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Investigation of Antiproliferative Effects of Home-Made and Commercial Apple Vinegars on Myeloma Cells

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ABSTRACT

Vinegar is an aqueous food product made by a succession of yeast and acetic acid bacteria activities from fruits that contain high carbohydrates such as apples and grapes. Vinegar has been used as a dietary spice and natural remedy since ancient times due to its therapeutic properties including antimicrobial, antidiabetic, and anticancer activities. It has been shown that some bioactive compounds exhibiting antioxidant activity in vinegars lead to anticancer activity. The aim of the present study was to investigate antiproliferative effect of commercial and home-made apple vinegars in native and neutralized form on myeloma cells. In order to neutralize the vinegars, sodium hydroxide (NaOH) was used. A serial two-fold dilutions of the vinegars (50%, 25%, 12.5%, 6.25%, 3.12%, 1.56%, 0.78%, 0.39%) prepared with cell medium were treated to the cells. The MTT (3-(4.5-Dimethylthiazol-2-yl)-2.5-Diphenyltetrazolium Bromide) assay was used to determine the cellular viability in the cells treated with the vinegars. In this study, while commercial vinegar possessed a stronger antiproliferative activity than home-made vinegar, all native vinegars possessed stronger antiproliferative effect than neutralized vinegars. Interestingly, when home-made vinegar (both native and neutralized) concentrations were from 6.25 to 1.56%, the cell viability increased. Apple vinegar exhibited antiproliferative activity on myeloma cells; however, further studies are required to clarify the mechanisms underlying this activity.

Türk Tarım – Gıda Bilim Ve Teknoloji Dergisi, 9(12): 2173-2178, 2021

Ev Yapımı Elma Sirkesi ve Ticari Elma Sirkesinin Miyeloma Hücreleri Üzerine Antiproliferatif Etkisinin Araştırılması

MAKALE BİLGİSİ

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ÖZ

Sirke, elma ve üzüm gibi yüksek karbonhidrat içeriğine sahip meyvelerden, maya ve asetik asit bakterinin aktiviteleri ile oluşturulan sulu bir gıda ürünüdür. Sirke, antimikrobiyal, antidiyabetik ve antikanser aktiviteleri dahil olmak üzere tedavi edici özelliklerinden dolayı eski çağlardan beri baharat ve ilaç olarak kullanılmaktadır. Sirkelerde antioksidan aktivite sergileyen bazı biyoaktif bileşiklerin antikanser aktiviteye yol açtığı gösterilmiştir. Bu çalışmanın amacı, ticari ve ev yapımı elma sirkelerin nötralize ve doğal hallerinin miyelom hücreleri üzerine antiproliferatif etkilerini araştırmaktır. Sirkeleri nötralize etmek için sodyum hidroksit (NaOH) kullanıldı. Hücrelerin iki kat seri dilusyonları (%50, %25, %12,5, %6,25, %3,12, %1,56, %0,78 ve %0,39) hücre mediumu ile gerçekleştirildi. MTT (3-(4,5-Dimethylthiazol-2-yl)-2,5-Diphenyltetrazolium Bromide) deneyi, sirke ile muamele edilen hücrelerde hücresel canlılığı belirlemek için kullanıldı. Bu çalışmada, ticari sirke, ev yapımı sirkeye göre daha güçlü bir antiproliferatif aktiviteye sahipken, tüm doğal sirkeler, nötralize sirkelere göre daha güçlü antiproliferatif etkiye sahipti. İlginç bir şekilde, ev yapımı sirke (hem doğal hem de nötrleştirilmiş) konsantrasyonları %6,25 ile %1,56 arasında değiştiğinde, hücre canlılığı arttı. Elma sirkesi, miyelom hücreleri üzerinde antiproliferatif aktivite sergiledi. Ancak, bu aktivitenin altında yatan mekanizmaları açıklığa kavuşturmak için daha fazla araştırma yapılması gerekmektedir.

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Introduction

Multiple myeloma (MM) is a type of cancer formed by malignant B-cell neoplasm characterized by uncontrolled growth of mutated plasma cells within the bone marrow. MM begins as monoclonal gammopathy of undetermined significance (MGUS) which is an abnormal protein in blood (Bianchi and Munshi, 2015). It progresses to smoldering (asymptomatic) myeloma and finally becomes overt (symptomatic) myeloma (Fairfield et al., 2016). The patients with MM may suffer from bone pain or exhibit nonspecific symptoms, such as nausea, vomiting, malaise, weakness, recurrent infections, and weight loss (Gerecke et al., 2016; Michels et al., 2017). According to International Agency for Research on Cancer (IARC), 36% of new cancer cases were detected in people over the age of 70 in 2018, and the prevalence of the cancer is expected to increase by more than twice the current number by 2040 (IARC, 2020). According to World Cancer Research Fund (WCRF), there were an estimated 18 million cancer cases around the world in 2018, of these cases 159.985 were MM (WCRF, 2018). Multiple myeloma accounts for 10% of all hematologic cancers. 85% of patients diagnosed with MM are older than 65 years old (Michels et al., 2017).

