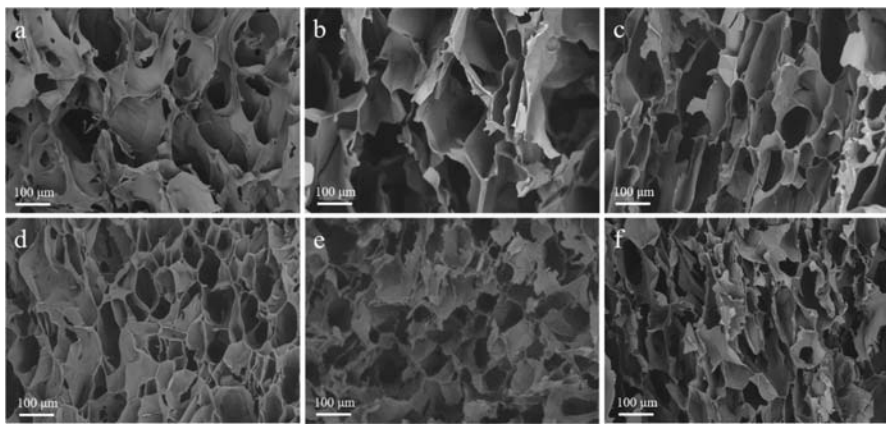


Figure 18.8 Representative SEM images of (a) SS/CMCS hydrogel, (b) SC450, (c) SC650, (d) SC850, (e) SC950, and (f) SC1050.
From Ji, Y., Zhang, X., Chen, Z., Xiao, Y., Li, S., Gu, J., Hu, H., & Cheng, G. (2022). Silk sericin enrichment through electrodeposition and carbonous materials for the removal of methylene blue from aqueous solution. *International Journal of Molecular Sciences, 23*(3). https://doi.org/10.3390/ijms23031668; Xiao, Y., Luo, R., Ji, Y., Li, S., Hu, H. & Zhang, X. (2022). Removal of copper(II) from aqueous environment using silk sericin-derived carbon. *International Journal of Molecular Sciences* (Vol. 23, Issue 19). https://doi.org/10.3390/ijms231911202.

diminished, and the pore structure became more densely packed. This observation can be attributed to the continuous contraction of the carbon framework with elevated heat treatment temperatures (Meng et al., 2014).

4. Dye adsorption experiments

Methylene blue, a widely utilized dye in the textile industry, was selected as a model molecule to study the adsorption properties of SS-derived carbon on organic dyes.

4.1 Effect of MB initial concentration

The initial dye concentration is a crucial factor that enhances the adsorption properties of adsorbents for dye molecules (Bellaj et al., 2024). To investigate this, experiments were conducted with initial methylene blue (MB) concentrations of 5, 10, 20, 40, 80, 120, 160, and 200 mg/L. The pH of the mixture was adjusted to 7 and maintained at 25°C in an incubator set to 150 rpm. As shown in Fig. 18.9, the adsorption capacity of all SC samples increased with the rise in initial MB concentration within the range of 5−80 mg/L. This increase can be attributed to the greater driving force of higher initial MB concentrations, which helps overcome the mass transfer resistance of MB between the aqueous and solid phases (Abd El-Monaem et al., 2024). Fig. 18.10 shows that the color of the MB solution turned transparent or light blue after the adsorption

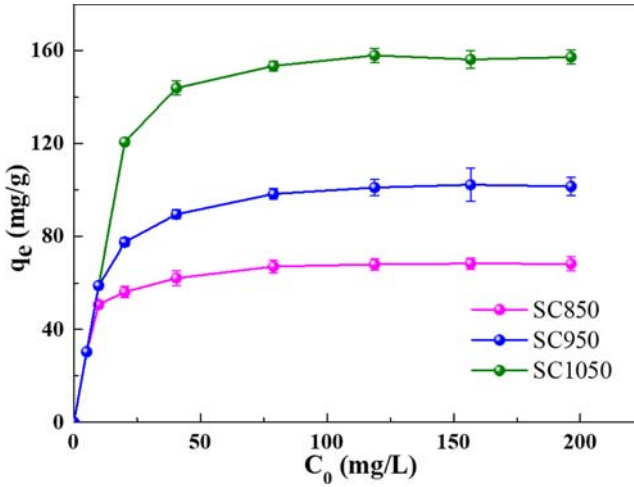


Figure 18.9 Effect of initial MB concentration on the adsorption process.
From Ji, Y., Zhang, X., Chen, Z., Xiao, Y., Li, S., Gu, J., Hu, H., & Cheng, G. (2022). Silk sericin enrichment through electrodeposition and carbonous materials for the removal of methylene blue from aqueous solution. *International Journal of Molecular Sciences, 23*(3). https://doi.org/10.3390/ijms23031668.

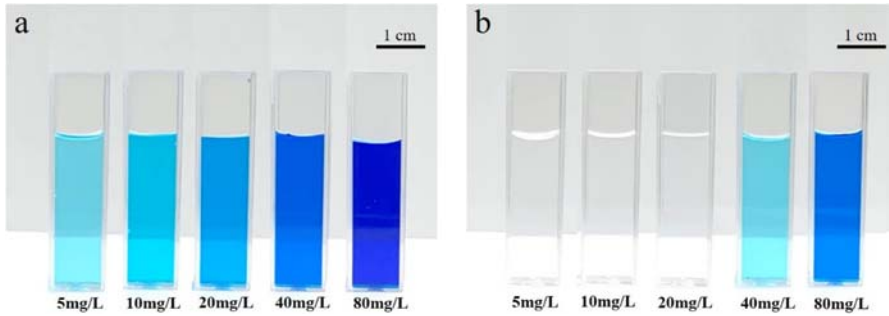


Figure 18.10 Photographs of MB solutions (a) before and (b) after adsorption by SC1050. From Ji, Y., Zhang, X., Chen, Z., Xiao, Y., Li, S., Gu, J., Hu, H., & Cheng, G. (2022). Silk sericin enrichment through electrodeposition and carbonous materials for the removal of methylene blue from aqueous solution. *International Journal of Molecular Sciences, 23*(3). https://doi.org/10.3390/ijms23031668.

experiment. It was observed that saturation was not reached at an initial MB concentration of 80 mg/L; therefore, this concentration was selected for subsequent experiments.

The percentage removal (R_e) and the equilibrium adsorption capacity (q_e, mg/g) were calculated using Eqs. (18.3) and (18.4), respectively:

$$R_e = \frac{(C_0 - C_e)}{C_e} \times 100\% \tag{18.3}$$

$$q_e = \frac{(c_0 - c_e) \times V}{M} \tag{18.4}$$

where C_0 and C_e represent the initial and equilibrium concentrations of MB in solution (mg/L), respectively; M denotes the SC dosage (mg); and V is the volume of MB solution (mL).

When the initial MB concentration reached or exceeded 120 mg/L, the q_e values for the SC samples remained constant, suggesting that the adsorption sites on the SC surface were fully saturated with MB molecules. Furthermore, as illustrated in Fig. 18.8, the adsorption capacity of the SC samples increased with higher carbonization temperatures. This can be attributed to the SC1050 sample, which exhibited the largest specific surface area (Table 18.3) and the highest degree of graphitization (Fig. 18.11), as determined by nitrogen adsorption−desorption isotherms and Raman spectroscopy, respectively.

It has been extensively documented that π−π stacking interactions significantly influence the adsorption of MB molecules onto carbonaceous adsorbents (Abd El-Monaem et al., 2024). An elevated degree of graphitization enhances such adsorption behavior by providing an increased number of sites for π−π stacking interactions. Consequently, it can be hypothesized that the adsorption mechanism of MB molecules

Table 18.3 Microstructural information of samples SC850, SC950, and SC1050.

Samples	BET surface area (cm^2/g)	BJH average pore diameter (nm)	Total pore volume (cm^3/g)
SC850	566.07	2.94	0.05
SC950	713.66	2.79	0.07
SC1050	1494.96	2.63	0.54

From Ji, Y., Zhang, X., Chen, Z., Xiao, Y., Li, S., Gu, J., Hu, H., & Cheng, G. (2022). Silk sericin enrichment through electrodeposition and carbonous materials for the removal of methylene blue from aqueous solution. *International Journal of Molecular Sciences, 23*(3). https://doi.org/10.3390/ijms23031668.

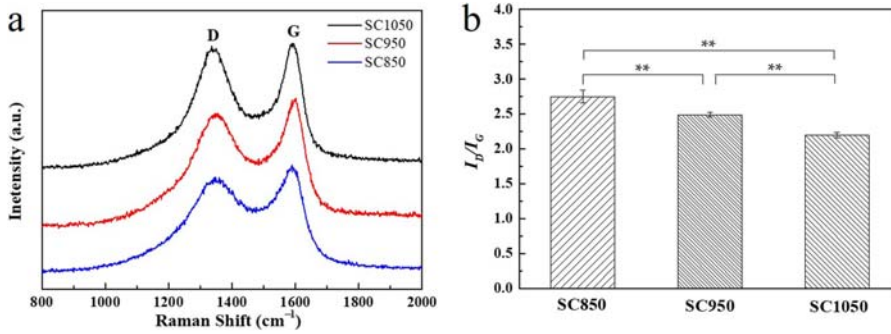


Figure 18.11 (a) Raman spectra and (b) calculated I_D/I_G values for samples SC850, SC950 and SC1050; lower I_D/I_G values typically indicate a higher degree of graphitization, reflecting a more ordered and perfect graphite structure (Mohamed et al., 2023) (n = 3, $*P < .05$, $**P < .01$).

From Ji, Y., Zhang, X., Chen, Z., Xiao, Y., Li, S., Gu, J., Hu, H., & Cheng, G. (2022). Silk sericin enrichment through electrodeposition and carbonous materials for the removal of methylene blue from aqueous solution. *International Journal of Molecular Sciences, 23*(3). https://doi.org/10.3390/ijms23031668.

onto the SC samples predominantly involves π−π stacking interactions. Our findings further suggest that both the degree of graphitization and the adsorption capacity of the SC samples are positively correlated with the carbonization temperature.

4.2 Effect of solution initial pH

The pH of the solution is a critical parameter in the adsorption process, as it influences both the surface charge of the adsorbent and the ionization state of dye molecules (Qin et al., 2016). To investigate the effect of initial pH on adsorption, 5 mg of SC1050 was added to an MB solution with an initial concentration of 80 mg/L at various initial pH levels (2, 4, 6, 8, 10, and 12). The adsorption experiments were conducted at 25°C in an incubator with a shaking speed of 150 rpm. As illustrated in Fig. 18.12a, the adsorption capacity of SC1050 increased markedly with the rise in initial pH from 2 to 10,

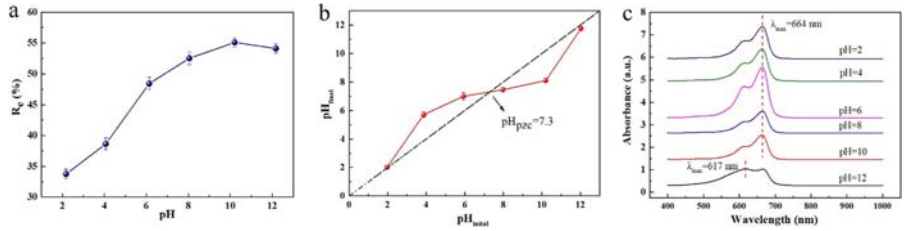


Figure 18.12 (a) The effect of the solution's initial pH on R_e of MB by SC1050; (b) pH_{pzc} of SC1050. (c) UV-Vis spectra of MB at different pH values.
From Ji, Y., Zhang, X., Chen, Z., Xiao, Y., Li, S., Gu, J., Hu, H., & Cheng, G. (2022). Silk sericin enrichment through electrodeposition and carbonous materials for the removal of methylene blue from aqueous solution. *International Journal of Molecular Sciences, 23*(3). https://doi.org/10.3390/ijms23031668.

with R_e increasing from 33.76 ± 0.80% to 55.11 ± 0.75%. Considering that the point of zero charge (pH_{pzc}) of SC1050 is 7.3 (Fig. 18.12b), at pH values below pH_{pzc}, the surface of SC1050 is positively charged. This positive charge induces repulsion between the cationic dye molecules (MBs) and the positively charged SC1050 surface, resulting in reduced MB adsorption. Conversely, at pH values above pH_{pzc}, the SC1050 surface becomes negatively charged, facilitating the adsorption of cationic MB molecules. However, a slight decrease in the adsorption capacity of SC1050 was observed at pH levels above 10, which is attributed to the instability of MB at high pH (evidenced by the peak position shift in the UV-Vis spectrum of MB at pH 12 in Fig. 18.12c) (Adamčíková et al., 2000), rather than a reduction in the adsorption capacity of SC1050.

4.3 The effect of adsorption temperature and the study for adsorption

To investigate the effect of temperature on the adsorption behavior of SC1050, 5 mg of SC1050 was introduced into an MB solution with an initial concentration of 80 mg/L and an adjusted pH of 10. The experiment was conducted at temperatures of 15, 25, 35, and 45°C in an incubator with a shaking speed of 150 rpm. As depicted in Fig. 18.13a, increasing the temperature from 15 to 45°C resulted in a decrease in the removal efficiency (R_e) from 47.53 ± 2.04% to 42.44 ± 1.36%, suggesting that the adsorption process is more favorable at lower temperatures.

The thermodynamic parameters, including Gibbs free energy (ΔG), enthalpy (ΔH), and entropy (ΔS), were determined using the van't Hoff equation (Lima et al., 2024):

$$\ln\left(\frac{q_e}{C_e}\right) = \frac{-\Delta H}{RT} + \frac{\Delta S}{R} \tag{18.5}$$

where R is the gas constant (8.314 J/mol/K), T is the adsorption temperature (K), ΔH is the change in enthalpy (kJ/mol), and ΔS is the change in entropy (J/mol/K).

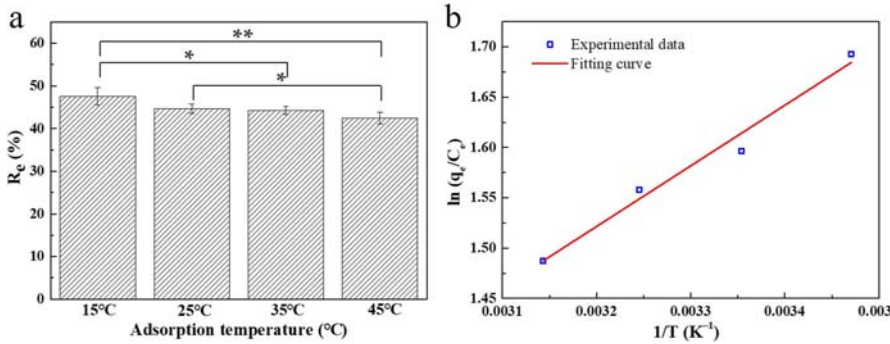


Figure 18.13 (a) The effect of adsorption temperature for the adsorption of MB onto SC1050 and (b) the plot for estimation of thermodynamic parameters (n = 3, $*P < .05$, $**P < .01$). From Ji, Y., Zhang, X., Chen, Z., Xiao, Y., Li, S., Gu, J., Hu, H., & Cheng, G. (2022). Silk sericin enrichment through electrodeposition and carbonous materials for the removal of methylene blue from aqueous solution. *International Journal of Molecular Sciences, 23*(3). https://doi.org/10.3390/ijms23031668.

The fitting curve is shown in Fig. 18.13b, and the calculated thermodynamic parameters are presented in Table 18.4. The negative values of ΔH indicate that the adsorption process is exothermic. The negative value of ΔS suggests a decrease in randomness at the solid−liquid interface during the adsorption process (Rashid et al., 2016).

The Gibbs free energy change (ΔG) was calculated using the following equation:

$$\Delta G = \Delta H - T\Delta S \tag{18.6}$$

where, T is the adsorption temperature (K), ΔH is the enthalpy change (kJ/mol), and ΔS is the entropy change (J/mol/K).

The negative values of ΔG indicate that the adsorption process is spontaneous. Furthermore, it is known that ΔG values for physisorption range from −20 to 0 kJ/mol, for a combination of physisorption and chemisorption from −20 to −80 kJ/

Table 18.4 Thermodynamic parameters for the adsorption of MB onto SC1050.

T (K)	ΔG (kJ/mol)	ΔH (kJ/mol)	ΔS (J/mol/K)
288.15	−0.98 ± 0.53	−5.01 ± 0.53	−3.39 ± 1.74
298.15	−1.02 ± 0.74		
308.15	−1.05 ± 0.75		
318.15	−1.08 ± 0.77		

From Ji, Y., Zhang, X., Chen, Z., Xiao, Y., Li, S., Gu, J., Hu, H., & Cheng, G. (2022). Silk sericin enrichment through electrodeposition and carbonous materials for the removal of methylene blue from aqueous solution. *International Journal of Molecular Sciences, 23*(3). https://doi.org/10.3390/ijms23031668.

mol, and for chemisorption from −80 to −400 kJ/mol (Arumugam et al., 2019). As shown in Table 18.4, the ΔG values for MB adsorption from 288.15 to 318.15 K were all within the range of −20 to 0 kJ/mol, indicating that the adsorption process favors a physisorption mechanism.

4.4 The effect of adsorption time and the kinetics of adsorption

To investigate the effect of adsorption time on MB uptake, 5 mg of SC1050 was added to an MB solution with an initial concentration of 80 mg/L (adjusted to pH 10). The experiment was conducted at 15°C in an incubator with a shaking speed of 150 rpm.

The amount of adsorption at time t, q_t (mg/g), can be calculated using Eq. (18.7):

$$q_t = \frac{(C_0 - C_t)}{M} \times V \tag{18.7}$$

where C_t is the MB concentration at time t (mg/L).

As shown in Fig. 18.14a, the initial adsorption was observed to be very fast, due to the availability of abundant vacant adsorption sites. The adsorption decreased significantly within 2 hours to give a gradual approach to an equilibrium, which was

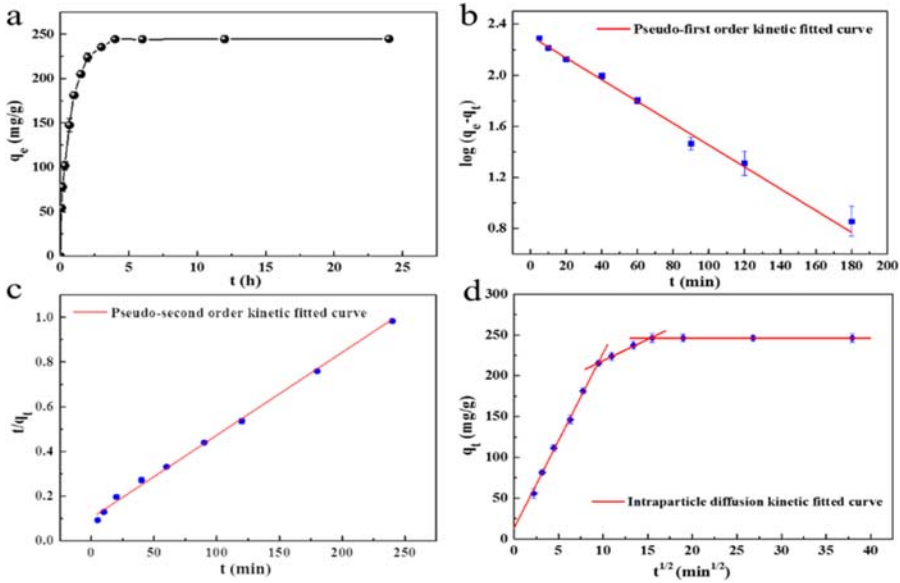


Figure 18.14 (a) The effect of adsorption time for the adsorption of MB onto SC1050 and plots for (b) pseudo-first-order, (c) pseudo-second-order, and (d) IPD models.
From Ji, Y., Zhang, X., Chen, Z., Xiao, Y., Li, S., Gu, J., Hu, H., & Cheng, G. (2022). Silk sericin enrichment through electrodeposition and carbonous materials for the removal of methylene blue from aqueous solution. *International Journal of Molecular Sciences, 23*(3). https://doi.org/10.3390/ijms23031668.

attributed to the saturation of adsorption sites or a pore diffusion process of the MB molecule. Finally, the adsorption reached a plateau after 4 hours incubation. Furthermore, the curves obtained were single, smooth, and continuous, which suggested the possibility of MB monolayer coverage onto the surface of SC1050.

The kinetic data were analyzed using the pseudo-first-order (Fig. 18.14b), pseudo-second-order (Fig. 18.14c), and intra-particle diffusion (IPD) (Fig. 18.14d) models (Abdelmegeed et al., 2024; Tawfik & Eltabey, 2024).

The pseudo-first-order model is described by Eq. (18.8):

$$\log\left(q_e - q_t\right) = \log q_e - \frac{k_1 t}{2.303} \tag{18.8}$$

where t is the adsorption time (minutes), and k_1 is the pseudo-first-order rate constant (minutes^{-1}).

The pseudo-second-order model is described by Eq. (18.9):

$$\frac{t}{q_t} = \frac{1}{k_2 q_e^2} + \frac{1}{q_e} t \tag{18.9}$$

where k_2 is the pseudo-second-order rate constant (g·mg/minutes).

The IPD model is described by Eq. (18.10):

$$q_t = k_i t^{1/2} + C_i \tag{18.10}$$

where k_i is the IPD rate constant (mg·g·minutes$^{-1/2}$), and C_i represents the boundary layer effect. A C_i value of zero indicates IPD is the sole rate-limiting step, whereas a nonzero C_i implies that other processes are also involved.

As shown in Table 18.5, the highest correlation coefficient (R^2) was obtained for the IPD model, suggesting that the adsorption mechanism was predominantly governed by intraparticle diffusion. The IPD curve (d) exhibited multilinear plots, indicating three distinct stages of adsorption: (1) external diffusion of MB molecules onto SC1050; (2) diffusion of MB molecules into the internal structure of SC1050; and (3) equilibrium. The nonzero C_i values imply that intraparticle diffusion was not the sole rate-limiting step (Zhao, Zhan, et al., 2020).

4.5 Study of adsorption isotherms

Adsorption isotherms elucidate the relationship between the amount of adsorbate and the equilibrium concentration of the adsorptive, which is essential for understanding the adsorption process. The Langmuir isotherm models monolayer adsorption on homogeneous surfaces, whereas the Freundlich isotherm describes multilayer adsorption on heterogeneous surfaces (Diao et al., 2024).

The Langmuir isotherm is represented by the equation:

Table 18.5 Kinetic parameters for the adsorption of MB onto SC1050 obtained by plotting.

Sample	Pseudo-first order			Pseudo-second order			Intra-particle diffusion		
	q_1	k_1	R^2	q_2	k_2	R^2	k_i		R^2
	(mg/g)	(1/minute)	(%)	(mg/g)	(g/mg/minutes)	(%)	(mg/g/minutes$^{1/2}$)	C_i	(%)
SC1050	202.21	0.02	98.63	269.54	1.32×10^{-4}	99.73	21.49	12.85	99.81

From Ji, Y., Zhang, X., Chen, Z., Xiao, Y., Li, S., Gu, J., Hu, H., & Cheng, G. (2022). Silk sericin enrichment through electrodeposition and carbonous materials for the removal of methylene blue from aqueous solution. *International Journal of Molecular Sciences, 23*(3). https://doi.org/10.3390/ijms23031668.

$$\frac{C_e}{q_e} = \frac{1}{q_{\max} \cdot K_L} + \frac{C_e}{q_{\max}} \tag{18.11}$$

where $q_{\max}$ denotes the maximum adsorption capacity (mg/g), and K_L is the Langmuir isotherm constant (L/mg).

The Freundlich isotherm is given by equation:

$$\ln q_e = \ln K_F + \frac{1}{n} \cdot ln\ C_e \tag{18.12}$$

where K_F represents the Freundlich isotherm constant (L/g), and n is the Freundlich exponent.

The efficiency of the Langmuir adsorption process can be evaluated using the dimensionless equilibrium parameter R_L, defined as:

$$R_L = \frac{1}{1 + K_L \cdot C_0} \tag{18.13}$$

For $0 < R_L < 1$, the adsorption progress is deemed favorable.

To investigate the adsorption behavior, 5 mg of SC1050 was introduced into MB solutions with initial concentrations of 5, 10, 20, 40, 80, 120, 160, and 200 mg/L (the pH was adjusted to 10). The experiments were conducted at 15°C in an incubator operating at 150 rpm. As depicted in Fig. 18.15a, q_e increased to 231.79 mg/g with rising initial MB concentrations, consistent with the findings in Section 4.1, which indicated that higher initial concentrations enhance the adsorption process.

The data were analyzed using both Langmuir and Freundlich isotherm models (Fig. 18.15b–c). The linear plots revealed that the adsorption adhered to the Langmuir isotherm model, as indicated by a higher R^2 value compared to the Freundlich model (Table 18.6). This implies that MB adsorption onto the SC1050 surface was monolayered, with no lateral interactions among adsorbed molecules, consistent with results from Section 4.4. The maximum monolayer adsorption capacity ($q_{\max,cal}$) derived from the Langmuir isotherm model was 234.72 mg/g. Furthermore, the separation factor (R_L) ranged between 0 and 1, indicating favorable adsorption behavior of MB onto SC1050 (Elbanna et al., 2024).

5. Cytotoxicity evaluation

The cytotoxicity of SC1050 was evaluated to ensure its safe usage. The phenotypes of HEK-293 cells in the control group, SC1050 group, and phenol group are shown in Fig. 18.16a. The cells in both the SC1050 and control groups exhibited a spindle or polygonal shape, and cell density gradually increased over time, indicating successful cell proliferation. In contrast, cells cultured in a 64 g/L phenol solution adopted a spherical shape with a limited number of cells.

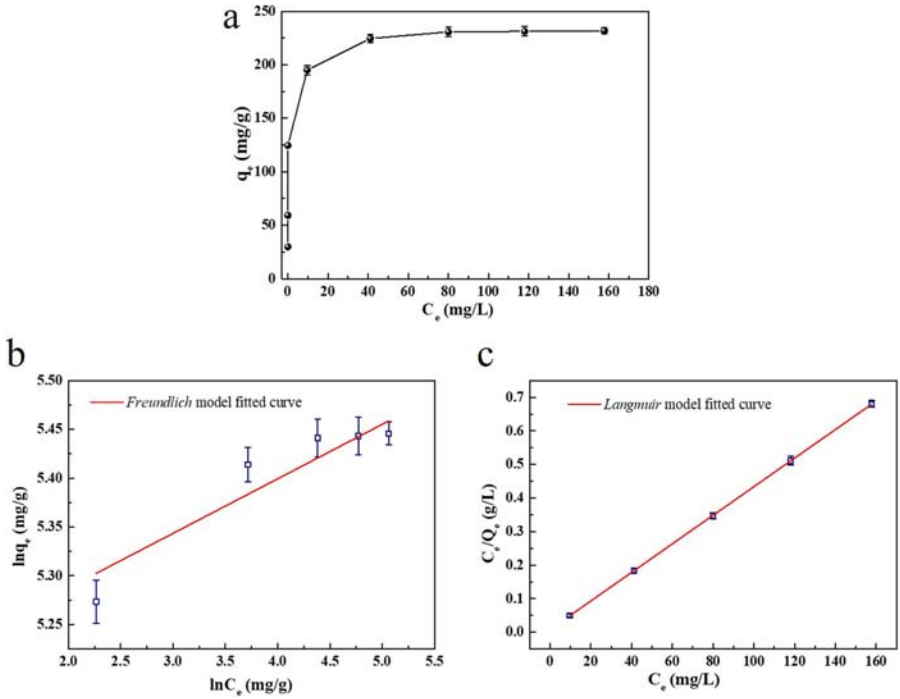


Figure 18.15 (a) Adsorption isotherm, (b) Langmuir fitting, and (c) Freundlich fitting. From Ji, Y., Zhang, X., Chen, Z., Xiao, Y., Li, S., Gu, J., Hu, H., & Cheng, G. (2022). Silk sericin enrichment through electrodeposition and carbonous materials for the removal of methylene blue from aqueous solution. *International Journal of Molecular Sciences, 23*(3). https://doi.org/10.3390/ijms23031668.

Table 18.6 Parameters of adsorption isotherms from Langmuir and Freundlich models.

Sample	Langmuir isotherm model			Freundlich isotherm model		
	R_L	K_L (L/mg)	R^2 (%)	n	K_F (L/mg)	R^2 (%)
SC1050	0.19	0.52	99.99	17.89	1.64	81.98

From Ji, Y., Zhang, X., Chen, Z., Xiao, Y., Li, S., Gu, J., Hu, H., & Cheng, G. (2022). Silk sericin enrichment through electrodeposition and carbonous materials for the removal of methylene blue from aqueous solution. *International Journal of Molecular Sciences, 23*(3). https://doi.org/10.3390/ijms23031668.

As depicted in Fig. 18.16b, the positive control group demonstrated a significantly lower OD_{450} value compared to the control and SC1050 groups. However, there was no statistically significant difference between the OD_{450} values of the control and SC1050 groups, indicating that SC1050 is nontoxic.

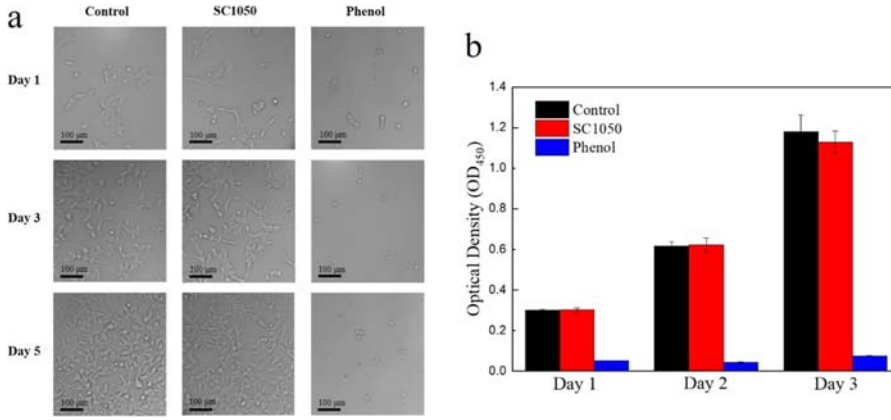


Figure 18.16 (a) HEK293 cell morphology for control, SC1050, and phenol groups of the CCK-8 assay on day 1, day 3, and day 5. (b) Toxicological effect of SC1050 on HEK-293 cells ($n = 3$, $^{*}P < .05$, $^{**}P < .01$).
From Ji, Y., Zhang, X., Chen, Z., Xiao, Y., Li, S., Gu, J., Hu, H., & Cheng, G. (2022). Silk sericin enrichment through electrodeposition and carbonous materials for the removal of methylene blue from aqueous solution. *International Journal of Molecular Sciences, 23*(3). https://doi.org/10.3390/ijms23031668.

6. The batch adsorption of Cu(II) ions

Copper (II) ions, as one of the most commonly encountered heavy metals, were selected to evaluate the adsorption behavior of SS-derived carbon.

6.1 Effect of initial concentration

The effect of the initial Cu(II) concentration on the adsorption capacity is depicted in Fig. 18.17. An increase in the initial Cu(II) concentration resulted in an enhanced adsorption capacity across all SC samples. Specifically, as the initial Cu(II) concentration was raised from 5 to 40 mg/L, the adsorption capacities of SC450, SC650, SC850, and SC1050 progressively increased. This enhancement is attributed to the elevated initial Cu(II) concentration, which augments the driving force of the adsorption process, thereby facilitating the removal of Cu(II) ions from the solution.

Moreover, SC samples pyrolyzed at 1050°C exhibited a higher adsorption capacity compared to those pyrolyzed at 450, 650, and 850°C. At a Cu(II) concentration of 40 mg/L, the equilibrium adsorption capacities for SC450, SC650, and SC850 were 11.71, 13.80, and 15.06 mg/g, respectively. When the pyrolysis temperature was increased to 1050°C, the adsorption capacity of SC1050 for Cu(II) reached 20.08 mg/g. SEM images suggest that this increase in adsorption capacity is likely due to the denser pore structure of SC1050, which provides a larger surface

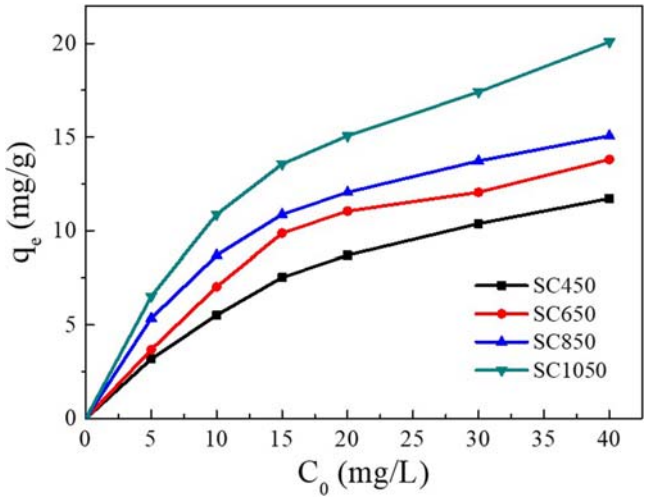


Figure 18.17 Influence of Cu(II) initial concentration on the adsorption capacity (pH = 5.0, adsorption temperature = 25°C, contact time = 24 h).
From Xiao, Y., Luo, R., Ji, Y., Li, S., Hu, H. & Zhang, X. (2022). Removal of copper(II) from aqueous environment using silk sericin-derived carbon. *International Journal of Molecular Sciences* (Vol. 23, Issue 19). https://doi.org/10.3390/ijms231911202.

area and more adsorption sites (Choudhary et al., 2020). Consequently, SC1050 was selected as the adsorbent for subsequent experiments.

6.2 Effect of pH

The initial solution pH is a critical parameter influencing the metal ion adsorption capacity of an adsorbent, as it affects the surface charge and ionization degree of the adsorbent, as well as the aqueous chemistry of the metal ions. Observations of turbidity, indicative of copper hydroxide suspensions, were noted in the Cu(II) solution when the pH was adjusted to 6. Therefore, a pH range of 4.5−5.5 was selected to investigate the impact of pH on Cu(II) adsorption. As illustrated in Fig. 18.18, SC1050 demonstrated the lowest Cu(II) ion adsorption capacity at a pH of 4.5. This reduced adsorption capacity can be attributed to the high concentration of H^+ ions in the solution, which compete with Cu(II) ions for active adsorption sites, thereby diminishing the adsorption of Cu(II) ions (Wang et al., 2018).

To further elucidate the adsorption mechanism, the zeta potential of SC1050 was measured at pH values of 4.5, 5.0, and 5.5. Fig. 18.18 indicates that at a pH of 5.5, the surface charge of SC1050 became more negative, which enhanced the electrostatic attraction between SC1050 and the positively charged Cu(II) ions, leading to more effective adsorption. Based on these findings, a pH of 5.5 was chosen for subsequent adsorption experiments.

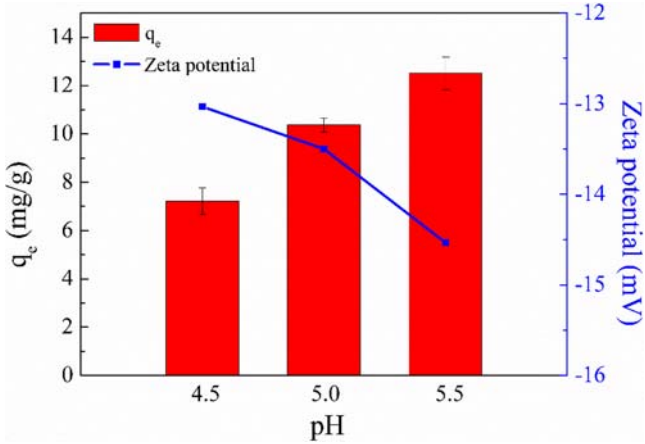


Figure 18.18 Effect of solution pH on the Cu(II) adsorption capacity of SC1050 and the zeta potential of SC1050 at three pH values (Cu(II) initial concentration = 15 mg/L, adsorption temperature = 25°C, contact time = 24 h).
From Xiao, Y., Luo, R., Ji, Y., Li, S., Hu, H. & Zhang, X. (2022). Removal of copper(II) from aqueous environment using silk sericin-derived carbon. *International Journal of Molecular Sciences* (Vol. 23, Issue 19). https://doi.org/10.3390/ijms231911202.

6.3 Effect of temperature on the sorption of Cu(II) ions and a thermodynamic study

The influence of temperature on the sorption of Cu(II) is illustrated in Fig. 18.19a. An increase in temperature was found to enhance the sorption of Cu(II) onto SC1050. This enhancement is likely due to the higher temperature providing sufficient energy for copper ions to interact with both the surface and internal structure of SC1050 (Cao et al., 2019).

The thermodynamic fitting curve is presented in Fig. 18.19b, with the corresponding thermodynamic parameters listed in Table 18.7. As indicated in Table 18.7, the negative ΔG values, which become more negative with increasing temperature, demonstrate that the adsorption process is more thermodynamically favorable at higher temperatures, suggesting a chemisorption mechanism (Wu et al., 2021). Additionally, the positive ΔH value indicates that the adsorption process is endothermic. The positive ΔS value further suggests that the increased temperature enhances the disorder at the solid−liquid interface, leading to a higher probability of successful collisions between Cu(II) ions and SC1050, thereby promoting Cu(II) adsorption (Wang et al., 2018).

6.4 Effect of contact time on the adsorption process and the adsorption kinetics

As depicted in Fig. 18.20, the adsorption capacity of SC1050 for Cu(II) ions varied with contact time and can be delineated into three distinct phases: an initial rapid

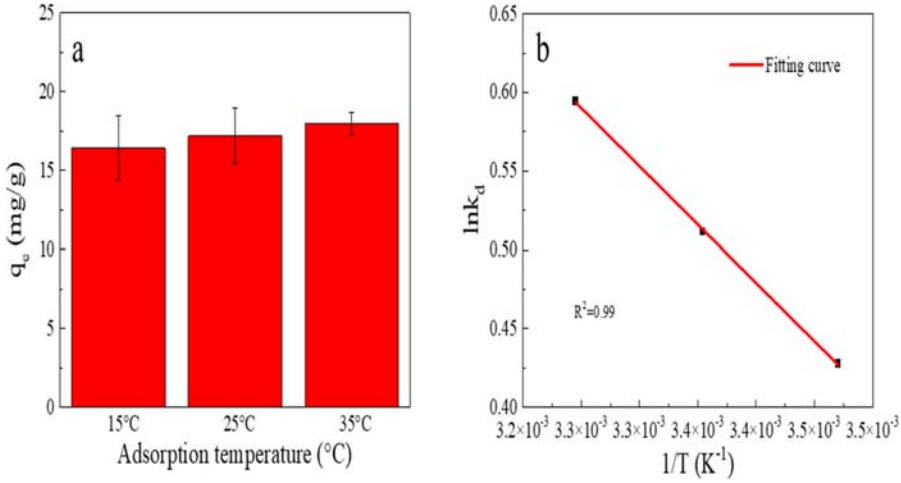


Figure 18.19 (a) Effect of temperature on Cu(II) adsorption onto SC1050 and (b) a van't Hoff plot for adsorption of Cu(II) onto SC1050 (Cu(II) initial concentration = 15 mg/L, pH = 5.5, contact time = 24 h).
From Xiao, Y., Luo, R., Ji, Y., Li, S., Hu, H. & Zhang, X. (2022). Removal of copper(II) from aqueous environment using silk sericin-derived carbon. *International Journal of Molecular Sciences* (Vol. 23, Issue 19). https://doi.org/10.3390/ijms231911202.

Table 18.7 Thermodynamic parameters for adsorption of Cu(II) onto SC1050.

T (K)	ΔG (kJ/mol)	ΔH (kJ/mol)	ΔS (J/mol·K)
288.15	−1.02	6.16	24.91
298.15	−1.27		
308.15	−1.52		

From Xiao, Y., Luo, R., Ji, Y., Li, S., Hu, H. & Zhang, X. (2022). Removal of copper(II) from aqueous environment using silk sericin-derived carbon. *International Journal of Molecular Sciences* (Vol. 23, Issue 19). https://doi.org/10.3390/ijms231911202.

adsorption phase within the first 30 minutes, a subsequent gradual slowdown from 30 minutes to 6 hours, and an equilibrium phase reached at 6 hours. This observation can be attributed to the fact that, during the early stage of the adsorption process, numerous available adsorption sites on the SC1050 surface were quickly occupied by Cu(II) ions, resulting in a high adsorption rate. However, as these sites became progressively saturated over time, the rate of adsorption decreased until equilibrium was achieved.

To further elucidate the kinetics of the adsorption process, both pseudo-first-order and pseudo-second-order kinetic models were applied to fit the experimental data. The corresponding fitting curves and calculated parameters are presented in and Table 18.8, respectively. The experimental data exhibited a better fit with the pseudo-second-order

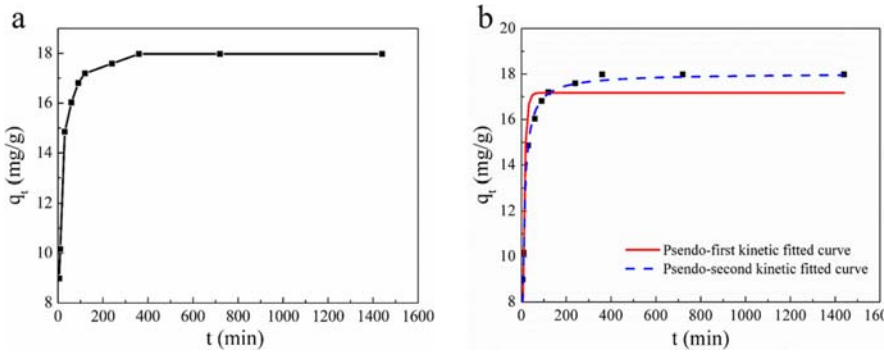


Figure 18.20 (a) Effect of contact time on the Cu(II) adsorption capacity of SC1050 and (b) pseudo-first-order and pseudo-second-order plots of Cu(II) sorption onto SC1050 (Cu(II) initial concentration = 15 mg/L, pH = 5.5, adsorption temperature = 35°C).
From Xiao, Y., Luo, R., Ji, Y., Li, S., Hu, H. & Zhang, X. (2022). Removal of copper(II) from aqueous environment using silk sericin-derived carbon. *International Journal of Molecular Sciences* (Vol. 23, Issue 19). https://doi.org/10.3390/ijms231911202.

Table 18.8 Pseudo-first order, pseudo-second order, and IPD models of Cu(II) adsorption onto SC1050.

Sample	$q_{e,exp}$ (mg/g)	Pseudo-first-order			Pseudo-second-order		
		$q_{e,cal}$ (mg/g)	$k_1 \times 10^{-3}$ (minutes^{-1})	R^2	$q_{e,cal}$ (mg/g)	$k_2 \times 10^{-3}$ (g/mg·minutes)	R^2
SC1050	17.98	17.17	0.11	0.87	18.02	0.01	0.97

From Xiao, Y., Luo, R., Ji, Y., Li, S., Hu, H. & Zhang, X. (2022). Removal of copper(II) from aqueous environment using silk sericin-derived carbon. *International Journal of Molecular Sciences* (Vol. 23, Issue 19). https://doi.org/10.3390/ijms231911202.

kinetic model, suggesting that the adsorption process of SC1050 was predominantly governed by chemisorption, which involves the sharing or exchange of electrons between Cu(II) ions and the SC1050 adsorbent (Stirling et al., 2018).