Complementary and Alternative Medicine (CAM) is a group of health care systems and practices that are not considered to be part of standard medical care (Garland et al., 2013). CAM has been recognized as a worldwide phenomenon among cancer patients. Many cancer patients have turned to CAMs as alternative ways to treat the cancer or lessen side-effects and toxicity of chemotherapy or radiation (Buckner et al., 2018). While the rate of using CAM treatment has reached 63% in some parts of the USA, this rate has reached 35% in Europe (Berretta et al., 2017). It has been reported that substances such as Echinacea, evening primrose oil (*Oenothera biennis*), Gingko biloba, milk thistle (*Silybum marianum*), garlic (*Allium sativum*), ginseng (*Panax ginseng*), Gingko biloba and St John's wort (*Hypericum perforatum*) are among the most commonly used natural substances for cancer treatment (Gratus et al., 2009; Tutun et al., 2020).

Vinegar can be made from any fermentable carbohydrate source such as apple, grape, pear and melon by a two-stage fermentation, first alcoholic and then acetous. Vinegar contains acetic acid, water and trace amounts of other chemicals including vitamins, mineral salts, amino acids, polyphenolic compounds (e.g., gallic acid, catechin, caffeic acid, ferulic acid) and non-volatile organic acids (e.g., tartaric, citric, malic, lactic) (Kahraman et al., 2021, 2022; Luzón-Quintana et al., 2021). The amounts of acetic acid and trace elements vary according to the production processes of vinegar and the type of material used in the production (Xia et al., 2020). Vinegar has been used in the treatment of numerous disorders such as wound, inflammations, cough, ulcers, and infectious diseases for a long time in traditional medicine (Johnston and Gaas, 2006; Chen et al., 2016). Previous studies have been shown that vinegar has antimicrobial (Sengun and Karapinar, 2005), antioxidant, antiobesity (Halima et al., 2018) and antiproliferative activities (Nanda et al., 2004), and beneficial effects on atherosclerosis (Setorki et al., 2010), hypertension (Kondo at al., 2001), diabetes (Mitrou et al., 2015). Vinegar contains polyphenols reducing cancer risk via preventing the formation of N-nitroso-compound which causes cancer in the body (Guo et al., 1997; Nishino et al., 2005; Johnston and Gaas, 2006). There is little evidence that apple vinegar can exert antiproliferative effects on cancer cells. Therefore, the aim of the present study was to investigate the antiproliferative effect of home-made and commercial apple vinegars in native and neutralized form on myeloma cells.

Material and Methods

Preparation of Home-Made Apple Vinegar

Apple vinegar sample used in the present study was made traditionally from apples via spontaneous fermentation. The apples called “Red delicious” were purchased from Isparta (Eğirdir distinct) province of Turkey. The procedure of vinegar production is given on the Figure 1. The vinegar samples were kept in the dark at 4ºC until required (about 1 month). The vinegar samples were filtered through a filter paper before tests.

Physicochemical Properties

The pH values of the vinegars were measured with a pH meter (Sartorius Basic Meter PB-11). Determination of total acidity of the vinegars was performed by titrimetric method (Gao et al., 2017) and the results were expressed as acetic acid equivalent (g acetic acid /L vinegar sample).

Cell Culture

Myeloma (F0 ATCC CRL-1646) cell line was maintained in Dulbecco’s Modified Eagle’s Medium (DMEM) containing 10% fetal bovine serum (FBS), 0.1% gentamicin, 1% sodium pyruvate and 2% L-glutamine in a cell incubator (Steri-Cycle i160, Thermo Scientific) at 37°C, in 5% CO_2 and 95% relative humidity.