Furthermore, the kinetics and rate-limiting steps of the adsorption process were elucidated using the IPD model. The IPD fitting curves for Cu(II) adsorption and the corresponding rate constants are presented in Fig. 18.21 and Table 18.9, respectively. As shown in Fig. 18.21, the plot exhibited multilinearity, corresponding to two distinct stages: the first linear portion represents the diffusion of Cu(II) through the solution to the external surface of SC1050, while the second linear portion describes the intraparticle diffusion. The rate constant for the first stage was greater than that of the second stage (Table 18.9), indicating that the initial adsorption was

Table 18.9 IPD rate constant for the adsorption of Cu(II) onto SC1050.

Sample	IPD	
	k_{i1} (mg/g·minutes$^{1/2}$)	k_{i2} (mg/g·minutes$^{1/2}$)
SC1050	1.85	0.15

From Xiao, Y., Luo, R., Ji, Y., Li, S., Hu, H. & Zhang, X. (2022). Removal of copper(II) from aqueous environment using silk sericin-derived carbon. *International Journal of Molecular Sciences* (Vol. 23, Issue 19). https://doi.org/10.3390/ijms231911202.

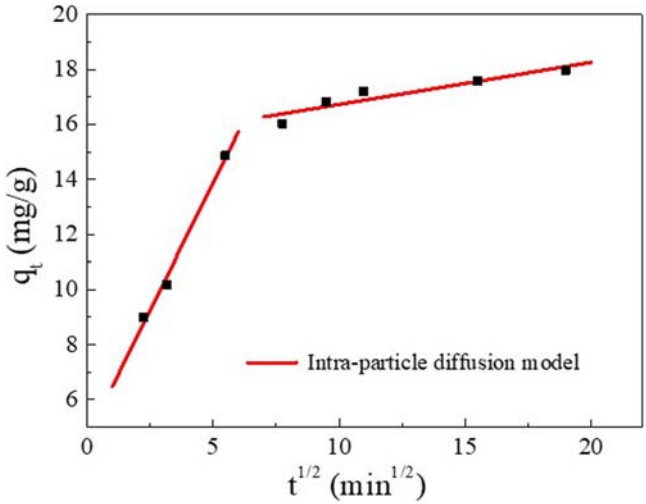


Figure 18.21 The IPD model for Cu(II) adsorption.
From Xiao, Y., Luo, R., Ji, Y., Li, S., Hu, H. & Zhang, X. (2022). Removal of copper(II) from aqueous environment using silk sericin-derived carbon. *International Journal of Molecular Sciences* (Vol. 23, Issue 19). https://doi.org/10.3390/ijms231911202.

rapid and primarily controlled by film diffusion, whereas the IPD governed the subsequent adsorption process (Stirling et al., 2018). Additionally, the fitting plot did not intersect the origin, suggesting that IPD was not the sole rate-limiting step (Wang et al., 2018).

6.5 Adsorption isotherm

Adsorption isotherms provide critical insight into the relationship between the adsorbate and adsorbent at equilibrium (Kanagalakshmi et al., 2024). The fitting plots and parameters for Cu(II) adsorption onto SC1050 are presented in Fig. 18.22 and Table 18.10. The data indicate that the Langmuir model accurately describes the adsorption process of Cu(II) onto SC1050 at 35°C, suggesting monolayer adsorption of

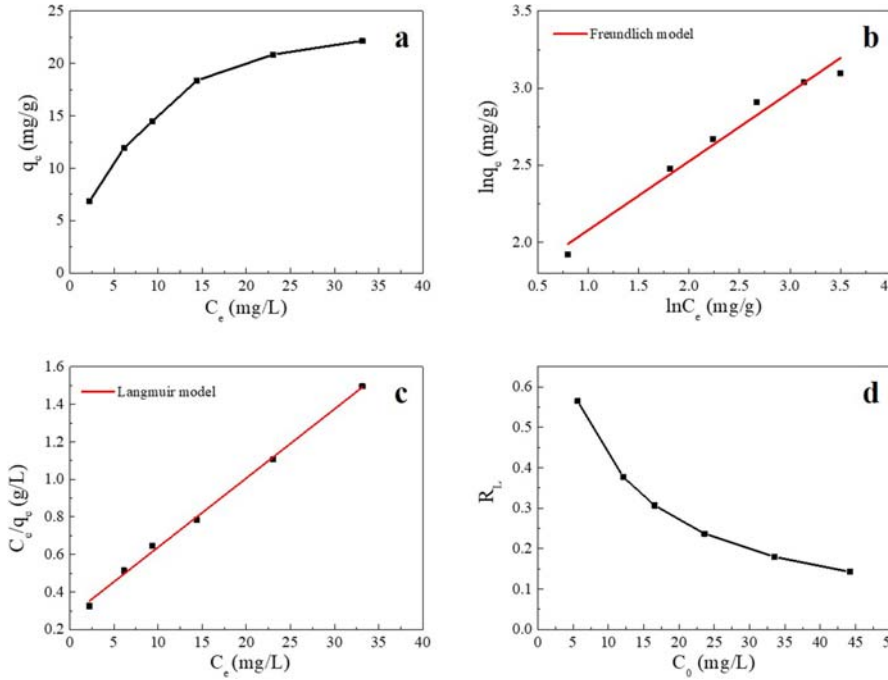


Figure 18.22 (a) Adsorption equilibrium isotherm of Cu(II) on SC1050, (b) the fitting plot of the Langmuir isotherm, (c) the fitting plot of the Freundlich isotherm, and (d) a plot of the separation factor versus initial Cu(II) concentration (pH = 5.5, adsorption temperature = 35°C, contact time = 24 h).
From Xiao, Y., Luo, R., Ji, Y., Li, S., Hu, H. & Zhang, X. (2022). Removal of copper(II) from aqueous environment using silk sericin-derived carbon. *International Journal of Molecular Sciences* (Vol. 23, Issue 19). https://doi.org/10.3390/ijms231911202.

Table 18.10 Langmuir and Freundlich isotherm parameters for Cu(II) adsorption onto SC1050.

Sample	Langmuir isotherm model			Freundlich isotherm model		
	$q_{max,cal}$ (mg/g)	k_L (L/mg)	R^2	n	k_F (L/mg)	R^2
SC1050	27.14	0.11	0.87	18.02	0.01	0.97

From Xiao, Y., Luo, R., Ji, Y., Li, S., Hu, H. & Zhang, X. (2022). Removal of copper(II) from aqueous environment using silk sericin-derived carbon. *International Journal of Molecular Sciences* (Vol. 23, Issue 19). https://doi.org/10.3390/ijms231911202.

Cu(II) ions on the SC1050 surface. Additionally, Fig. 18.22d shows that the R_L values derived from the Langmuir model were all greater than 0 but less than 1 across all initial concentrations, signifying that the adsorption process of Cu(II) onto SC1050 was favorable.

6.6 Determination of Cu adsorbed on SC using ICP–OES

SC1050 was immersed in a 15 mg/L Cu(II) solution for 24 hours to assess its copper adsorption capacity. Postimmersion, inductively coupled plasma optical emission spectrometry (ICP-OES) was employed to quantify the copper content on SC1050. As indicated in Table 18.11, there was a significant increase in copper content on SC1050 in the experimental group compared to the control group, which was not exposed to the Cu(II) solution.

7. Adsorption capacity of activated carbon derived from SS/CMCS

Activation during carbonization can lead to a high degree of porosity and a large surface area in carbonaceous materials (Guo et al., 2024; Yan et al., 2023), therefore promoting their adsorption capacity. In order to improve the adsorption capacity of the carbonaceous adsorbents derived from SS, a two-step activation process was developed to activate the SS/CMCS precursor.

7.1 Activated carbon preparation

In the first step, the lyophilized hydrogels were placed in a tube furnace and heated under a nitrogen flow of 150 mL/minutes. The temperature was gradually increased from room temperature to 150°C at a rate of 10°C/minutes and maintained at 150°C for 1 hours. Subsequently, the nitrogen flow was turned off. The temperature was then raised from 150 to 450°C at a rate of 5°C/minutes and held at 450°C for 2 hours. After cooling to room temperature, the samples were immersed in KOH solutions of various concentrations for 2 hours (Fig. 18.23a and b). The samples were then dried in an oven at 60°C and labeled as AC(X), where X indicates the concentration of KOH in mol/L. Next, the sample AC(X) was placed back in the tube furnace, and the carbonization procedure was repeated, but with the final activation temperature reached at a heating rate of 2°C/minutes. The samples were held at various activation temperatures for 2 hours. The resulting sericin-derived activated carbon was labeled as ACY(X), where Y indicates the final activation temperature in Celsius (°C).

Table 18.11 Cu content in SC1050.

Group	Cu content (mg/L)
Control	0.012 ± 0.017
Experimental	0.212 ± 0.007

From Xiao, Y., Luo, R., Ji, Y., Li, S., Hu, H. & Zhang, X. (2022). Removal of copper(II) from aqueous environment using silk sericin-derived carbon. *International Journal of Molecular Sciences* (Vol. 23, Issue 19). https://doi.org/10.3390/ijms231911202.

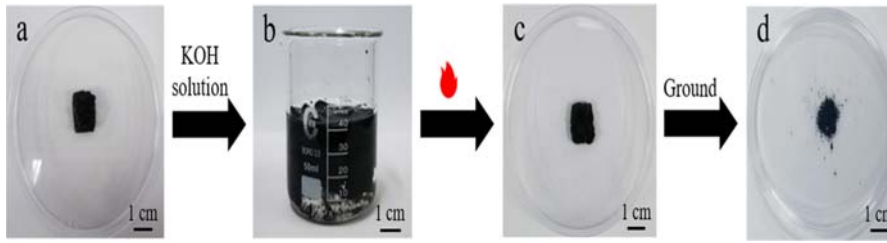


Figure 18.23 (a) SS-/CMCS-derived carbon; (b) the activation process; (c) SS/CMCS-derived activated carbon; (d) grind powder for adsorption experiments.
From Li, Shiwei, Li, Mengyan & Zhang, Xiaoning. (2024). Activated carbon derived from silk sericin for efficient adsorption of methylene blue in aqueous solutions. *Macromolecular Research*, 32(5), 443−452. https://doi.org/10.1007/s13233-023-00237-3.

7.2 Effect of KOH dosage on MB adsorption

To investigate the effect of KOH concentration on the methylene blue adsorption performance of activated carbon derived from SS, three different concentrations of KOH solution (1.7, 3.4, and 5.1 mol/L) were used. Fig. 18.24a shows that the adsorption capacity of AC750 increased with increasing KOH concentration up to 3.4 mol/L, after which it decreased. The highest adsorption capacity, 878.92 mg/g, was achieved with a KOH concentration of 3.4 mol/L. Additionally, a illustrates that AC750(X) exhibited increased adsorption capacity with higher initial MB concentrations. This increase is

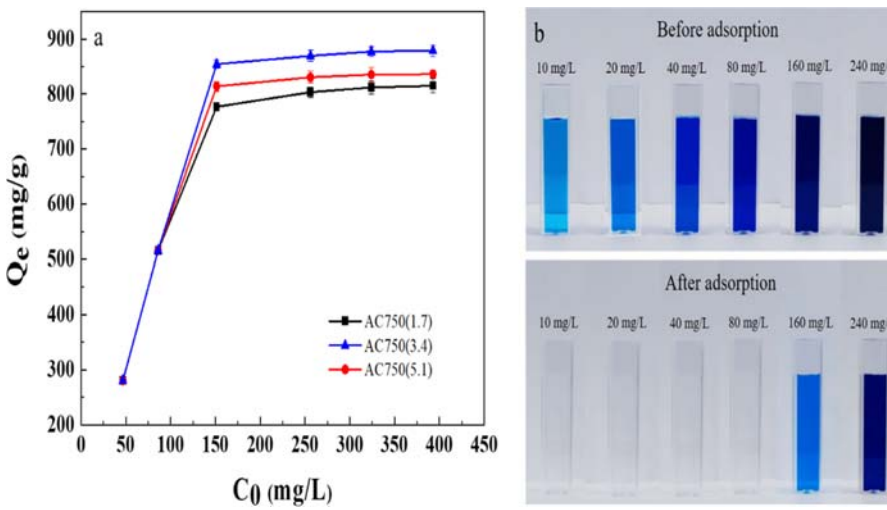


Figure 18.24 (a) Adsorption of AC750(X) on MB under different initial concentrations; (b) representative images of the MB solutions before and after the adsorption by AC750(3.4).
From Li, S., Li, M., & Zhang, X. (2024). Activated carbon derived from silk sericin for efficient adsorption of methylene blue in aqueous solutions. *Macromolecular Research*, 32(5), 443−452. https://doi.org/10.1007/s13233-023-00237-3.

attributed to the concentration driving force overcoming the resistance to mass transfer of MB across the interface between the aqueous and solid phases (Liu et al., 2011). Fig. 18.24b presents the adsorption performance of AC750(3.4) on MB solutions with varying initial concentrations.

Based on the data in Table 18.12, increasing the KOH dosage during the activation process resulted in a larger BET specific surface area and total pore volume. However, when the KOH concentration reached 5.1 M, the excessive pore expansion caused the carbon skeleton to collapse, thereby reducing the specific surface area, total pore volume (Chen et al., 2018), and methylene blue adsorption capacity. Consequently, a KOH concentration of 3.4 M was chosen for subsequent investigations.

7.3 Effect of activation temperature on adsorption capability

The activation temperature plays a critical role in the KOH activation of carbonaceous materials (Wang et al., 2023). As the activation temperature increased from 550°C to 950°C, sample AC750(3.4) exhibited the highest adsorption capacity (Fig. 18.25). According to Table 18.13, this result is likely due to AC750(3.4) having the largest total pore volume and BET specific surface area. Consequently, an activation temperature of 750°C was chosen for further investigation.

7.4 SEM characterization

The micromorphology of samples AC550(3.4), AC750(3.4), and AC950(3.4) was examined using SEM. Fig. 18.26a shows that at an activation temperature of 550°C, the surface of the activated carbon exhibits small, crater-like structures. This pitting may be due to incomplete activation of KOH at the lower temperature. At 750°C (Fig. 18.26b), KOH reacts with carbon to form K_2CO_3, which then decomposes to release CO_2 (Zhao, Yu, et al., 2020), resulting in the development of interconnected porous structures. However, at 950°C, the sample displays shrinkage and a damaged carbon structure, likely caused by sintering of volatile molecules that narrows the pores (Lua & Yang, 2005).

Table 18.12 BET specific surface area and total pore volume of AC750(X).

Sample	BET surface area (m^2/g)	Total pore volume (cm^3/g)
AC750(1.7)	608.27	0.025
AC750(3.4)	1384.99	0.251
AC750(5.1)	645.01	0.023

From Li, S., Li, M., & Zhang, X. (2024). Activated carbon derived from silk sericin for efficient adsorption of methylene blue in aqueous solutions. *Macromolecular Research*, 32(5), 443−452. https://doi.org/10.1007/s13233-023-00237-3.

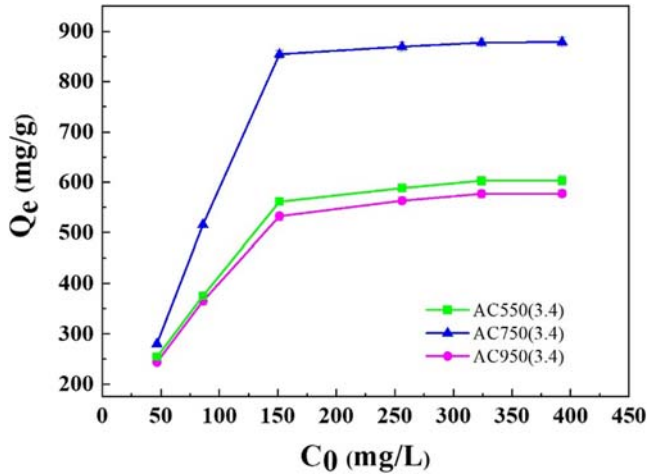


Figure 18.25 Influence of activation temperature on MB adsorption by AC*Y*(3.4).
From Li, S., Li, M., & Zhang, X. (2024). Activated carbon derived from silk sericin for efficient adsorption of methylene blue in aqueous solutions. *Macromolecular Research*, 32(5), 443−452. https://doi.org/10.1007/s13233-023-00237-3.

Table 18.13 BET specific surface area and total pore volume of AC*Y*(3.4).

Sample	BET surface area (m^2/g)	Total pore volume (cm^3/g)
AC550(3.4)	202.26	0.022
AC750(3.4)	1384.99	0.251
AC950(3.4)	333.36	0.024

From Li, S., Li, M., & Zhang, X. (2024). Activated carbon derived from silk sericin for efficient adsorption of methylene blue in aqueous solutions. *Macromolecular Research*, 32(5), 443−452. https://doi.org/10.1007/s13233-023-00237-3.

7.5 Adsorption kinetics experiment

According to the kinetics curve plot in Fig. 18.27a, the adsorption process of AC750(3.4) can be divided into three stages. The first stage is an initial rapid adsorption, during which 51.56% of MB is adsorbed within the first 2 hours. This rapid adsorption occurs due to the abundance of unoccupied adsorption sites. The second stage, characterized by slower adsorption, shows a decreased adsorption rate as some adsorption sites become less accessible to MB molecules. The third stage, dynamic equilibrium, is reached when all adsorption sites are occupied (Chen, Wang, et al., 2024).

To determine the adsorption mechanism, the experimental data were fitted to pseudo-first-order, pseudo-second-order, and intraparticle diffusion models (Fig. 18.27b−d) (Abdelmegeed et al., 2024; Tawfik & Eltabey, 2024). As shown in Table 18.14, the pseudo-second-order kinetics model has the highest correlation

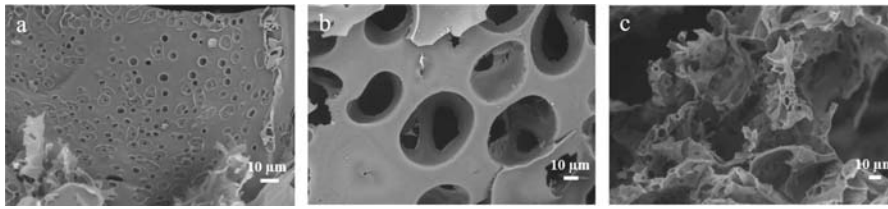


Figure 18.26 SEM images of (a) AC550(3.4), (b) AC750(3.4), and (c) AC950(3.4).
From Li, S., Li, M., & Zhang, X. (2024). Activated carbon derived from silk sericin for efficient adsorption of methylene blue in aqueous solutions. *Macromolecular Research*, 32(5), 443−452. https://doi.org/10.1007/s13233-023-00237-3.

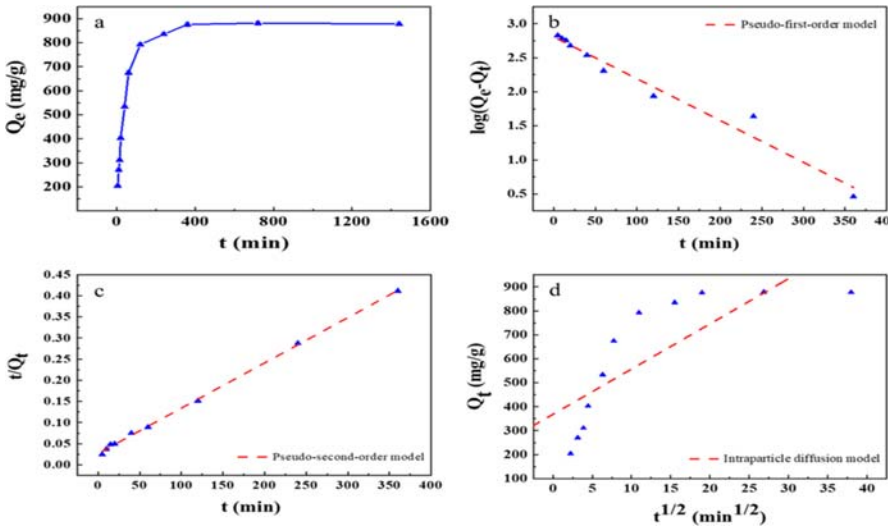


Figure 18.27 Adsorption kinetics study. (a) Adsorption performance of AC750(3.4) in various adsorption times and its fitting into the (b) pseudo-first-order, (c) pseudo-second-order, and (d) intraparticle diffusion models.
From Li, S., Li, M., & Zhang, X. (2024). Activated carbon derived from silk sericin for efficient adsorption of methylene blue in aqueous solutions. *Macromolecular Research*, 32(5), 443−452. https://doi.org/10.1007/s13233-023-00237-3.

coefficient (R^2) among the three models. Additionally, the equilibrium adsorption capacity calculated by the pseudo-second-order model (Q_2) closely matches the experimental measurement (Qe). Therefore, the pseudo-second-order model provides the best description of the adsorption kinetics, suggesting that the rate-limiting step of the adsorption process is the valency force between MB molecules and AC750(3.4), generated through electron sharing/exchange (Choudhary et al., 2020; Wu et al., 2019).

Table 18.14 Kinetic parameter data for MB adsorption onto AC750(3.4).

Sample	Pseudo-first order			Pseudo-second order			Intraparticle diffusion		
	Q_1 (mg/g)	K_1 (minutes^{-1})	R^2 (%)	Q_2 (mg/g)	K_2 (g/mg/minutes)	R^2 (%)	K_i (mg/g·minutes$^{1/2}$)	C_i	R^2 (%)
AC750	641.94	0.0141	96.37	934.57	0.00004	99.87	85.85	1.793	60.31

From Li, S., Li, M., & Zhang, X. (2024). Activated carbon derived from silk sericin for efficient adsorption of methylene blue in aqueous solutions. *Macromolecular Research*, 32(5), 443−452. https://doi.org/10.1007/s13233-023-00237-3.

7.6 pH effects on MB adsorption

From Fig. 18.28, it can be observed that increasing the pH from 2 to 10 results in enhanced MB adsorption, with a peak adsorption capacity of 898.8 mg/g. However, further increasing the pH from 10 to 12 reduces the adsorption capacity to 863.2 mg/g. The pH of the solution significantly impacts adsorption by affecting the surface charge of the adsorbent (Li et al., 2025). To explore this effect, the zeta potential of AC750(3.4) at various pH values was measured, revealing a more negative zeta potential with increasing pH.

The experimental results show that activated carbon exhibits higher adsorption capacity for MB molecules in basic solutions compared to acidic ones. This can be attributed to the increased negative charge on the surface of AC750(3.4) with rising pH, which enhances its interaction with the positively charged MB molecules. The decrease in adsorption capacity at pH 12 is due to a hypsochromic shift in the absorption spectrum of MB, rather than a loss in the adsorption capacity of AC750(3.4) (Ji et al., 2022).

7.7 Temperature's effect on MB adsorption and thermodynamic interpretation

Fig. 18.29a shows that the adsorptive performance of AC750(3.4) for MB decreases as the adsorption temperature increases, with the highest removal rate occurring at 5°C. Using the van't Hoff equation, the enthalpy (ΔH) and entropy (ΔS) changes were derived from the experimental data (Fig. 18.29b), and these were used to calculate

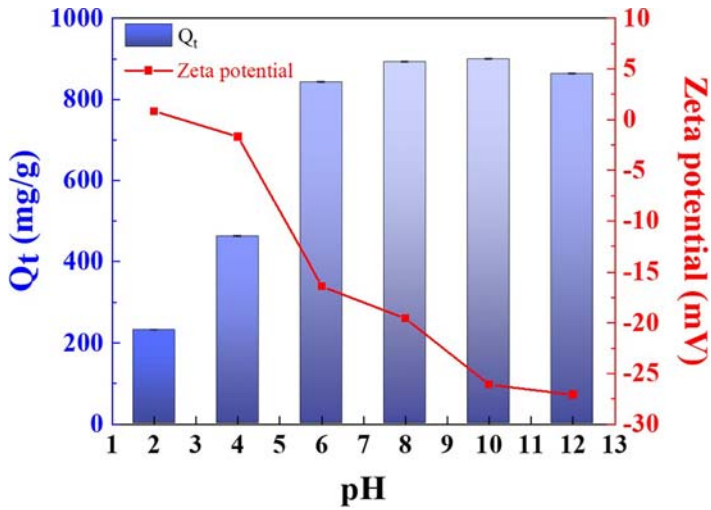


Figure 18.28 MB adsorption and the corresponding zeta potential at various solution pH values. From Li, S., Li, M., & Zhang, X. (2024). Activated carbon derived from silk sericin for efficient adsorption of methylene blue in aqueous solutions. *Macromolecular Research*, 32(5), 443−452. https://doi.org/10.1007/s13233-023-00237-3.

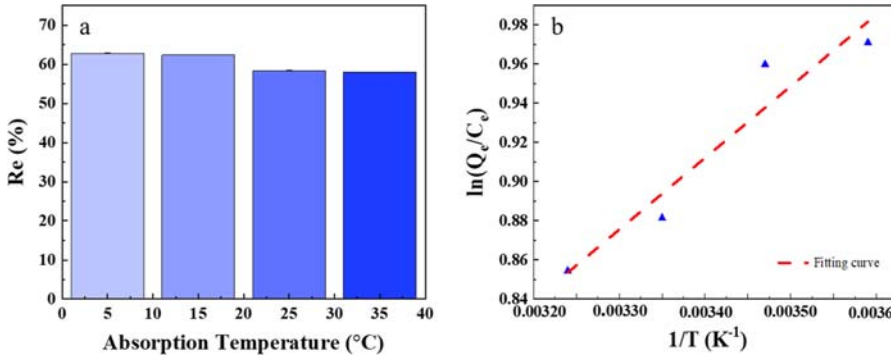


Figure 18.29 (a) Effect of temperature on MB sorption; (b) van't Hoff thermodynamic plot. From Li, S., Li, M., & Zhang, X. (2024). Activated carbon derived from silk sericin for efficient adsorption of methylene blue in aqueous solutions. *Macromolecular Research*, 32(5), 443−452. https://doi.org/10.1007/s13233-023-00237-3.

the changes in free energy (ΔG). It should be noted that this method assumes the effect of temperature on enthalpy and entropy changes is negligible (Lima et al., 2024; Na et al., 2020). Table 18.15 reveals that the ΔG values are negative at all four adsorption temperatures, indicating that the adsorption process is spontaneous. The consistent ΔG values suggest that the equilibrium position is independent of the adsorption temperature. Additionally, the adsorption process is exothermic, as indicated by a negative ΔH, making it more favorable at lower temperatures (Asman et al., 2024). The negative ΔS value suggests a decrease in energy dispersion at the AC750(3.4)/solution interface during adsorption, implying that the adsorbed MB molecules are more constrained than those in the solution phase (Chen, Hu, et al., 2024).

7.8 Adsorption isotherm

Under optimal pH and temperature conditions, the SS-based activated carbon prepared in this study achieved a maximum adsorption capacity of 964.63 mg/g (Fig. 18.30a), surpassing other SS-based adsorbents (Hong et al., 2020; Ji et al., 2022; Kwak et al., 2018) and comparable to biomass-derived activated carbons (Table 18.16). To

Table 18.15 Thermodynamic parameters of adsorption processes from the van't Hoff equation.

T (K)	ΔG (kJ/mol)	ΔH (kJ/mol)	ΔS ($J \cdot K^{-1} \cdot mol^{-1}$)
278.15	-2.26 ± 0.29	-3.045 ± 0.62	-2.768 ± 1.137
288.15	-2.23 ± 0.27		
298.15	-2.20 ± 0.26		
308.15	-2.19 ± 0.29		

From Li, S., Li, M., & Zhang, X. (2024). Activated carbon derived from silk sericin for efficient adsorption of methylene blue in aqueous solutions. *Macromolecular Research*, 32(5), 443−452. https://doi.org/10.1007/s13233-023-00237-3.

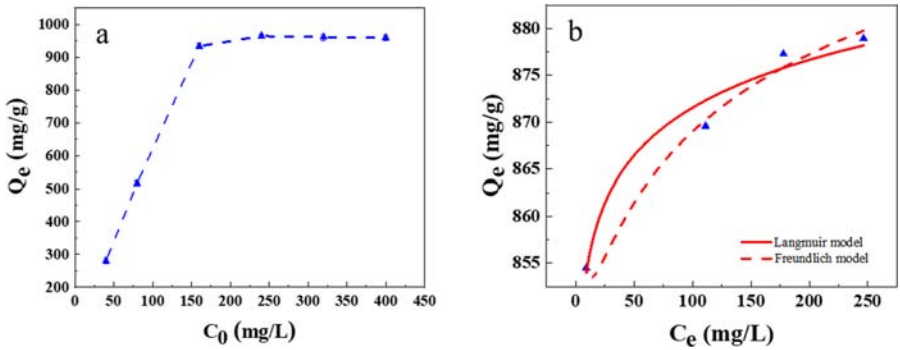


Figure 18.30 (a) Adsorption capacity of AC750(3.4) for MB at various initial concentrations; (b) adsorption isotherm curves for MB adsorbed by AC750(3.4).
From Li, S., Li, M., & Zhang, X. (2024). Activated carbon derived from silk sericin for efficient adsorption of methylene blue in aqueous solutions. *Macromolecular Research*, 32(5), 443−452. https://doi.org/10.1007/s13233-023-00237-3.

Table 18.16 MB adsorption capacity of activated carbon recently reported. Q_m is the maximum adsorption capacity.

Sources of biochar	Q_m (mg/g)	Activator	References
Cellulose, xylan, and lignin	666	H_3PO_4	Lai et al. (2023)
Paper	497	NaOH	Zhang et al. (2023)
Cocoa pod husk	445	KOH/NaOH/K_2CO_3/Na_2CO_3	Yeboah and Zhou (2021)
Bamboo	199.72	H_3PO_4	Tang et al. (2023)
Pine sawdust	160	CO_2/H_2O	Liu et al. (2022)
Chickpea peel	523.56	KOH	Jahan et al. (2023)
Eucalyptus residue	977	H_3PO_4	Han et al. (2020)
Banana peels	1584.95	KOH	Yu et al. (2018)
Quinoa husk	561.72	KOH	Chen et al. (2018)

From Li, S., Li, M., & Zhang, X. (2024). Activated carbon derived from silk sericin for efficient adsorption of methylene blue in aqueous solutions. *Macromolecular Research*, 32(5), 443−452. https://doi.org/10.1007/s13233-023-00237-3; Copyright (2024), with permission from the Springer Nature.

elucidate the adsorption mechanism and determine the maximum capacity of AC750(3.4), adsorption isotherm models were applied. The Langmuir and Freundlich models were used for analysis (Fig. 18.30b) (Diao et al., 2024). Data in Table 18.17 indicate that the Langmuir model provided a more accurate representation of the adsorption process than the Freundlich model, as evidenced by a higher coefficient of determination (R^2). These results suggest that the adsorption of MB on

Table 18.17 Parameters for the Langmuir and Freundlich isotherm models.

Sample	Langmuir isotherm model			Freundlich isotherm model		
	R_L	K_L (L/mg)	R^2 (%)	n	K_F (L/mg)	R^2 (%)
AC750(3.4)	0.092	0.0085	99.97	0.834	3.793	84.71

From Li, S., Li, M., & Zhang, X. (2024). Activated carbon derived from silk sericin for efficient adsorption of methylene blue in aqueous solutions. *Macromolecular Research*, 32(5), 443−452. https://doi.org/10.1007/s13233-023-00237-3.

SS-derived activated carbon involves chemisorption, involving electron transfer, exchange, or sharing between MB and the activated carbon. Furthermore, it implies monolayer coverage of MB on uniformly distributed active sites with similar affinities (Choudhary et al., 2020). The value of R_L lies between 0 and 1 indicating favorable adsorption (Salah Elbanna et al., 2024).

7.9 Physicochemical characteristics of AC750(3.4)

Based on the elemental composition in Table 18.18, carbon and oxygen are the primary elements in the SS/CMCS hydrogel. However, after activation and carbonization, carbon becomes the dominant element in AC750(3.4), with a significant reduction in oxygen, nitrogen, and hydrogen. This results in lower H/C, O/C, and (N + O)/C ratios, indicating the development of aromatic and hydrophobic characteristics, as well as a reduction in polar functional groups (Kim et al., 2020).

The surface functional groups of AC750(3.4) were analyzed using FTIR both before and after MB adsorption (Fig. 18.31). A broad peak between 970 and 1300 cm^{-1} corresponds to C−O stretching (Xue et al., 2022), while the peak at 1384 cm^{-1} indicates C−N stretching, suggesting nitrogen incorporation into the carbon structure (Lota et al., 2016). These nitrogen and oxygen sites on the surface enhance electrostatic interactions with cationic MB, contributing to efficient adsorption (Rehman & Park, 2019). The peak at 1631 cm^{-1} is attributed to C═C stretching in aromatic rings (Elizalde-González et al., 2017), and π-electron donor-acceptor interactions between MB and the SS-derived carbon further improve adsorption performance. The FTIR spectrum of AC750(3.4) post-MB adsorption shows overlapping peaks with pure MB, confirming MB adsorption on AC750(3.4)'s surface.

8. Future directions

The separation of sericin from solutions can be efficiently achieved through electrochemical deposition at low voltage within a short timeframe. By employing a parallel circuit design, multiple electrochemical deposition experiments can be conducted simultaneously, significantly enhancing both experimental efficiency and yield.

Table 18.18 Elemental contents of SS/CMCS hydrogel and AC750(3.4).

Materials	Elemental contents (%)					O/C (mol/mol)	H/C (mol/mol)	(N + O)/C (mol/mol)
	N	C	H	S	O			
SS/CMCS hydrogel	7.24	42.48	6.098	0.257	36.63	0.647	1.723	0.793
AC750(3.4)	0.9	84.96	0.644	0.224	5.612	0.04957	0.0910	0.0586

From Li, S., Li, M., & Zhang, X. (2024). Activated carbon derived from silk sericin for efficient adsorption of methylene blue in aqueous solutions. *Macromolecular Research*, 32(5), 443−452. https://doi.org/10.1007/s13233-023-00237-3.

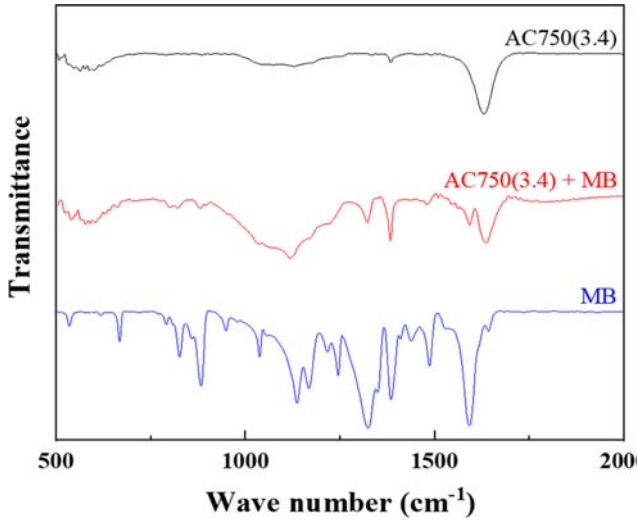


Figure 18.31 FTIR spectra of MB and AC750(3.4) before and after MB adsorption.
From Li, S., Li, M., & Zhang, X. (2024). Activated carbon derived from silk sericin for efficient adsorption of methylene blue in aqueous solutions. *Macromolecular Research*, 32(5), 443−452. https://doi.org/10.1007/s13233-023-00237-3.

The recovery and carbonization of sericin is an energy-intensive process. According to the life cycle assessment, the sericin recovery scenario has higher ecosystem impacts than the nonrecovery scenario, and the highest impact was from the nonrenewable energy usage (Capar et al., 2022). To address this challenge, utilizing green and renewable energy sources, such as wind and solar power, integrating advanced heating technologies, and optimizing reactor designs are crucial. These strategies can help reduce the energy consumption, thereby improving the sustainability of SS-derived activated carbon production.

Moreover, exploring low-energy, efficient regeneration technologies are essential to ensure that sericin-based carbon adsorbents retain their high adsorption performance after regeneration. Achieving continuous regeneration and use of adsorbents can reduce the frequency of replacement and waste generation, enhancing sustainability.

The activation process is crucial for increasing the specific surface area and pore structure of SS-derived activated carbon, thereby enhancing its adsorption capacity. However, the activation process also poses challenges such as potential environmental pollution from chemical activators, operational complexity, and increased costs. Therefore, researching and developing more efficient, environmentally friendly, and cost-effective activation processes is a critical direction for the future.

Last but not the least, the effluents from textile industry generally include adsorbates other than organic dyes and heavy metal ions, which might affect the adsorption capacity of SS-derived carbon. Therefore, it is important to consider the matrix background of the effluents while optimizing the adsorption condition.

Overall, these strategies and research directions can help optimize the production and application of SS-derived carbon adsorbents, ensuring their effectiveness and sustainability in environmental applications.

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Sericin-based 'green' and sustainable biomaterial for waste-water purification as a bioremediation strategy

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Divya Susan Koshy [1,2], *Rohit Saxena* [2] *and Ruchi Agrawal* [1,2,3,4]
[1]Deakin University, Geelong, VIC, Australia; [2]Center for Excellence in Agriculture Nanotechnology, TERI-Deakin Nanobiotechnology Center, Gurugram, Haryana, India; [3]Department of Biotechnology, TERI School of Advanced Studies (TERI SAS) University, New Delhi, India; [4]Renewable Resources and Enabling Sciences Center, National Renewable Energy Laboratory, Golden, CO, United States

1. Introduction

Water pollution refers to the contamination of water bodies such as rivers, lakes, oceans, and groundwater by harmful substances, making them unsuitable for its intended use and damaging aquatic ecosystems (Khan et al., 2022). The everyday production of wastewater from factories and industries releases pollutants like heavy metals, pharmaceuticals, cosmetics, organic dyes, solvents, and other persistent pollutants (Manasa & Mehta, 2020, pp. 197−219). Agricultural runoff carries fertilizers, pesticides, and animal waste into water systems (Satlewal et al., 2022). Excessive nutrients like nitrogen and phosphorus from fertilizers can cause algal blooms, depleting oxygen levels in the water and leading to fish kills. Pesticides can harm aquatic organisms and disrupt ecosystems. Improper disposal of household chemicals and garbage also contribute to water pollution (Wato et al., 2020). Untreated sewage and wastewater from urban areas can contain pathogens, organic matter, and chemicals, contaminating water bodies and posing risks to public health (Eriksson et al., 2003; Shahidul Islam & Tanaka, 2004). Mining operations can introduce various pollutants into water bodies, including heavy metals like mercury, arsenic, and lead. These pollutants can leach into groundwater or be carried by runoff into nearby streams and rivers, causing long-term damage to aquatic ecosystems and human health (Shahidul Islam & Tanaka, 2004). Accidental oil spills from ships, pipelines, or offshore drilling platforms can have devastating effects on marine environments. Oil coats the surface of the water, suffocating marine life and causing widespread ecological damage. It also poses risks to coastal communities and industries dependent on fishing and tourism (Shahidul Islam & Tanaka, 2004). The proliferation of plastic waste is a significant concern for water bodies worldwide. Plastics take hundreds of years to decompose and can accumulate in oceans, lakes, and rivers, harming marine animals through ingestion

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and entanglement. Microplastics, small plastic particles, also pose risks to aquatic life and human health. The lack of established guidelines on these micropollutants makes it difficult to control their discharge from the above-mentioned sources and can pose harmful threats to both humans and aquatic organisms (Shahidul Islam & Tanaka, 2004). Therefore, it is necessary to decontaminate wastewater before it can be discharged into rivers and lakes to avoid exacerbating groundwater pollution. To address these ecological challenges, significant efforts have been made to enhance the efficacy of remediation methods and to innovate new techniques for detecting, quantifying, and improving the efficiency of samples. The various remediation techniques involve photocatalytic degradation (Chong et al., 2010; Som et al., 2020), enzymatic degradation (Kaushal et al., 2021; Saravanan et al., 2021), chemical degradation (Gupta et al., 2012), and physical separation techniques like flocculation, coagulation (Ho et al., 2019; Prakash et al., 2014), and adsorption (Carabineiro et al., 2011; Guilherme L. Dotto & McKay, 2020; Hua et al., 2012; Ihsanullah et al., 2015; Matei et al., 2021; Sreeprasad et al., 2011; Streit et al., 2019; Zubair et al., 2020). In order for any of the aforementioned techniques to demonstrate exceptional efficacy, the type of material used is crucial; it must be inexpensive, readily tuneable, chemically and mechanically robust, and widely accessible. The silk protein known as sericin is one such substance that scientists have studied in the last 10 years.

In this context, the environmental friendliness, biodegradability, and efficacy of biopolymer-based materials in eliminating a variety of contaminants have attracted a great deal of interest (Kaur, Singh, et al., 2024; Kaur et al., 2024; Sharma, Kochar, et al., 2024; Sharma et al., 2024; Raj et al., 2024; Satlewal et al., 2023). Sericin, a byproduct of silk protein, has been identified as a particularly interesting option for use in water purification processes. Hydroxyl, carboxyl, and amino groups are just a few of the functional groups that make sericin a hydrophilic protein that helps remove impurities from water via adsorption (Kwak & Lee, 2018).

Silk sericin is a protein-based waste product from the sericulture (Salunkhe & Jadhav, 2018) and textile industry (Aramwit et al., 2012; Orlandi et al., 2020) that is dumped in tonnes in water systems. Materials based on sericin are significant because of their many attributes. Sericin has strong binding affinities for organic pollutants, heavy metals, and dyes. It also forms films, is highly biocompatible, and has the potential to be functionalized. These properties enable the creation of advanced materials like fibers, membranes, composite, and nanomaterial adsorbents (Fig. 19.1) (Jaramillo-Quiceno et al., 2023; Sharma et al., 2022; Satlewal et al., 2021). Furthermore, sericin is a sustainable substitute for traditional water purification materials because of its biodegradability, which guarantees that it does not contribute to long-term environmental damage. By utilizing sericin protein, the researchers demonstrate that sericin-based materials have great potential for water purification due to their unique properties and efficient removal of contaminants. This innovative approach not only provides a sustainable solution for water treatment but also holds the promise of transforming sericin from a waste product into a valuable resource for environmental preservation and resource utilization in the silk industry.