Cell Viability Test

The cells were seeded in 96-well plates ($3x10^5$ cells/mL) and cultured in 5% CO_2 incubator at 37°C overnight. Commercial apple vinegar was purchased at a local market in Burdur province of Turkey. To determine whether the antiproliferative effect was due to the acid content of the vinegars, both vinegar samples were neutralized with 1 N NaOH. Two-fold serial dilutions (50%, 25%, 12.5%, 6.25%, 3.12%, 1.56%, 0.78%, 0.39%) of both the neutralized and native forms of the vinegars were prepared with DMEM (Dulbecco′s Modified Eagle′s). DMEM was used as negative control and 0.1% Triton X-100 was used as positive control. MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide, Sigma) test was used to assess the effect of the vinegars on viability of myeloma cells. After 24 h of treatment, the medium was removed from the plates. The MTT was dissolved in PBS to prepare stock solution (5 mg/ml). MTT was added to each well at a final concentration of 0.5 mg/ml and then the plates were incubated for 3 h in dark at 37ºC. MTT solution was removed from the wells and 150 µl dimethyl sulfoxide was added to each well to dissolve the formazan crystals formed. The plate was kept on a horizontal shaker (Thermo scientific) for 30 minutes. Absorbances were measured at 570 nm with a microplate spectrophotometer (Multiskan Go, Thermo Scientific). The half maximal inhibitory concentration (IC_{50}) values were calculated as previously described (Tutun et al., 2020).

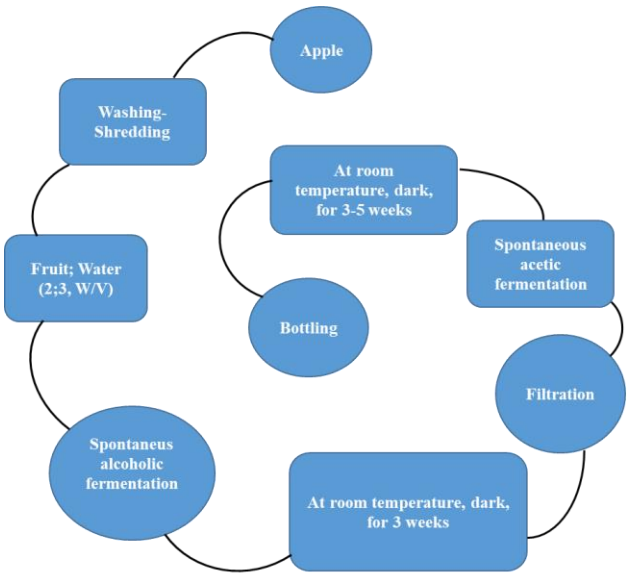


Figure 1. Home-made apple vinegar production scheme

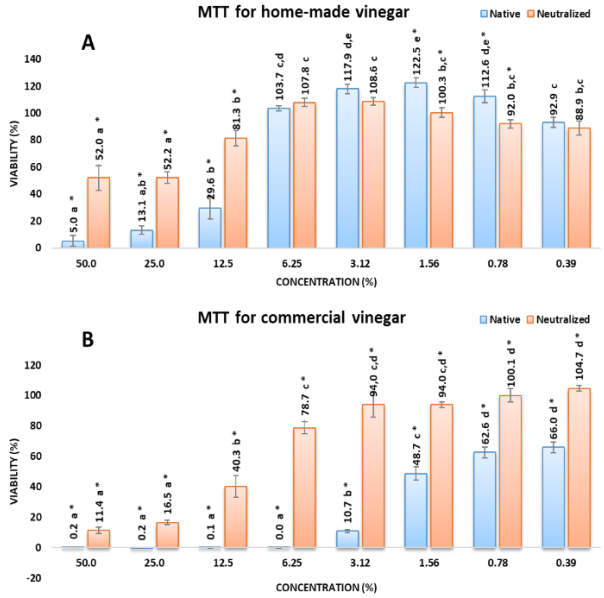


Figure 2. The cell viability in myeloma cells by using MTT assay. (A) Viability of the cells treated with home-made apple vinegars (both native and neutralized) for 24 h. (B) Viability of the cells treated with commercial apple vinegars (native and neutralized). Values are expressed as means ± SD. Small letters (a,b,c,d,e) and asterisk (*) indicate the subsets determined via Tukey pairwise comparison based on dosages and types of vinegar, respectively (p-value<0.05).

Statistical Analysis

Each concentration of the vinegars on viability of the cell was evaluated in triplicate. IC_{50} values were calculated using the Microsoft Excel program. Antiproliferative performances of vinegars were compared via One-way MANOVA. Tukey's test was chosen for post-hoc pairwise comparisons and to determine homogeneous subsets. IBM SPSS Statistics 22 was used.

Results

In this study, the pH values of home-made apple vinegar and commercial apple vinegar were 3.18 and 2.86, respectively. While the total acidity of home-made was 10.2 grams acetic acid /L sample, the total acidity commercial vinegar was 40.2 g/L. 4.4 ml and 1.9 ml of 1 N NaOH were used to neutralize 10 ml of commercial vinegar and home-made vinegar, respectively.