The objective of this chapter is to provide an overview of the current state of water purification technologies and discuss the role of sericin-based materials in addressing

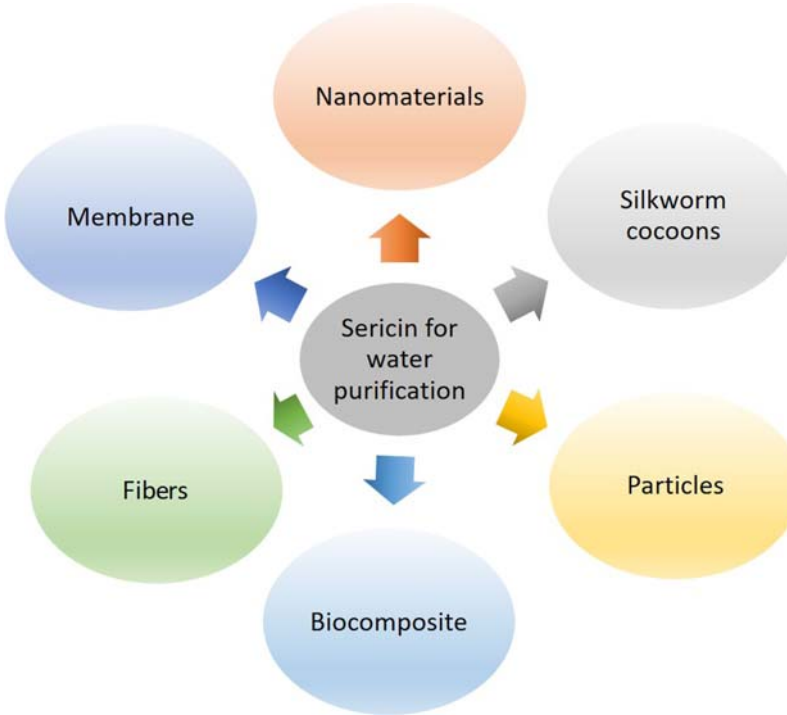


Figure 19.1 Sericin-based materials for wastewater treatment.

the limitations of traditional methods. It will explore the unique properties of sericin that make it suitable for water purification, the mechanisms through which sericin-based materials remove contaminants, and the potential applications of these materials in creating more efficient, eco-friendly water treatment systems.

2. Types of sericin-based materials for water purification

Sericin, a natural protein extracted from silkworms, has emerged as a promising material for water purification due to several key properties:

1. **High purity and recovery rate**: Sericin can be obtained with a high recovery rate using membrane separation techniques, ensuring its effective utilization in water purification processes (Li et al., 2015).
2. **Biological properties**: Sericin exhibits significant biocompatibility, antibacterial, antioxidant, and moisturizing properties. These characteristics make it suitable for developing membranes that can effectively filter and purify water while providing additional benefits like reducing microbial contamination (Kunz et al., 2016).

3. **Environmental impact**: Utilizing sericin, which is typically a by-product of silk production, helps in managing and reducing wastewater pollution. This not only aids in environmental protection but also promotes sustainable use of natural resources (Silva et al., 2022).
4. **Versatility in applications**: Research has shown that sericin can be integrated into advanced materials such as reduced graphene oxide (r-GO) to enhance the performance of water purification membranes. This versatility in doping materials illustrates the potential of sericin to contribute to innovative solutions in water treatment technologies (Deka et al., 2022).
5. **Presence of functional groups**: Sericin possesses intrinsic characteristics such as hydrophilicity, amphotericity, antioxidative, antifouling, and antimicrobial properties and is nontoxic. The presence of functional groups such as carboxyl, hydroxyl, and amino groups makes sericin a best candidate for biosorption (Verma & Subbiah, 2017).

2.1 Silkworm cocoons

The possibility of employing silkworm cocoons as a biosorbent to extract artificial dyes from wastewater produced by the food sector was investigated by Dusi et al. (2018) (schematic presented in Fig. 19.2). The study examined the impact of pH on the adsorption of tartrazine dye onto *Bombyx mori* silkworm cocoons throughout a pH range of 2.0−8.0. The findings indicated that the highest removal of the dye occurred at lower pH values. This can be explained by the interactions between the negative charge of the tartrazine dye's sulfonate group ($-SO_3^-$) and the positive charges of the surface amino acids found in both proteins of the silkworm cocoons, such as the protonation of the amide groups ($-NH_2$). At the initial tartrazine concentration of 250 mg/L, the greatest tartrazine mass adsorbed was 63.71 mg/g. The initial hours of interaction with the silkworm cocoon demonstrated a higher rate of tartrazine adsorption; however, the rate of adsorption decreased significantly after 3 hours. About 73.9% of the tartrazine was adsorbed from an aqueous solution containing

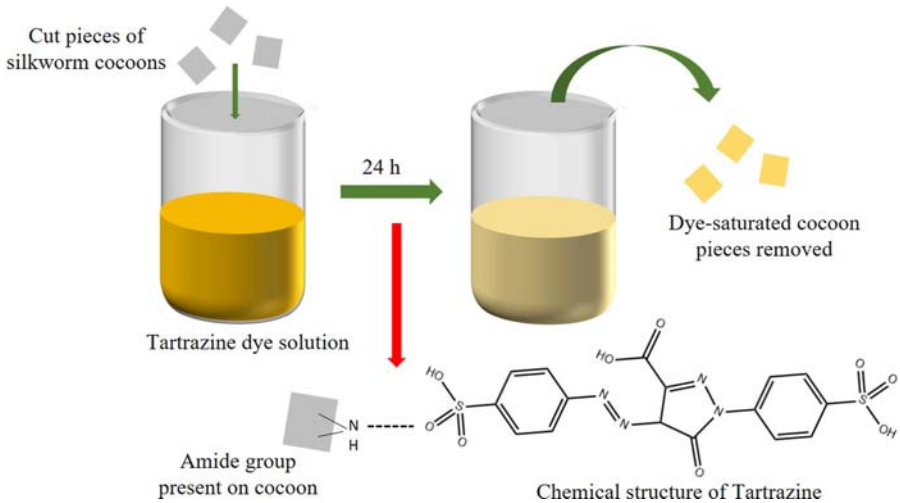


Figure 19.2 Silkworm cocoons used for biosorption of tartrazine dye.

50 mg/L of the azo dye in the first 6 hours. Less than 6.92% of the tartrazine was extracted from the solution at 6 and 24 hours; however, the adsorption rate decreased from 0.021 to 0.003 mg/g/minutes, meaning that 85.4% of the adsorption velocity was lost. Even while tartrazine can still be absorbed by the silkworm cocoon, it is claimed that the biosorption process is approaching steady state after a 24 hours period. Because of the diminishing active sites of the biosorbent and the decreasing mass transfer potential between the liquid and solid phases, the adsorption rate decreases steadily (Dusi et al., 2018). Activated red mud (maximum adsorption capacity of 136.56 mg/g) (Bacioiu et al., 2017), biomass from Spirulina platensis (363.2 mg/g) (Dotto et al., 2013), *Moringa oleifera* seeds (91.27 mg/g) (Reck et al., 2018), peach palm waste (maximum removal efficiency of 94.7%) and cassava waste (74.4%) (Dos Santos et al., 2021), and hydrochars from *Pinus caribaea* (23 mg/g) (Silva Andrade et al., 2023) have all been used as biosorbents for the effective removal of tartrazine over the last 10 years. While silkworm cocoons can be used directly from the environment, these biosorbents demonstrated superior removal efficiency but needed to be treated in order to activate.

2.2 Sericin-based particles

Chen et al. (2012) studied the adsorption of Acid Yellow 34 (AY 34), copper(II) phthalocyanine-3,4′,4″,4‴-tetrasulfonic acid (CuPcTSA) and methylene blue (MB) using sericin powder. To reduce its solubility, sericin was repeatedly boiled, which altered its structure from a random coil to a beta-sheet. At room temperature and pH 2.5, the adsorption capacities of sericin were 400 mg/g for AY 34 and 150 mg/g for CuPcTSA. When the pH was lowered to 1.5, the adsorption capacities increased to 1286 mg/g for AY 34 and 350 mg/g for CuPcTSA. This increase is attributed to the electrostatic interaction between protonated sericin and the negatively charged anionic dyes AY 34 and CuPcTSA at lower pH levels. As the pH rises, sericin becomes negatively charged, leading to increased repulsion between the sericin and the dyes. Although CuPcTSA is more negatively charged than AY 34, its larger structure limits adsorption to the surface of the sericin (Chen et al., 2012).

Sericin microspheres or beads have been widely studied for drug delivery; however, Kwak et al. (2013) demonstrated the use of sericin beads for the removal of chromium (VI) [Cr(VI)]. The sericin solution was prepared in LiCl/DMSO (dope solution), which was then dropped into alcohol coagulants like methanol and ethanol that resulted in sericin beads. Finally, the sericin beads were subjected to cross-linking using glutaraldehyde which increased the insolubility of the beads. The maximum adsorption capacity (q_e) of sericin beads coagulated in methanol for Cr(VI) was observed to be 36 mg/g at pH 2. Sericin is positively charged below isoelectric point (pI; between 4 and 5) and negatively charged above pI. Also, Cr(VI) exists as $HCrO_4^-$ and $Cr_2O_7^{2-}$ between pH 2 and 6. Therefore, positively charged sericin has better affinity to anionic Cr(VI) at pH 2. Additionally, the nature of coagulant also plays an important role in altering the adsorption capacity. In the present study, sericin beads coagulated in methanol have better adsorption efficiency. The more hydrophilic nature of methanol to that of ethanol makes the hydrophilic domain of sericin to face toward the surface that means,

more functional groups become available for Cr(VI) adsorption. The Brunauer-Emmett-Teller (BET) model of adsorption isotherm indicated multilayer adsorption. Even though the sericin beads have compact structure, the chromate ions can potentially penetrate within the beads because of the sericin or the concentration gradient (Kwak et al., 2013).

The adsorption of Cu(II) onto sericin powder followed pseudo-second-order according to a study conducted by Gimenes et al. (2016) that implied the adsorption occurs due to the difference between the concentrations at the adsorbent surface and in solution, and mass transfer is limited only by external resistance. The Langmuir isotherm showed monolayer adsorption process indicated chemical complexation interaction between Cu(II) and functional groups of sericin. The negative Gibbs free energy (ΔG_{ads}) and enthalpy (ΔH_{ads}) indicated the adsorption was spontaneous and exothermic, respectively, which suggested chemisorption process. Furthermore, the negative entropy (ΔS_{ads}) suggested the surface of sericin changed from random coil to organized conformation (Gimenes et al., 2016).

Silva et al. (2016) conducted a study on the biosorption of Bordeaux S dye using sericin powder. They observed that the maximum dye removal reached 214 mg/g under pH 2 and 20°C conditions. The adsorption process was attributed to the interaction between the positive charge present on sericin and the negative charge on the dye's sulfonate group. Furthermore, the reduced adsorption rate at higher temperatures was linked to the weakened electrostatic interaction between the functional groups of sericin and the sulfonate group of the dye. The kinetics of adsorption followed a pseudo second-order model, where adsorption was driven by the concentration gradient between the adsorbent surface and the solution. The negative values of ΔG_{ads} and ΔH_{ads} suggested that the adsorption was spontaneous and exothermic, respectively. On the other hand, the positive ΔS_{ads} indicated increased randomness at the solid−solution interface, with structural changes and enhanced affinity between the dye and sericin. The negative ΔH_{ads} also pointed toward physical interaction mechanisms governing the adsorption process, suggesting that electrostatic interaction could be one of the contributing mechanisms (Silva et al., 2016).

Verma and Subbiah (2017) focused on removing ibuprofen via an integrated adsorption-membrane filtration, wherein, the racemic mixture of ibuprofen nonspecifically binds to sericin for complete removal. Sericin was used as an adsorbent for ibuprofen to form bigger complex molecules that can be separated easily via reverse osmosis (RO) filtration. The negatively charged ibuprofen (10 mg/L) at pH 8 adsorbed onto protonated sericin (10 g/L, ∼250 kDa, pH 4) at 40°C and filtered through RO membrane (DOW Filmtec) with molecular weight cut off 200−400 Da ensured complete removal of ibuprofen. At higher temperature like 40°C, the random coil structure of sericin increased due to destabilization of protein, which opened up large number of functional groups that complexed with ibuprofen. The charge-based interaction and random coil structure enhanced the adsorption capacity of sericin and selective removal of ibuprofen (Verma & Subbiah, 2017).

In general, the targeted pollutant forms a complex with the polar functional groups on sericin powder or particles (Fig. 19.3), which can be extracted from the treated

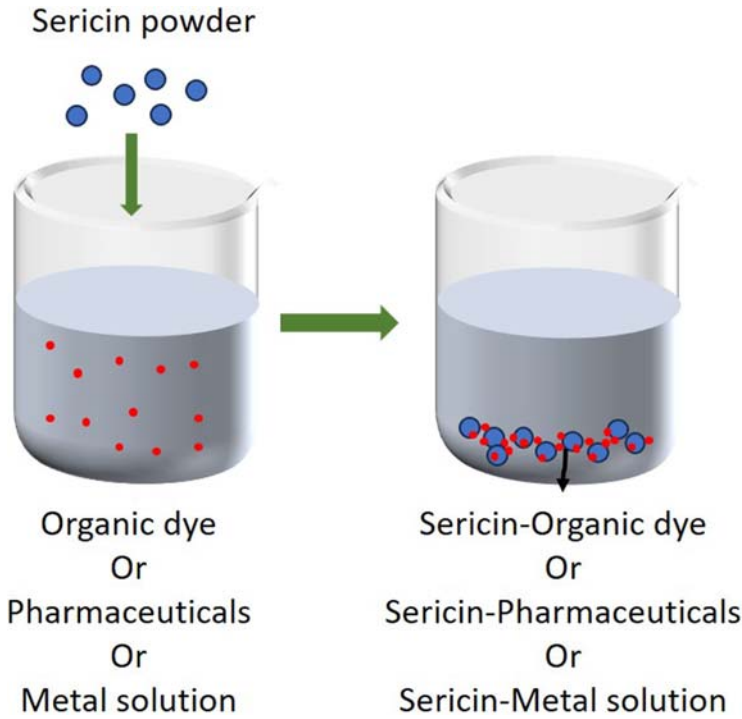


Figure 19.3 Pollutant adsorbed sericin particle for wastewater treatment.

solution via membrane filtration or centrifugation. However, the sericin particle's potential for reuse is yet unclear. As a result, the use of sericin to purify water requires a more sustainable strategy.

2.3 Sericin-based fibers

One-dimensional continuous nano- and micro-scale fibers may now be created easily, affordably, and effectively with electrospinning (Li & Xia, 2004; Sharma, Allardyce, et al., 2024). The resulting fibers are very porous, have a large surface-to-volume ratio, are easily prepared, and are flexible. These properties enable them to effectively adsorb contaminants through chemical or physical interactions (Wu et al., 2013). To date, a lot of work has gone into selecting appropriate polymers, adding functional groups, or creating unique surface structures in order to create effective electrospun fiber adsorbents (Huang et al., 2014; Mahto et al., 2014; Min et al., 2016). Given their abundance and inexpensive cost, natural polymers like sericin provide for appealing adsorption materials.

In order to remove the cationic dye methylene blue from an aqueous solution, Zhao et al. (2015) produced a water-insoluble sericin/β-cyclodextrin/poly (vinyl alcohol) composite nanofiber adsorbent by electrospinning and thermal crosslinking. Although

they are both stable, nontoxic, and soluble in water, β-cyclodextrin and sericin cannot be utilized directly as adsorbents to remove contaminants from wastewater. While the presence of functional groups on sericin makes them good precursors for adsorbents, the unique toroid-shaped molecular structure of β-cyclodextrin forms noncovalent host−guest inclusion complexes with a variety of solid, liquid, and gaseous substances. At 293, 313, and 333 K, respectively, the maximal adsorption capacities are 187.97, 229.89, and 261.10 mg/g (Zhao et al., 2015). Another study produced an MB-imprinted sericin/poly(vinyl alcohol) (PVA) electrospun fiber adsorbent using the molecular imprinting approach. Cross-linked polymers with cavities tailored to a particular analyte are used to create molecularly imprinted polymers (MIPs). Copolymerization of cross-linking and functional monomers with an imprinting molecule or template results in the formation of these cavities (Murray & Örmeci, 2012). In this study, increased sensitivity and selectivity of MB dyes are achieved during wastewater treatment by co-polymerizing sericin and PVA around the MB molecule as a template and then removing the MB molecule. Due to the competing adsorption between the available H+ and MB molecule with the functional groups (carboxyl groups, amino groups, etc.) from sericin, MB, being a cationic dye, is negatively impacted by high concentrations of H+ at low pH levels. More functional groups become deprotonated at higher pH values, which is advantageous for the electrostatic adsorption process' ability to adsorb more cationic MB (Zhao et al., 2017).

The two methods covered in this section both aim to increase the targeted pollutant's adsorption selectivity and sensitivity. They accomplish this by either adding a trapping agent to a sericin-based fiber or by co-polymerizing and cross-linking the fiber to produce specific recognition sites as illustrated in Fig. 19.4.

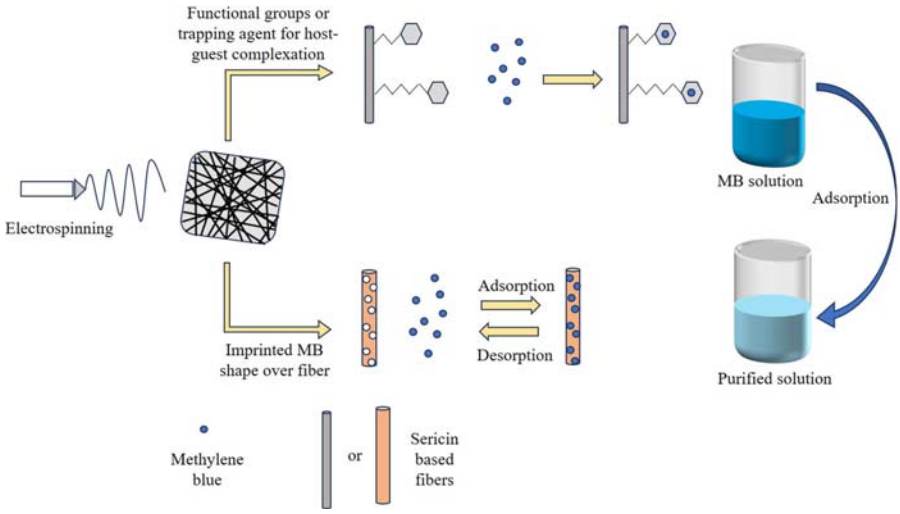


Figure 19.4 Schematic illustration of sericin-based fiber modification for methylene blue (MB) adsorption.

2.4 Sericin-based biocomposite

Sericin is a readily accessible protein composed of 18 different amino acids, many of which possess strong polar side chains like carboxyl, hydroxyl, and amino groups. These polar groups facilitate easy cross-linking, copolymerization, and blending with other polymers, resulting in enhanced biodegradable and environmentally friendly materials (Dash et al., 2009). On the other hand, alginate is a naturally occurring exopolymer made up of β-1,4 linked D-mannuronic and L-guluronic acids. This polysaccharide is biodegradable, inexpensive, and readily available due to its abundant natural sources. Alginic acid and its carboxylic salts are biopolymers with notable properties such as biocompatibility, biodegradability, viscosity enhancement, and the ability to gel with multivalent cations. Encapsulation in polymeric matrices makes alginate a highly promising option for improving the structural properties of biomaterials. Both the polymers sericin and alginate undergo sol−gel transition. Further, the addition of metal ions and thermal-crosslinking at temperature like 100°C makes the biocomposite less water soluble and effective for removal of toxic heavy metals (da Silva et al., 2016; de Andrade et al., 2018; de Andradea et al., 2016; Silva et al., 2017). The various methods utilized for creating the sericin-alginate (SA) biocomposite are shown in Table 19.1 below. The operating conditions and efficiency of these sericin-alginate (SA) biocomposite materials are compiled in Table 19.2.

da Silva et al. (2016) prepared SA biocomposite via an ionic gelation process by mixing 2.5% w/V sericin in sodium alginate (1%−3% w/V) further each blend was dripped into aqueous and alcoholic $CaCl_2$ (3% w/V) solution. Then, the particles were subjected to cross-linking at 40, 100, 125, and 150°C temperatures. Both sericin and alginate are less soluble in alcohol than in water. Alcohol maintains the structure of hydrogel beads, decreasing the solubility of the protein that helps in the cross-linking process. The random coil and α-helix structure decreases. The biocomposites cross-linked at 40 and 100°C had better adsorption capacity for Cu and Zn than higher temperatures. The removal efficiency for Cu was 72%−75%, whereas Zn was 62%−65%. The best cross-linking temperature was found to be 100°C (da Silva et al., 2016). A study conducted by de Andradea et al. (2016) used SA biocomposite thermally cross-linked at 100°C for the removal of chromium (Cr(III)). The maximum adsorption capacity for Cr(III) at pH 3.5 and 40°C was 0.1015 mmol/g (de Andradea et al., 2016). The same SA biocomposite was employed in another investigation by de Andrade et al. (2018) to remove Cr(IV); however, the study found that Cr(IV) was reduced to Cr(III) prior to biosorption. According to the authors, absorbed Cr(IV) onto the surface of the sericin−alginate biocomposite is first reduced to Cr(III) by means of surface-present electron−donor groups such −OH, O═C, and O−CH3 and is then released back into the solution. Additionally, Cr(III) has biosorption kinetics that are five times faster than Cr(IV) (de Andrade et al., 2018). However, the main challenge remained the water solubility and lower adsorption capacity of SA biocomposites. Therefore, to tackle these challenges, cross-linking agents like poly(ethylene glycol) diglycidyl ether (PEG) (Da Costa et al., 2023; Talles Barcelos da Costa et al., 2023; Silva et al., 2017), poly(vinyl alcohol) (PVA) (Barcelos da Costa et al., 2021; Costa et al., 2021; Da Costa et al., 2021; Talles Barcelos da Costa

Table 19.1 Preparation of sericin-alginate (SA) biocomposites.

Sericin-alginate biocomposites				
Cross-linking agent	**Calcium (2+) ion**	**Temperatures for cross-linking**	**Targeted pollutants**	**References**
–	Aq and alc $CaCl_2$	40, 100, 125 & 150°C	Cu & Zn	da Silva et al. (2016)
–	Aq $CaCl_2$	100°C	Cr(III)	de Andradea et al. (2016)
Poly(ethylene glycol) diglycidyl ether (PEG)	Aq and alc $CaCl_2$ Aq and alc $Ca(NO_3)_2$	100°C	Cu, Ni, Cd, Zn, Pb, Cr, Pd, Pt, Au & Ag	Silva et al. (2017)
–	Aq $CaCl_2$	–	Cr(VI) & Cr(III)	de Andrade et al. (2018)
Polyvinyl alcohol (PVA) **Proanthocyanidins (PAs)**	Aq $Ca(NO_3)_2$	100°C	Pd, Pt, Au & Ag	Santos et al. (2019)
PVA	Aq $Ca(NO_3)_2$	100°C	Ytterbium (Yb)	da Costa et al. (2020)
PAs	Aq $Ca(NO_3)_2$	100°C	Au	das Gracas Santos et al. (2020)
PAs	Aq $Ca(NO_3)_2$	100°C	Au	Das Graças Santos et al. (2020)
PVA	Aq $Ca(NO_3)_2$	100°C	Yb	Barcelos da Costa et al. (2021)
PVA	Aq $Ca(NO_3)_2$	100°C	Dysprosium (Dy)	da Costa et al. (2021)
PVA	Aq $Ca(NO_3)_2$	100°C	Lanthanum (La)	Da Costa et al. (2021)
PVA	Aq $Ca(NO_3)_2$	100°C	La	Costa et al. (2021)
PVA	Aq $Ca(NO_3)_2$	100°C	Yb	da Costa et al. (2022)
–	Aq $CaCl_2$	100°C	Cu	Dusi et al. (2022)
PEG **PVA** **PAs**	Aq $CaCl_2$	100°C	Europium (Eu) Erbium (Er)	Talles Barcelos da Costa et al. (2023)
PEG	Aq $Ca(NO_3)_2$	100°C	Eu	Da Costa et al. (2023)
PVA	La(NO3)3 Ca(NO3)2/ La (NO3)3 Ca(NO3)2	100°C	La & Yb	da Costa et al. (2024)

Table 19.2 Operating conditions and efficiency of these SA biocomposite materials.

Biocomposite	Targeted pollutants	pH	Temperature	Time	Removal efficiency (%) or maximum adsorption capacity (q_{max})	References
SA (aq)	Cu	4.0–4.5	25	24 hours	72.2%	da Silva et al. (2016)
	Zn				65.2%	
SA (alc)	Cu				74.5%	
	Zn				63.9	
SA	Cr	3.5	40	4 hours	0.1015 mmol/g	de Andradea et al. (2016)
SAPEG	Cu	3.0–3.5	25	24 hours	65%–75%	Silva et al. (2017)
	Ni				12%–23%	
	Cd				62%–79%	
	Zn				15%–30%	
	Pb				66%–83%	
	Cr				69%–74%	
	Pd				87%–89%	
	Pt				66%–74%	
	Au				98%–99%	
	Ag				60%–63%	
SA	Cr(VI)	2.0	55	50 hours	0.7577 mmol/g	de Andrade et al. (2018)
	Cr(III)	3.5	30	210 minutes	0.023 mmol/g	

Continued

Table 19.2 Operating conditions and efficiency of these SA biocomposite materials.—cont'd

Biocomposite	Targeted pollutants	pH	Temperature	Time	Removal efficiency (%) or maximum adsorption capacity (q_{max})	References
SAPVA	Pd	2.5–3.0	25	24 hours	95.6%	Santos et al. (2019)
	Pt				~70%	
	Au				96.2%	
	Ag				<20%	
SAPAs	Pd				88.3%	
	Pt				~70%	
	Au				99.6%	
	Ag				<20%	
SAPVA	Yb	4.5–5.0	55	24 hours	0.642 mmol/g	da Costa et al. (2020)
SAPAs	Au	2.5–3.0	30	24 hours	201.13 mg/g	das Gracas Santos et al. (2020)
SAPAs	Au	2.5–3.0	25	4.5 days	57.9 mg/g	Das Graças Santos et al. (2020)
SAPVA	Yb	5.0	25	5 hours	0.142 mol/kg	Barcelos da Costa et al. (2021)
SAPVA	Dy	5.0	25	390 minutes	0.139 mmol/g	da Costa et al. (2021)
SAPVA	La	5.22	–	450 minutes	0.152 mol/kg	Da Costa et al. (2021)
SAPVA	La	5.0	55		0.644 mmol/g	Costa et al. (2021)
SAPVA	Yb	5.0	25	76 hours	128.39 mg/g	da Costa et al. (2022)
SA	Cu	3.5	20	6 hours	87.27 mg/g	Dusi et al. (2022)

SAPEG (0.4g in 40 mL)	Eu (1.0 mmol/L) Er (1.0 mmol/L)	5.0	25		0.258 mmol/g 0.259 mmol/g	Talles Barcelos da Costa et al. (2023)
SAPVA (0.4g in 40 mL)	Eu (1.0 mmol/L) Er (1.0 mmol/L)				0.251 mmol/g 0.252 mmol/g	
SAPAs (0.4g in 40 mL)	Eu (1.0 mmol/L) Er (1.0 mmol/L)				0.189 mmol/g 0.194 mmol/g	
SAPEG	Eu	5.0	55	24 hours	0.633 mmol/g	Da Costa et al. (2023)
SAPVA-La	La Yb	4.5−5.0	25	24 hours	100% 94.33%	da Costa et al. (2024)
SAPVA-Ca	La Yb				98.45% 92.06%	
SAPVA-La/Ca	La Yb				99.21% 94.05%	

et al., 2023; da Costa et al., 2020, 2021, 2022; Santos et al., 2019), and proanthocyanidins (PAs) (Talles Barcelos da Costa et al., 2023; das Gracas Santos et al., 2020; Das Graças Santos et al., 2020) were added to the sericin−alginate blend. Crosslinking involves creating a three-dimensional network by connecting polymer chains and is often used to improve the mechanical properties and water resistance of biopolymer materials. The process relies on the reactive groups in the crosslinking agent interacting with functional groups on the polymer chains. In sericin, polar side chains such as amino, hydroxyl, and carboxyl groups act as nucleophilic centers for bonding, while in alginate, the carboxyl group is the main target for the crosslinking agent (Santos et al., 2019).

In order to adsorb hazardous and precious metals, Silva et al. (2017) employed PEG diglycidyl ether as a cross-linking agent in an SA biocomposite that was thermally crosslinked with aqueous and alcoholic $CaCl_2$ and $Ca(NO_3)_2$ at 100°C. For Cu, Cd, Pb, and Zn, the addition of PEG somewhat increased the biosorption capacity; however, precious metals such as Pd, Pt, Au, and Ag showed no change as they attained their maximal adsorption capacity without PEG. Ni showed the least amount of decline. Furthermore, there was no discernible difference in the sericin-alginate-PEG biocomposites' ability to adsorb Ca^{2+} ions in alcoholic or aqueous solutions. Changes to the secondary structure, according to the authors, do not improve the adsorbent's ability to absorb these metals (Silva et al., 2017). Palladium (Pd), platinum (Pt), silver (Ag), and gold (Au) were removed from two new low water-soluble sericin-alginate biocomposites by Santos et al. (2019) by employing PVA and PA. In comparison to the sericin−alginate biocomposite made by da Silva et al. (2016), the one made without PVA and PAs exhibited less water solubility. This variation in solubility was ascribed to the application of $Ca(NO_3)_2$ at elevated concentrations. The random coil and α-helix structure of sericin are changed to β-sheet structure by the presence of PVA and PAs, making the biocomposite more water-stable. The following is the sequence in which sericin-alginate-PVA and sericin-alginate-PAs exhibited metal affinity: gold > palladium > platinum > silver. For Ag, the removal effectiveness of both biocomposites was less than 20%, while it was over 70% for Pt. For the sericin-alginate-PVA biocomposite, the greatest removal efficiency for Au and Pd was 95.6% and 96.2%, respectively, whereas for the sericin-alginate-PAs, it was 88.3% and 99.6%. Additionally, this investigation showed that the adsorption of noble metals was not adversely affected by the inclusion of an additional cross-linking agent (Santos et al., 2019). According to da Costa et al. (2020) at 55°C, SAPVA biocomposites' highest ytterbium (Yb) adsorption capability was 0.642 mmol/g. For five consecutive cycles, these biocomposites showed excellent elution and regeneration efficacy. Moreover, Yb ions were specifically absorbed by these biocomposites from a mixture of harmful metal ions, such as Cd^{2+}, Zn^{2+}, and Ni^{2+} ions (da Costa et al., 2020). Furthermore, according the study by Barcelos da Costa et al. (2021), adding PVA to SAPVA did not increase the SA biocomposites' porosity or surface area (Barcelos da Costa et al., 2021). das Gracas Santos et al. (2020) reported the maximum adsorption capacity of Au to be 237.60 mg/g at 30°C using SA-PAs biocomposites (das Gracas Santos et al., 2020), whereas using SA-PAs in a fixed bed column for

adsorption of Au, the maximum removal efficiency of 98.39% was achieved (Das Graças Santos et al., 2020).

In order to tackle water pollution brought on by organic dyes, solvents, and oils, Wu et al. (2018) set out to build sustainable materials from silk fibroin and sericin. They were successful in creating sericin carbon aerogel (SCB) and regenerated silk fibroin film (rSFF). If rSFF was superior to raw silk fibroin fibers in terms of absorbing azo dyes, then SCB was superior to it when it came to absorbing oils and organic solvents, especially chloroform. Both materials showed promise for recycling as they retained their high absorption efficiency after multiple cycles. The study found that by utilizing sericin, a byproduct of the silk industry, these novel materials provide efficient and environmentally friendly ways to cure water contamination (Wu et al., 2018).

The goal of Kwak and Lee was to increase the efficiency of removing hexavalent chromium (Cr(VI)) from contaminated water by using biomass-based adsorbents. They produced silk sericin beads functionalized with polyethylenimine (PEI) to boost the beads capacity to absorb Cr(VI). The process involved transforming sericin beads with PEI and then confirming the change with a range of analytical techniques, such as scanning electron microscopy (SEM) and Fourier transform infrared spectroscopy (FTIR). Their results showed that compared to untreated sericin beads (345.56 mg/g), sericin beads treated with PEI had a much higher capacity to remove Cr(VI) (365.35 mg/g). The results of the study indicate that since sericin beads treated with PEI can both adsorb and convert Cr(VI) to the less dangerous Cr(III), they hold promise as a material for effectively remediating Cr(VI) from aqueous solutions (Kwak & Lee, 2018).

2.5 Sericin-based membrane

Membranes play a crucial role in wastewater treatment as they act as a selective barrier, letting water through while keeping contaminants out. Advances in membrane materials and related engineering disciplines have surely contributed to their broad application in water treatment and reuse as well as resource recovery, considerably improving treatment efficiency and reducing costs (Zuo et al., 2021). In pressure-driven technology, there are four processes based on the membrane's pore size: microfiltration (MF), ultrafiltration (UF), nanofiltration (NF), and reverse osmosis (RO) (He et al., 2019). A membrane's pore structure and the material's physical and chemical characteristics mostly determine its performance (Lee et al., 2016). The different types of materials used for membrane preparation widely reported are polymers (Ahmad & Ooi, 2013; Kim et al., 2002; Liu et al., 2011; Lohokare & Agarwal, 2008; Qin et al., 2003; Saljoughi, 2012; Shibutani et al., 2011; Soyekwo et al., 2014; Yuliwati, 2011) and inorganic materials (DeFriend et al., 2003; Kumar et al., 2014; Mohmood et al., 2013). Despite the widespread usage of polymer-based membranes, inorganic membranes have recently attracted a lot of attention due to their remarkable resistance to heat, chemicals, and mechanical pressures, as well as their recyclability and usually photocatalytic qualities. The primary disadvantage of the majority of the polymeric membranes is that they have a significant fouling tendency due to their intrinsic hydrophobicity, which frequently results in higher operating costs, shorter

lifespans, irreproducible separation performance, and a restricted application range. Chemical/thermal stability, oxidation/pH resistance, and mechanical strength are generally not exhibited simultaneously by most of the polymeric membrane materials. Improved permeation flux, resistance to pollution, stability of operating pressure, and longevity of membrane service life have all received a lot of attention. Transforming these polymeric membranes into hydrophilic surfaces is one way to modify their surface. Due to the hydrophobic character of many foulants, such as proteins and organics, it is widely acknowledged that improving the membrane's hydrophilicity may lessen fouling problems. Hydrophilic polymeric membranes can be made using a variety of techniques (Lee et al., 2016). Cross-linking polymers with hydrophilic organic materials, like sericin, is one such method.

Gimenes et al. (2007) combined with poly(vinyl alcohol) (PVA) and chemically crosslinked with dimethylurea to create water-selective pervaporation membranes. With 8.5 weight percent water in the feed, the sericin/PVA blend membranes showed preferential permeability toward water, resulting in a separation factor of 145−172 at a permeating water concentration of 93.1−94.1 weight percent. The great hydrophilicity of both sericin and PVA was shown to improve the preferred sorption of water in the membrane, which was the main cause of this high selectivity. There was a trade-off between permeability and selectivity when the crosslinking density of the membranes was observed to increase while decreasing the sorption uptake and improving the sorption selectivity. Overall, the sericin/PVA blend membranes demonstrated superior performance compared to membranes made from either sericin or PVA alone for ethanol dehydration by pervaporation (Gimenes et al., 2007).

Lukka Thuyavan et al. (2015) concentrated on employing phase inversion to create biopolymer sericin and polyvinylpyrrolidone (PVP) to create membranes based on polyethersulfone (PES). When compared to clean PES membranes, the sericin-incorporated membranes showed enhanced hydrophilicity, pure water permeability, and antifouling characteristics. Out of all the membranes that were examined, the combination of both PVP and sericin produced the loose porous membrane structure with the maximum average pore radius of 22 nm. Additionally, compared to the pristine PES membrane, this membrane demonstrated a 34-fold greater pure water permeability. Overall, the PES/sericin/PVP membrane demonstrated better characteristics and achieved maximum cadmium removal when used with the polyethyleneimine (PEI) ligand (Lukka Thuyavan et al., 2015).

Verma and Subbiah (2019) has demonstrated that sericin-coated microfiltration membranes can effectively remove drug-based micropollutants from water. Functional groups like amide, carboxyl, and hydroxyl that are provided by the sericin coating can interact with medication molecules through hydrogen bonding and charge-based interactions. These membranes were shown in research to be capable of eliminating antibiotics and nonsteroidal antiinflammatory medications (NSAIDs) at concentrations as low as 20 $\mu g\ L^{-1}$. The removal efficiency was influenced by interactions such as hydrogen bonding and charge-based interactions, with anionic drugs being removed more effectively than their uncharged counterparts. The drugs that were removed with the highest efficiency were ibuprofen, diclofenac, amoxicillin, ciprofloxacin, estrone, and β-estradiol. The membranes also demonstrated the ability to regenerate

effectively, maintaining their filtration capacity over multiple cycles, which is crucial for practical applications in water treatment systems (Verma & Subbiah, 2019).

Another innovative application involves sericin-doped reduced graphene oxide membranes, which have been evaluated for their potential in forward osmosis (FO) processes. These membranes show promise for crystallizing antibiotics, indicating their versatility beyond traditional filtration methods. The incorporation of sericin enhances the membrane's properties, making it suitable for various separation applications in water purification (Deka et al., 2022).

Ding et al. (2023) have looked at combining the durability of fibroin with the biocompatibility of sericin to maximize their advantages. The natural combination present in the silkworm cocoon (SC) is one potential resource. Regrettably, SC's inherent hydrophobicity and erratic mechanical properties make it unsuitable for treating greasy wastewater. To get over these limitations, a low-cost method was created to improve the mechanical and hydrophilicity properties of SC. To enhance the hydrophilicity and antifouling properties of the SC surface, a supramolecular gel (SMG) was applied, accompanied by an intermediate modification layer containing polydopamine particles (PDPs). The resulting SC@P-SMG membrane has outstanding self-cleaning properties, strong mechanical strength, and good antifouling properties. According to Ding et al. (2023), it shown promise in cleaning wastewater that included methylene blue, Pb^{2+} ions, and emulsified oil. The membrane is a viable option for a number of water treatment applications due to its excellent filtration efficiency, flux, and reusability (Ding et al., 2023).

Sericin-based membranes represent a noteworthy advancement in water purification technologies, particularly for the removal of pharmaceutical contaminants. They are an invaluable contribution to the fields of environmental engineering and water treatment because of their special qualities as well as their capacity to regenerate and retain high efficiency. Further investigation and advancement may expand their potential uses and efficacy in other purifying procedures.

2.6 Sericin-based nanomaterials

Intriguing advancements in the creation of nanoflowers through the cooperative interaction of biological molecules and metal ions have also been made throughout the last 10 years. The synergistic functionalities of these hybrid materials have been greatly improved by this breakthrough (Ge et al., 2012). A hierarchical flower-like structure has a significantly wider surface area than more compact structures like solid spheres or polyhedra, and its capabilities are further expanded by the presence of porosity. Furthermore, compared to free molecules in solution, the biomolecules that are trapped and immobilized in the center of the nanoflowers exhibit higher activity, durability, and stability. Constrained biomolecules supply active surface functional groups that are especially necessary for the use of hierarchical designs in adsorption and separation processes (Koley, Sakurai, & Aono, 2016; Koley, Sakurai, Takei, & Aono, 2016).

Koley, Sakurai, and Aono (2016) developed hybrid nanoflowers composed of sericin and copper for the purpose of removing heavy metals such as Pb^{2+}, Cd^{2+}, and Hg^{2+} from water systems. They achieved this by adding an aqueous solution of

copper sulfate ($CuSO_4$, 1 mM) to 10 mM phosphate buffered saline (pH 7.4) containing sericin (0.1 mg/mL). After thorough mixing and incubation at room temperature for 12 hours, a blue-colored precipitate with flower-like structures formed. Each petal consisted of multiple nanosheets (15−30 nm) arranged in multilayer configurations, featuring numerous pores or rifts on their surfaces (Koley, Sakurai, & Aono, 2016). The morphology of these hybrid materials depended primarily on the concentration of precursor molecules, pH, temperature, and reaction time (Ge et al., 2012). For the adsorption study, 5 mg of ShNFs was introduced into a 20 mL of heavy metal solution (15 mg/mL) with continuous stirring for 2 hours. All three different types of nanoflowers (Sl, ML, and SP) exhibited effective adsorption capabilities; however, SP hybrid demonstrated exceptional performance by removing 525 mg/g of Pb(II). In contrast, the adsorption capacities of prepared copper phosphate precipitate without sericin and annealed hybrid nanoflowers were notably low. Furthermore, these ShNFs demonstrated selective removal of Pb(II) over Ca(II). This selectivity could be attributed to similar electronegativities of Pb(II) and copper (II) phosphate, whereas Ca(II) has a lower electronegativity. Additionally, Pb(II), being a borderline Lewis acid, likely has a higher affinity for the borderline Lewis base orthophosphate ion present in the nanoflowers. The adsorption of Pb(II) was further confirmed through SEM imaging of the nanoflowers, revealing elongated needle-like structures on their surfaces (Koley, Sakurai, & Aono, 2016).

A similar study was conducted using sericin and hydroxyapatite, a well-known adsorbent material. In this research, Pb(II) was completely eliminated within 15 minutes. Conversely, hydroxyapatite alone exhibited lower adsorption capacity even after 2 hours. The removal efficiencies for Hg(II), Cd(II), and Pb(II) were 42.5%, 89.5%, and 99.9%, respectively, within the initial 15 minutes. Additionally, sericin-hydroxyapatite nanoflowers were utilized for the removal of Congo Red dye, an anionic dye. Approximately 50% of the dye was adsorbed within the first 4 hours, after which the adsorption rate decreased as active sites became occupied. The functional groups of Congo Red, such as amine and sulfonate, likely engaged in strong interactions, such as electrostatic or hydrogen bonding, with the hydroxyl, carboxyl, and amine groups of sericin present in the nanoflowers (Koley, Sakurai, Takei, & Aono, 2016).

Magnetite nanoparticles gained extensive research interest in the last decade due to their high natural magnetization, low toxicity, and easy removal from treated solution via an external magnetic field. However, nanoparticles tend to form aggregates because of their high surface-to-volume ratio, resulting in the loss of their unique characteristics making surface modification a requirement (Zhu et al., 2018). To overcome this limitation, Chamchoy et al. (2021) modified magnetite nanoparticles with sericin. The polar functional groups of sericin form coordination and hydrogen bonds with the magnetite nanoparticles. The sericin-modified magnetite nanoparticles formed uniform octahedral shapes and the presence of functional group such as ionizable carboxylic acid side chains from the sericin enhanced the adsorption removal efficiency for MB from 44% to 60% (Chamchoy et al., 2021).

Metal-organic frameworks (MOFs), an emerging class of porous materials made of organic and metal-containing linkers, are another highly investigated class of

nanomaterials (Zhou & Kitagawa, 2014). MOFs are renowned for having pore sizes that may be adjusted, incredibly large surface areas, and movable internal surface characteristics. Interesting features for MOFs are provided by the total physical properties of the inorganic and organic components as well as any potential synergistic interactions between the two (Zhou et al., 2012). Das, Seo, Yang, Kumar Patra, et al. (2023), Das, Seo, Yang, Nguyen, et al. (2023) combined the properties of two individual metals like Au and Ag with sericin. This bimetallic-sericin nanoparticle exhibited therapeutical properties along with photocatalytic degradation ability. The degradation efficiency of bimetallic-sericin nanoparticles reached 34.7% in 3 hours for MB (Das, Seo, Yang, Kumar Patra, et al., 2023, Das, Seo, Yang, Nguyen, et al., 2023). In a different study, Das and colleagues synthesized sericin-gold nanoparticles, in which the sericin solution served as a capping and reducing agent. The redox reaction is said to be aided by sericin's phenylalanine, tryptophan, and tyrosine contents. FTIR verified that sericin was present in the nanoparticle (Das, Seo, Yang, Kumar Patra, et al., 2023, Das, Seo, Yang, Nguyen, et al., 2023). When exposed to light, the sericin-gold nanoparticles promoted the photocatalytic destruction of methyl orange (MO) and MB dyes. For MO, the maximal degradation efficiency was 9.8% at 1 hours, while for MB, it was 44.8% after 5 hours (Das & Patra, 2023).

Using two distinct sericin copper phosphate nanoflowers, Koshy et al. (2024) created them according to the molecular weight of the sericin. The authors used sodium carbonate to extract low-molecular-weight sericin (below 160 kDa) and guanidine hydrochloride to extract high-molecular-weight sericin (500−200 kDa). When compared to low-molecular-weight sericin hybrid nanoflowers and copper phosphate precipitate, the high-molecular-weight sericin hybrid nanoflowers displayed more peroxidase-like activity. It was observed that high-molecular-weight sericin hybrid nanoflowers had a 33% elimination effectiveness for ciprofloxacin in 24 hours (Koshy et al., 2024). One drawback of these nanoflowers was that they were not very reusable.

3. Conclusion and opportunity for further research and development

Silk protein sericin is a natural polymer extracted from the silkworm *Bombyx mori*, known for its eco-friendliness and biocompatibility. It has become a promising material in water treatment due to its polar functional groups, which allow effective binding to contaminants. For the extraction of heavy metals from wastewater, sericin, either alone or in combination with other natural polymers such as alginate, has proven to be an inexpensive and effective solution. Its affordability and natural abundance make it an attractive option. One drawback is the limited reusability of sericin-based materials, which may degrade after multiple use cycles, impacting their long-term viability. This degradation is primarily caused by the material's inherent properties like (i) water solubility, which makes it prone to dissolving or breaking down when exposed to aqueous environments, limiting its longevity in applications such as water

treatment, (ii) pH and temperature sensitivity leading to a rapid loss of mechanical integrity and performance after repeated use, and (iii) biodegradability. While sericin's biodegradability is beneficial for environmental safety, it also reduces the material's reusability, as it breaks down over time. Additionally, using silkworm cocoons as an adsorbent for organic dye worked well due to their unique structure and composition. Silkworm cocoons, mainly composed of silk fibroin, possess excellent adsorption capabilities. The porous and fibrous nature of the cocoon provides a large surface area, facilitating effective dye adsorption. This natural material offers a sustainable, cost-effective alternative to synthetic adsorbents and is particularly advantageous in water treatment due to its biocompatibility and biodegradability. Sericin-based fibers, membranes, and nanomaterials have demonstrated excellent adsorption properties, making them highly effective for water purification and removal of pollutants like dyes and heavy metals. Sericin-based fiber and membranes can efficiently adsorb dyes and are easily separated from solutions, enabling recyclability and reuse without significantly compromising their removal efficiency. Nanomaterials incorporating sericin further enhance adsorption due to their nanoscale size, providing a greater surface area for interaction. They have also garnered attention for their potential in water treatment, particularly in degrading organic contaminants through mechanisms similar to enzymatic reactions. This enzyme-like activity helps break down harmful organic substances in water, offering an eco-friendly solution for water purification. The catalytic-like behavior of sericin nanomaterials opens new avenues for their integration into water treatment membranes, where their reactive properties can enhance the degradation of organic contaminants. Additionally, the nanomaterial structure increases the surface area for interaction with pollutants, further improving their efficiency. While studies on these enzyme-mimicking properties are limited, ongoing research suggests great potential for expanding the use of sericin-based nanomaterials in sustainable water treatment technologies. This emerging field encourages more investigation into the synergy between sericin nanomaterials and membranes, with potential applications ranging from industrial wastewater treatment to advanced filtration systems.

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Circular economy in silk industry

20

Manjunath B.S., Bharat Tandon, Shakthi Prakash M.R., Vivek Mishra and Tapan Kumar Dash
Fibroheal Woundcare Private Limited, Bangalore, Karnataka, India

1. Introduction: Circular economy in silk industry

In the process to minimize wastes, emphasis has been given to collect, recycle, and use the recycled waste as input raw material. The recycled waste may be employed to be used in the same industry to promote circular material flow or can be adopted in other industry linearly producing different products generating no waste. The concept was adopted to reduce the environmental impact of single-use items after economic boom around 1950, and initially, it was especially made for the plastic industry where single-use plastic was of major environmental concern. Gradually, the practice of reduce, recycle, and reuse were adopted in many other industrial sectors and the impact on environment as well as the associated economic value chains were had to be sustainable to be explored in an inclusive manner. In a report by Accenture, a circular economy could unlock $4.5 trillion of value by 2030 (Masterson, 2022). Apart from material flow and cost component of circular economy, CO_2 emission also being considered to be important factor determining efficacy of adopted circular economy policy. Hence, while designing economy process, not only current operational value chain but also life cycle (source, procurement, transportation, consumption, storage, recovery, and discharge) of all the associated value chain must be considered for an optimal resource efficient model (Clark et al., 2016; Lofthouse & Prendeville, 2018). For the time being, focus has been given to five different areas such as plastics, electronics, food, textiles, and capital equipment in 2021 for different global actions for circular economy (Veldhoven & van, 2022). The advantages or benefits of using a circular or sustainable economic value chain for environment, society, and industry are presented in Fig. 20.1.

The adoption of circular in processing is not a single- or one-time operation; it is 3s a continuous effort to minimize waste. As 100% circularity is not achievable, the effort may lead to marginal impact for short time, but progressive long-term impact will be measurable. As per a report by World Economic Forum, design, business model, and policy are the key factors to be considered to make the process more sustainable and circular. Detailed consideration of these parameters is illustrated in Fig. 20.2.

World Economic Forum suggests to incorporate or consider the sustainability during the design of product and material life cycle. Reusability, recyclability, minimization of raw materials, choosing process, or/and materials to minimize carbon emission and disposal of wastes are to be reviewed in the design stage itself to make the product life cycle more sustainable (Mcginty, 2024). In other methods using product as a

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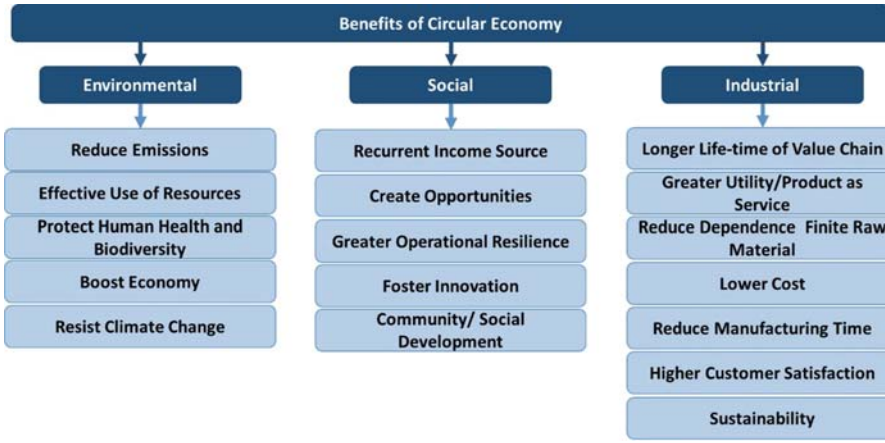


Figure 20.1 Benefits of adopting circular economy (Cavallo, 2017; Hartley et al., 2023; Lacy et al., 2020; Mcginty, 2024; Morten Rossé, 2016; Vermeulen et al., 2024).

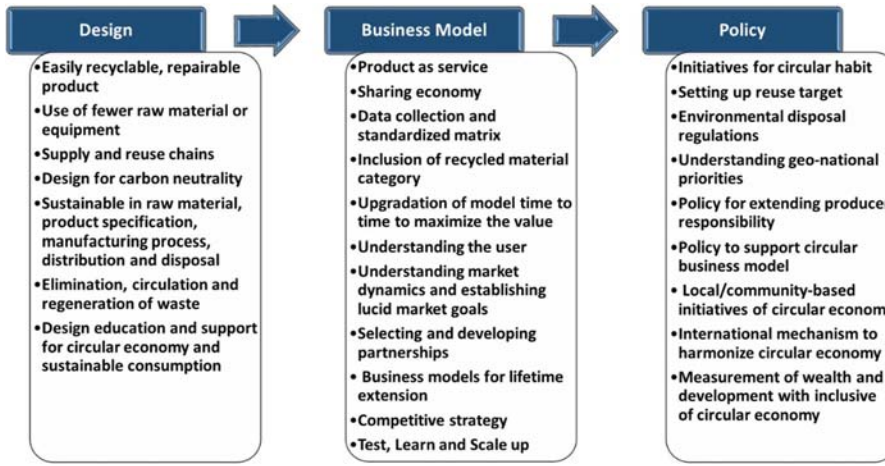


Figure 20.2 Process of adoption of circular economy (Hotta et al., 2019; Dam, 2020; Deutz et al., 2024; Ferasso et al., 2020; Geissdoerfer et al., 2020; Lofthouse & Prendeville, 2018; Loyens et al., 2023; Brett Melles & Velenturf, 2023).

service, where multiple users can use the product in their operation, sharing of facility, developing appropriate collaborative businesses, and continual improvement in process as well as value chain provides ways for sustainable business models. Furthermore, the policy maker must educate, initiate, measure, and target the circular economy while prioritizing circular business models (Mcginty, 2024; European Parliament, 2023; Vermeulen et al., 2024). Here in this chapter, we shall discuss about the circular economy in the silk industry how the resources can be used less, used longer, used again, and make the environment cleaner with special emphasis on the Indian silk industry.

2. Processes in silk industry

Production of silk-based textile or silk industry is a combination of multiple process involving farmers, sericulture, silk reelers/weavers, and textile manufacturers (Fig. 20.3) (Sharma, 2020). So far, these processes are done in distinct locations based on the feasibility of each process; hence, multiple linear economic value chains are involved before it reaches to user. Further, each process in the economic value chain will be discussed with respect to how circular economy principles can be adopted.

The silk production process start from formers where mulberry tree saplings mostly provided/sold by government entities planted and typically takes 3–6 months to grow. The leaves from mulberry tree are then harvested to feed the silk worm. In a separate value chain, silk moth mating undertaken in a controlled environment where each female silk moth lays more than 350 eggs. As in the case of India, silk rearers typically get the silk eggs laid by female silk moth from government agencies such as regional silk offices and the eggs are then incubated until the eggs hatch into larvae. The larvae feed on mulberry leaves, and in the process of 4 weeks, they grow to about 3–4 inch and accumulate necessary proteins for spinning of silk. As the silkworm starts spinning of silk filaments to form its cocoon, it attaches to a support and starts spinning the silk thread around it, which takes about 3–5 days to produce cocoon. The cocoons are sent to silk reelers for silk thread production (Babu, 2012). Parallelly, in each batch, few mating pairs of male female silk worms kept aside to prepare eggs for next cycle. Reelers then degum the cocoon by boiling the cocoon in water in the presence of mild soap or alkali or enzyme to remove out continuous and noncontinuous filaments,

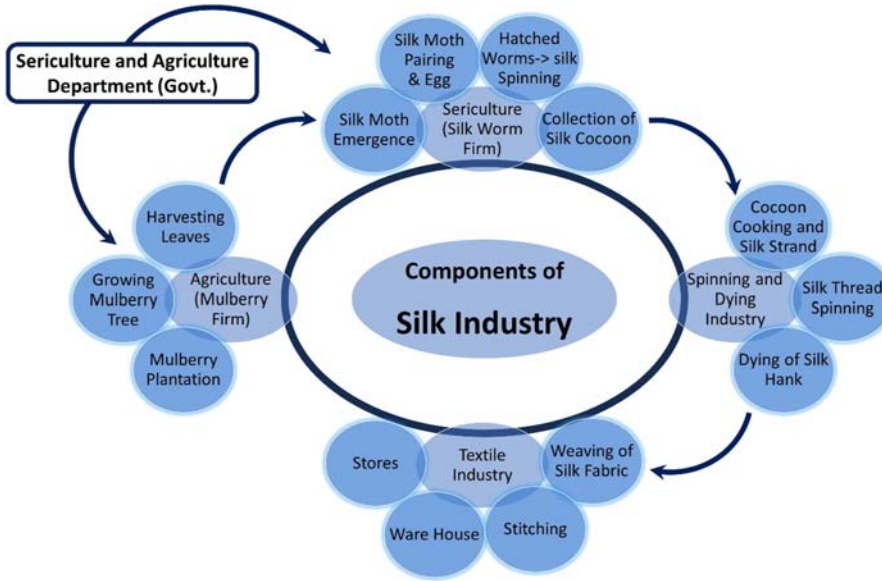


Figure 20.3 Process involved in silk-based textile industry (Reddy, 2020; Shahriar, 2019; Vernus et al., 2024).

where continuous threads further twisted to produce silk yarn. Further, the silk yarn dyed as per the requirement and supplied to the textile industry for further processing. Last two steps of silk processing namely, degumming and dying are the major source of environmental effluents where adoption of circular economy principles is much desired. Silk weavers then weave silk fabric form yard using different feasible techniques. Somewhere stitching is also done if required, and the product is ready to take to warehouse followed by silk stores.

3. Sustainability in silk industry and its importance

The four stages of production of silk-based textile are done at different places, for instance first two mulberry cultivation and sericulture farmers generally prefer nonindustrial location, preferably agriculture prevalent locality. However, the process of silk reeling and textile processing essentially localized in the industrial zone. Because of locality differences transportation from site of origin to site of next processing in the textile industry should also be considered while designing policy for the silk-based textile industry. The inputs of each process, output, and the byproducts of each process are illustrated in Fig. 20.4 (Lu et al., 2022; Reddy, 2020; Reddy et al., 2021).

Furthermore, harvesting mulberry leaf and production of cocoon in the silk rearing site may not need environmental nod for the process as these are greener processes and most the biproducts generated are biodegradable in nature without causing significant environmental hazard. However, the other two, especially degumming and reeling, and dying industry can pose significant increase in environmental carbon content and chemical pollution, hence need careful attention toward making it sustainable or circular. Hence, silk worm litter from the rearing stage; silkworm pupa, sericin solution, dying effluent, and silk floss from silk spinning stage and unused/used silk cloths

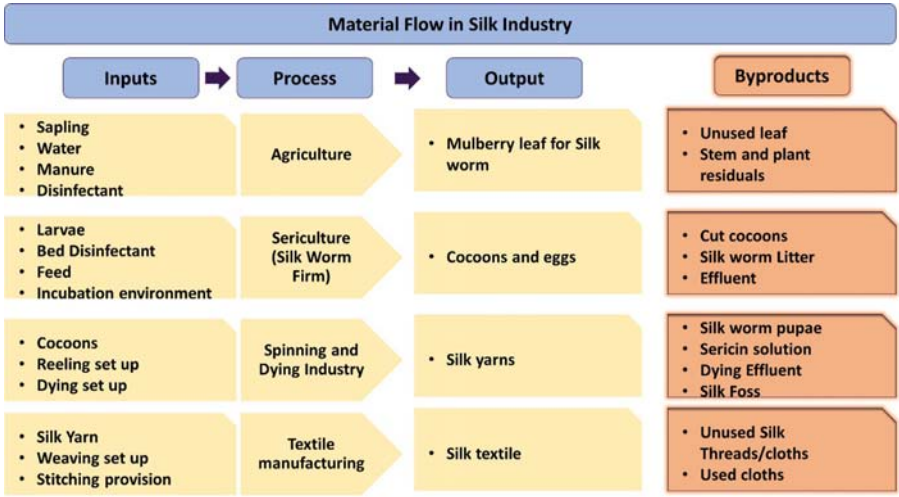


Figure 20.4 Byproducts generated at different stage of silk-based textile industry.

are the byproducts generated from the silk industry need to be either recycled or utilized for other value-added products for reduction of waste. The chemical composition of these byproduct and possible implication to make the silk industry more sustainable are presented in Fig. 20.5 (Javali et al., 2015; Reddy, 2020).

As illustrated in the Fig. 20.5, silk worm litter is the foremost byproduct in the value chain that can be adopted for value added development for liner economy. Since the exact quantification of amount of litter and the composition of litter is not fixed, it can be given as a composite, and many demonstrations shown its application in various implications. However, as the environmental half-life is low with mixture of components, its current harvesting is not very impressive for sustainable economy. The second waste generated in silk processing chain is silkworm pupae, it is generated both by silk rearing centers while taking out silk moth for mating and in the boiling process for silk reeling. The sericulture industry produces pupae in a cleaner form, mostly used for mating purposes; hence, majority of pupae waste is contributed by degumming and reeling industries. The quantity of pupae generated is also significantly large where approximately 2 kg of pupae is generated for a kg of cocoon. Interestingly, silk pupae consist of oil, proteins, and polysaccharides, which can be explored for their nutraceutical, medicinal, and food applications (Javali et al., 2015; Qayoom & Manzoor, 2024;

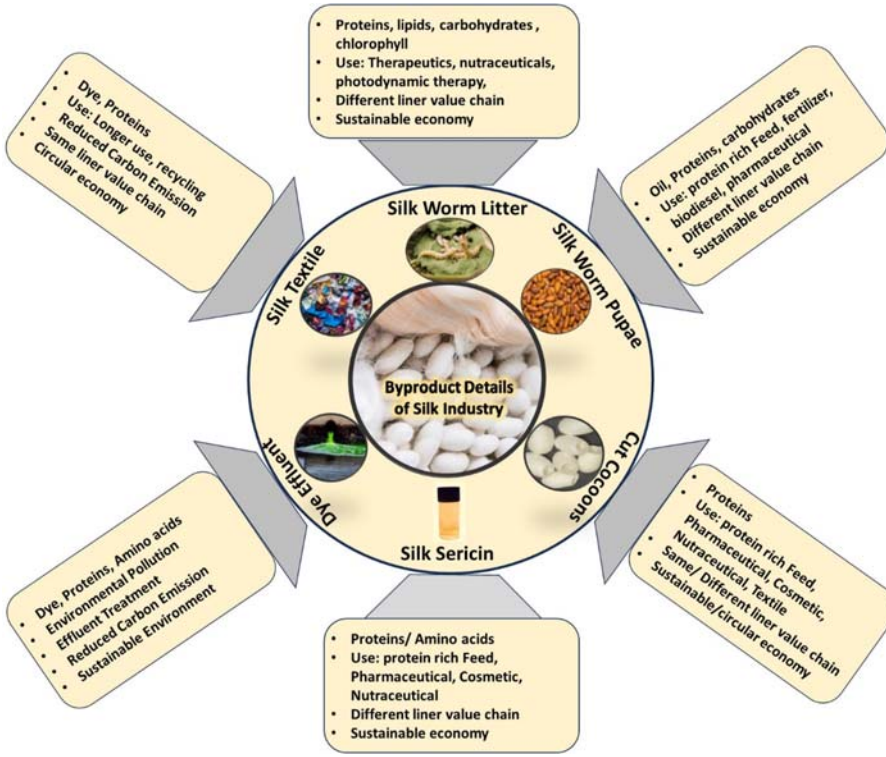


Figure 20.5 Chemical nature of different byproduct of silk industry, their possible use, and applicable sustainable or circular economy strategy (Reddy et al., 2021).

Roopa Reddy et al., 2021; Sashina & Yakovleva, 2023). Hence, the left-over pupae in the reeling industry are sun dried or freeze dried, milled, and processed as powder for consumption. Further, the pupae residues are cold pressed or ultrasonicated for extraction of pupae oil and employed for generation of above-mentioned value-added products. The other waste generated during the process of preparation of hatching process is cut cocoons left over after pupae is taken for transforming them to silk moth and using them for egg production in egg processing center. Cut cocoon mainly consists of more than 90% protein, and it can be employed in silk thread rearing in combination of other threads such as cotton polyester, etc. In addition, for most of biomaterial, cosmetic and nutraceutical applications of silk protein utilize cut cocoon both for research and industrial production process. Hence, the liner value chain utilizing cut cocoon for sustainable and value-added economy is considered to be heading the line, for sustainability of the silk industry. In the processing step, while reeling the silk filament to make yarn, cocoons are boiled in alkaline medium to separate the threads. In this process, limited amount of sericin goes into the boiling solution; however, since the same solution is used continuously, effluent containing 1%−2% of sericin along with pupae waste gets accumulated in the reeling process. Further, to soften the yarn hanks as such or after weaving into silk cloth, it is treated with boiling water for 2−3 h followed by hot water washing. In both, the process 20%−30% w/w of sericin with respect to the raw cocoon goes into solution at a dilution varying between 1:20 and 1:40 w/w. Hence, 20−40 L of wastewater containing sericin gets generated per kg of cocoons while processing in to silk hank or weaved cloth. Considering the volume, this is the largest produced waste material in the entire value chain of the silk industry and silk processing. Hence, more efficient ways to handle silk sericin and its application in different filed have been explored.

In further processing step, dying of silk thread or yarn produces dye containing effluent, which is most common all textile-based industries, such as cotton, polyester, etc., and all other dying industries. Dye recovery and purifying the effluent prior to their drainage to water bodies has been an important regulation followed. For recovery of dye from the dying solution, various materials have been designed based on the chemical and molecular behavior of dye used. Dye recovery and processing has been an important domain of research for promotion of circular economy. In practical scenario, even if there are challenges associated with reuse of dye, separation of unused dye is an essential effluent treatment process before discharge. This is not limited to the silk industry; all dying industries are considered while designing policy for environmental protection form textile effluents. This effort may not contribute directly to the economy but will certainly protect the environment and provide sustainable progress. In an alternative process, development of a new opportunity for the coloration of silk fabrics using a protein extracted from the silkworm pupae extracted from the cocoons during the yarn manufacturing process was demonstrated by Orlandi et al. (2020). The final product of silk industry, that is, silk clothing is subject to circular economy by adoption strategies to increase the life span, sharing the facility for different materials, and reprocessing of used fabric till its useable as fabric. However considering the volume of waste and unexplored potential, we shall emphasize in this chapter on silk sericin based materials for tissue engineering or pharmaceutical application.

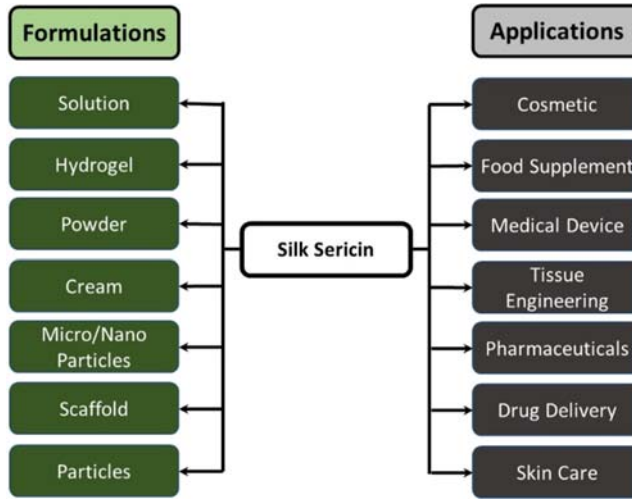


Figure 20.6 Application of silk sericin and formulations developed from silk sericin.

4. Silk sericin: A potential unexplored economy from silk industry

Silk sericin is having many biomedical applications because of its biocompatible, biodegradable, and nontoxic in nature. Its formulations have been trialled in different formulations such as gel, microparticles, nanoparticles, scaffolds, etc., for various application as illustrated in Fig. 20.6 (Orlandi et al., 2020; Roopa Reddy et al., 2021). The research interest is based on the observations of its antioxidant, moisturizing, antiinflammatory, and photo protective activity (Fan et al., 2009; Kumar et al., 2018; Saad et al., 2023; Silva et al., 2022). Hence, treatment of waste from the silk industry will not only avoid environmental hazards but also facilitate the use of silk industry waste in to value added products. Additionally in a recent study, Koshy et al. demonstrated sericin-derived nanoflowers for ciprofloxacin remediation in copper-catalyzed manner (Koshy et al., 2024). Hence, if the effluent from the reeling industry can be treated for sericin recovery, it will be impactful for social, financial, and environmental improvement (Saad et al., 2023).

5. Sericin containing effluent as a protein contaminant for environment and factors affecting its environmental degradation

5.1 Effect of protein contaminants and environmental impact of sericin from silk industry

Majority of protein contaminants to the environment is released from meat processing industry, tannery, silk industry, and food industries. Protein in wastewater can have negative effects on the environment due to presence of ammonia, particulate nitrogen,

organic carbon, and other organic matter. Other protein contaminants are produced as a result of microbial degradation of waste from waste of food and beverage industries (Drewes & Croue, 2002; Holbrook et al., 2005; Marsal et al., 2010; Spiller et al., 2020). Aerosols from wastewater causes respirator inflammatory response and the cultivated foods using the silk industry effluent may lead to heavy metal and organic pollutant, causing adverse effects on health (Wu, 2020). The environmental impact has been accessed in terms of pH, biochemical oxygen demand (BOD), chemical oxygen demand (COD), and total dissolved solids (TDS) from bleaching and dyeing process. The evaluation also involves lead and cadmium contamination in the effluent as well as surrounding soil (Sittitoon et al., 2015).

When it comes to the silk industry, India is the largest producer of silk cocoons with an annual turnover of 2.6 lakh tons in the year 2022 as per a report from Helgi Library (Which Country Produces the Most Silkworm Cocoons? Charts, 2023). Silk processing leaves about 30,000 tons of effluent in which major protein containing effluent is sericin, which is glue-like protein present about 20%−30% in silk cocoon. In the spinning process, the cocoons are generally put into boiling water to separate out the sericin bound threads. The sericin accumulated in boiling water along with pupa waste is considered as a major effluent from silk-based textiles industries. In a study, it was found that areas with waste from the silk industry had higher pH, BOD, COD, and TDS (Sittitoon et al., 2015). Other than the silk processing industry, textile wastes also contribute to environmental pollution by silk and related industries. However, since textile waste are solid and can be gathered, it can be transformed in to value added product in different ways as described in a recent review by Lu et al. (2022). On the other hand, waste from silk processing industry is mainly effluent; hence, it is important to treat and manage protein wastewater to minimize its negative effects on the environment and human health.

5.2 Type of silk sericin and environmental sources of sericin

As per the distribution of sericin in silk fiber, its classified in to three types such sericin A, sericin B, and sericin C with a nitrogen content of 17.2%, 16.8%, and 16.6%, which are present in the outer middle and adjacent layer of fibroin, respectively. Glycine, serine, aspartic acid, and threonine are most abundant amino acid in sericin, while sericin B and C contain tryptophan and proline (Das et al., 2022; Padamwar & Pawar, 2004; Saad et al., 2023). Water solubility of sericin is attributed to its 45.8% hydrophilic amino acids with polar hydroxyl, carboxylic, and amino group especially serine, which is present in sericin more than 32%.

Since the environmental degradation of sericin is affected by its chemical nature, here in this segment, we shall be elaborating about the various factors affecting chemical properties such as source, molecular weight, extraction procedure, environmental pH, etc., (Fig. 20.7). Other than the chemical nature, the physical state of sericin modulated by the self-assembly of sericin plays a crucial role in its degradation.

Sericin composition is mainly affected by its biological source or strain of silk cocoon, the distribution in the cocoon, and process of isolation of sericin. The species of silk cocoon make a difference in the properties of sericin we obtain. As

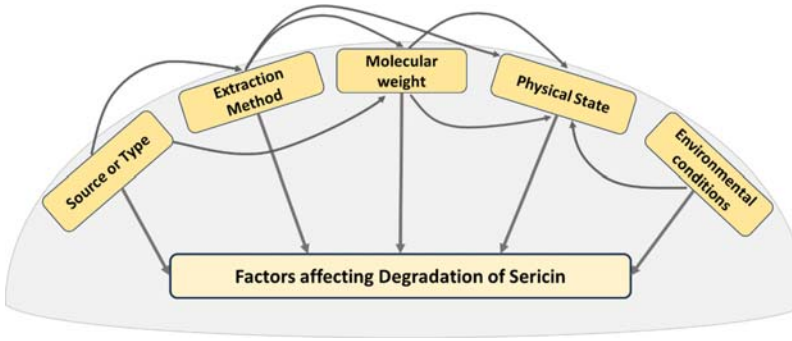


Figure 20.7 Factors affecting degradation of sericin.

indicated in Fig. 20.8, the molecular weight range of sericin obtained from *A. yamamai* silk cocoons was higher in comparison to that of from, species such as *B. mori* and *C. trifenestrata*. Furthermore, to obtain an optimal yield of 54%−55%, the conditions for degumming were found to be 0.24% NaOH, 0.025% NaOH+0.475% Na_2CO_3, and 0.5% Na_2CO_3 for different cocoons source of *B. mori, A. yamamai,* and *C. trifenestrata,* respectively (Karimazawa et al., 2019). It is important to note that, sericin from silkworm before and after spinning had mostly random coils, hence, no major change of degradation behavior in the silk spinning process (Teramoto et al., 2006).

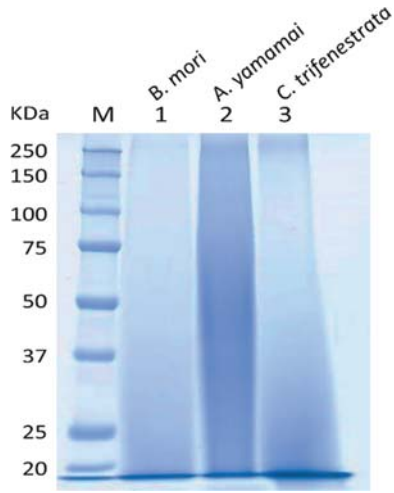


Figure 20.8 Molecular weight of sericin from different sources.
Reproduced from Karimazawa, M., Urita, S., Yamashita, T., Suzuki, K. (2019). High-yield degumming methods for preparing sericin from cocoons of mulberry and non-mulberry silkworms. Japanese Society of Sericultural Sciences, Japan Journal of Insect Biotechnology and Sericology, 88 (1), 1−6. https://doi.org/10.11416/jibs.88.1_001.

5.3 Extraction procedure

Extraction of sericin may be done in various ways such as alkali mediated at high-temperature and high-pressure extraction, ultrasonic extraction, enzymatic extraction, etc. These extraction methods produce sericin with different molecular features and hence possess different features in terms of their physical stability and degradation behavior (Table 20.1). Alkali-mediated extraction gives optimal yield, but the sericin obtained is largely degraded and generally a high-molecular-weight range has been observed. In addition, it was shown to partially affect the fibroin, and there are a lot of possibility that traces of fibroin also leaches out in the extracted sericin in this process. During the extraction process, degradation of sericin by thermal treatment starts in repetitive region near aspartate residue (Anis, 2024; Teramoto et al., 2006). An eco-friendly process by degumming of sericin by combining ultrasound and enzyme was described by Mahmoodi et al. where in alcalase and savinase were used along with ultrasonic treatment to effectively remove sericin from Persian silk (Mahmoodi et al., 2010).

In another approach, Pandya et al. demonstrated bacterial isolates for degumming of silk fibers, and the report suggested *Bacillus subtilis* and *Pseudomonas fluorescens* as optimal bacteria's for degumming of silk fibers with an efficiency of 87% (Bhavna & Soniya, 2021; Miguel & Álvarez-López, 2020). These extracellular proteases from Bacillus species were found to give sericin of 10−12 kDa in alkaline conditions with high specificity and in comparison, to commercially available alcalase proteases, serine protease from *Bacillus halodurans* demonstrated better degumming ability (Miguel & Álvarez-López, 2020; Yakul et al., 2019). Endrawati et al. optimized method of extraction of sericin using response surface methodology from *Attacus atlas*

Table 20.1 Different methods of degradation and their impact on parameters (Bascou et al., 2022; Da Silva et al., 2014; Hasegawa, 2012; Miguel & Álvarez-López, 2020).

	High temp and high pressure	**Autoclaving in alkali/ chemical**	**Enzymatic extraction**	**Ultrasonic extraction**
Molecular weight and range	High molecular weight and broad range: 35−150 kDa	Uneven and broad range: 15−75 kDa	Low molecular weight and narrow range: 0.3−10 kDa	High molecular weight and broad range: 30−95 kDa
Yield	Moderate	High	Moderate	High
Degradation behavior	Intact	Highly degraded	High	High
Eco-friendliness	High	Low	High	High
Process time	Moderate	Faster	Moderate	Moderate

and *Samia cynthia ricini,* wherein NaOH concentration of 0.08 and 0.03 N at a temperature of 130.52°C and 113.20°C for 71.71 and 33.78 min was reported to be optimal with a yield of 17.39 ± 1.24% and 20.24 ± 2.30%, respectively (Cahya Endrawati et al., 2023). Among different degumming methods, enzymatic and high temperature and high pressure are considered to be more environment friendly compared to other chemical methods and most preferred method for industry using enzymes such as trypsin, papain, bacterial proteases, alkalases, etc. However, the cost of enzymatic degumming is higher limiting its widespread adoption in industries.

5.4 Molecular weight

The second factor affecting properties of sericin is its distribution; it was reported that middle, anterior, and posterior segments of middle silk gland were having a molecular weight distribution of 400 kDa, 250 kDa, and 150 kDa, respectively (Takasu et al., 2002). After silk spinning solubility of sericin is affected by its position in the cocoon thread, that is, sericin in the outer layer of the fiber water (α-sericin) is highly soluble in warm, whereas sericin located in the inner layer (β-sericin; adjacent to fibroin) has limited solubility in hot water and can be only removed with high pressure, high temperature, or in presence of alkalis (Miguel & Álvarez-López, 2020; Mondal et al., 2007). Furthermore, as indicated previously, method of extrication affects the molecular weight there by transition into β-sheets as well as rate of degradation also modulated (Saad et al., 2023).

5.5 Physical state

In most of the extraction procedures or effluent sources, sericin is found to be in solution state; however, based on the environmental condition, the self-assembly and molecular structure change ultimately affecting its physical state (Wu et al., 2007). In solution state, sericin exists in random coil structure, but depending on the concentration, temperature, pH, molecular weight, etc., it rearranges from random coil to β-sheets, which lead to transformation of solution to the gel state. Although the gelation is reversible in nature depending on the pH, but the reversibility depends on the type of sericin. Sericin C is hydrophobic lead to leave insoluble residues in this process. In addition, the presence of certain additives, which affect transition from random coil to β-sheets, also affect the solubility. For instance, poly (Na acrylate) increases the solubility of sericin, while polyacrylamide, formaldehyde, or resin finishing agents promote insolubility (Padamwar & Pawar, 2004; Silva et al., 2022).

6. Sustainable approach for silk industry current state and practical challenges

Since the sericin protein is a potent cosmetic ingredient for skin health and moisture retention, controlling the extraction process and posttreatment can promote the silk industry toward sustainability and circular economy. Hence, exploring the sustainable

implications of sericin can have environmental, economic, and social impact. Different methods adopted for separation of sericin are ethanol-mediated precipitation, tray drying, freeze drying, membrane filtration, etc., (Fig. 20.9) (Aramwit et al., 2012). In a demonstration, Sonjui et al. presented a polysulfonate and polydioxolane composite membrane for sericin recovery from degumming waste water and sericin of molecular weight 10−250 kDa could be recovered from the process (Azanaw et al., 2022; Sonjui et al., 2009). In another study, it was observed that after membrane filtration of degummed effluent in 20−300 kDa filters was able to remove out 97% of sericin contaminant but was having high COD level; hence, a reverse osmosis process is essential to make the permeated water suitable for further use (Fabiani et al., 1996). In other approaches, effluent treatment process for silk industry wastes has been described using filtration of SBR technology adopted biochemistry tower, sand filtration, active carbon adsorption, and filtration sequentially (Zhou, 2014).

With the available options to recover sericin, cost of processing is also an important factor for industrial applicability and economic viability. In a recent study by Capar et al., a process for industrial recovery of sericin was presented as depicted in Fig. 20.10, and the economics of the process has been evaluated. Total cost for sericin



Figure 20.9 Methods adopted for removal of sericin from silk industry (Capar & Pilevneli, 2024; Padamwar & Pawar, 2004; Wu et al., 2007).

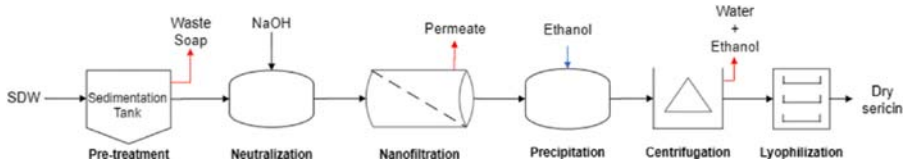


Figure 20.10 Process for industrial recovery of sericin.
Adopted from Capar, G., Pilevneli, T., Yetis, U., Dilek, F.B. (2022). Life cycle assessment of sericin recovery from silk degumming wastewaters. Sustainable Chemistry and Pharmacy, 30, 100889. https://doi.org/10.1016/j.scp.2022.100889.

processing unit was estimated to be in the range of €140,000- €2,600,000 for a 15 years of plant lifetime. The life time recovery has to be reduced from 15 to 5 years by increasing the unit cost of recovered sericin from €89 to €1300 per kg (Capar & Pilevneli, 2024).

In a different study for evaluation of life cycle assessment of sericin recovery, it was reported that environmental impact of sericin is further processed for recovery in comparison to discharge after treatment. In the process of recovery, the impact score of climate change was 50%; for natural resources, it was 34%; and for human health, it was 15% (Capar et al., 2022). Considering the constraints and economics, membrane filtration process followed by enzymatic process is considered to be most suitable method to produce sericin, which can used for healthcare and cosmetic application. However, for application in food, ethanol-mediated precipitation of sericin was reported to be a method of choice. On the other hand, ethanol-mediated precipitation increases the crystallinity of sericin and leads to higher crystallinity with aggregated strands of sericin (Fabiani et al., 1996; Teramoto & Miyazawa, 2005; Vaithanomsat & Kitpreechavanich, 2008; Wu et al., 2007). A different foaming column method of sericin extraction from the degumming solution was proposed where in foaming waste sericin solution passing through polycarbonate column along with compressed air to induce foaming. Foam stability was dependent on concentration of sericin, pH, flow rate, length of membrane, and pore diameter; hence, foaming will be collected in an optimal condition to concentrate sericin. It was reported that foam column length of 400 mm, at a pH of 4.0, air flow rate of 200 mL/min and pore diameter of 180 μm given an optimal recovery percentage of 80.29% (Li et al., 2018). In a unique method of treatment, Thanushree et al. removed sericin from silk protein containing effluent by electrochemical coagulation method. Out of electrodes used for electrolysis aluminum electrode at a voltage of 12v was able to remove 90% of chemical oxygen demand (Thanushree et al., 2013).

In addition, the value-added products of sericin will increase the socio-economic conditions of silk farmer and value chain associated with production of cocoons and silk thread (Astudillo et al., 2014; Javali et al., 2015; Silvia Mara Bortoloto Damasceno Barcelos, Salvador, Barros, et al., 2021). So far silk sericin has been adopted in shampoo, creams, and lotions for antiaging, antiinflammatory, antiwrinkle, antioxidant, dry skin, eczema, sun damage, silk moisturizing, skin conditioning, etc., (Bergfeld et al., 2015; Johnson et al., 2020). In context to Indian scenario, most of the silk proteins used in cosmetic by multinational companies are imported as multicomponent semifinished good and incorporated in the final product. Appropriate measures/policy need to be taken to being these silk-based ingredients can be developed to fulfill the requirement of beauty and cosmetic industry. Some attempts have been made by Indian manufacturers such as Fibroheal (Fibroscar, Silk n Soft etc.), Fabindia (Silk protein Facewash, Silk protein lotion etc.), Earth Rhythm (Silk Protein Shampoo bar), The Moms Co (Natural Protein Conditioner), etc. to adopt silk protein in different products. Still there is immense opportunity to explore the nontextile application of silk protein and wide spread use in healthcare and cosmetic industry.

Finally, when the textile is being considered, in an overall estimate of textile industry, the textiles which undergo reuse of recycling have been estimated to be only 18%,

whereas about 85% of textiles goes in to solid land fill (Gupta et al., 2021). When it comes to overall silk industry, although the value chain is not circular, many liner value chains have been established to reduce the emission. In a study by Barcelos et al., it was reported that in certain processing extensions of silk industry value chain such as inclusion of biodigester, along with an electric motor generator, engagement with reverse logistics (for packaging), and the establishment of an agro-industrial cooperative could provide more than 98% circularity in the process (Barcelos, Salvador, Barros, et al., 2021). In another study, an IoT model was proposed to track the life cycle of textile and initiate the recycling process at suitable time indicated by the end user for promotion of recycling and circular economy (Alves et al., 2022).

7. Conclusion

The principle and practice of circular economy have been getting global attention to protect environment. The yardsticks of circularity and its impact on environment, sustainability, and economic feasibility are different for different industries. In the silk industry, although the number of processes involved is multiple, the processes contributing to environmental hazard are limited such as silk worm litter, sericin solution, dying effluent, cut cocoons/silk floss, unused/used silk cloths, etc. Out of these wastes, dyeing effluent and silk cloths can be recycled to use in the same industry to promote circularity. On the other hand, the wastes such as litters, sericin solution, and cut cocoons have been explored in parallel liner economy to result in various value-added products, hence contribute to sustainable economy. Dyeing effluent is the major cause of concern followed by sericin for the environment and must be taken into consideration for reducing carbon emissions/pollution. Interestingly, silk sericin solution because of its chemical and biological attributes can be adopted in versatile application, hence is an attractive nutritional and cosmetic ingredient. Hence, with appropriate measures taken to collect sericin from silk industry in a controlled manner and processed to utilize for different implication in healthcare, cosmetic, food industries, etc., it will be a significant step toward sustainable economy supporting waste to wealth benefit in circular economy policy.

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About the editors

Sabu Thomas
Professor Sabu Thomas is the Director of the School of Nanoscience and Nanotechnology at Mahatma Gandhi University, Kottayam, Kerala, India. He is also a Senior Visiting Professor at Christ University, Bangalore, India. Additionally, Professor Thomas is a former Vice Chancellor of Mahatma Gandhi University.

Sneha Sabu Mathew
Sneha Sabu Mathew is a Research Scholar at Mahatma Gandhi University, India.

Hanna J. Maria
Dr. Hanna J. Maria is a Research Associate at the School of Energy Materials, Mahatma Gandhi University, India.

Rangam Rajkhowa
Professor Rangam Rajkhowa received his bachelor's degree in Textile Technology from Anna University, India, a master's degree in Fibre Science and Technology from the Indian Institute of Technology, India, and a PhD in Engineering from Deakin University, Australia.



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