IC_{50} values for native and neutralized commercial apple vinegars were 0.84% and 9.98%, respectively. IC_{50} values for native and neutralized home-made apple vinegars were 12.27% and 46.78%, respectively. There was a statistically significant difference in antiproliferative performance of vinegars based on dosage, $F = 34.571$, $p < .0001$; Wilk's $\Lambda = 0$. Native commercial vinegar possessed a stronger antiproliferative activity than home-made vinegar (both native and neutralized) and neutralized commercial apple vinegar (Figure 2). The antiproliferative activity of neutralized vinegars on myeloma cells were significantly less compared to native vinegars. While the antiproliferative effect of native commercial vinegar increased in a dose-dependent manner, no linear dose response was observed in both native and neutralized home-made vinegars. The home-made vinegar exerted a markedly different effect on the viability of myeloma cells. A weak inhibition in growth of myeloma cells was observed at high concentration of neutralized home-made vinegar. Interestingly, when home-made vinegar concentrations were between 6.25 and 0.78% for native and between 6.25 and 1.56% for neutralized, the cell viability increased compared to the negative control (DMEM treated only). The findings of this study indicated that the antiproliferative effect of home-made vinegar was content and dose-dependent.

Discussion

Cancer is the leading cause of death globally, with an estimated 9.6 million deaths in 2018 and responsible for approximately 1 in every 6 deaths worldwide (WHO, 2020). There are a large number of researches indicating that some alternative therapies are safe and effective when used with chemotherapy (Adams and Jewels, 2007; Xu et al., 2007; Bilir et al., 2018; Aktaş et al., 2020). Due to their numerous pharmacological and biological activities, several natural products derived from plants have been used for treatment and prevention of human disorders for thousands of years (Demirtaş et al., 2019; Fu et al., 2019). The current interest focuses on determination of the antiproliferative effects of these natural products on cancer cells (Gill et al., 2005; Tavakoli et al., 2012; Huang et al., 2019; Tutun et al., 2020). Vinegar, which is a plant-based product, has been widely consumed for treating several human disorders such as hyperglycemia, hyperlipidemia, cancer and oxidative stress due to their bioactive substances and various beneficial effects on health (Gheflati et al., 2019; Mohamad et al., 2019; Ousaaid et al., 2020).

In this study, pH values of commercial (2.86) and home-made (3.18) vinegars were in line with previous studies (Gerbi et al., 1998; Akbaş and Cabaroğlu, 2010; Sung et al., 2014). Total acidity is an important indicator for assessing the quality of vinegar (Zhao et al., 2018). The commercial vinegar (40.2 g/L), with the exception of

home-made vinegar (10.2 g/L), complied with regulatory limits for total acidity (Turkey National Standard: TS 1880 EN 13188:2003, total acidity ≥40g/L).

Apple vinegars have high phenols, proteins and flavonoids which show potent antioxidant activity and anticancer effect against several cancer cells (Boyer and Liu 2004; Budak et al., 2011; Batra and Sharma, 2013; Anantharaju et al., 2016). Many studies suggest that the antiproliferative activity in cancer cells could be related to the antioxidant properties of the tested compounds (Li et al., 2007; Grigalius and Petrikaite, 2017). Vinegars obtained from sugar cane (Mimura et al., 2004), Kurosu (Nanda et al., 2004), Izumi (Baba et al., 2013) have been shown anticancer activity by obstructing the differentiation of human cancer cells via programmed necrosis and promotion of apoptosis (Ali et al., 2017). A paper has been indicated that apple vinegar exhibited antiproliferative effect on colon cancer cell line (HT-19) (Dubey et al., 2019). In this study, both native vinegars inhibited the growth of myeloma cells. Commercial native vinegar has been found to be very strong antiproliferative activity, compared home-made native vinegar. Acetic acid, which is a constituent of vinegar, has been shown to have anticancer effects via a mechanism involving oxidative stress leading to apoptosis in the cancer cells and these effects of acetic acid depend on the concentration of the chemical (Okabe et al., 2014; Terasaki et al., 2018). Native commercial vinegar demonstrated a higher antiproliferative effect than native home-made vinegar, which can be attributed to the presence of lower organic acid content of the latter. There was a decrease in the antiproliferative activity of both neutralized home-made and commercial vinegars compared to native vinegars. Commercial neutralized vinegar showed a stronger antiproliferative effect than home-made neutralized vinegar. Interestingly, home-made vinegar (both native and neutralized) increased cell growth compared to control wells in the dose range of 6.25 to 1.56%, while decreasing cell growth at high and low doses. Apple vinegars contain various bioactive components such as polyphenols (Budak et al., 2015; Bakır et al., 2016) showing anticancer activity (Abdal Dayem et al., 2016). The difference in antiproliferative activity between commercial and home-made vinegars may be attributed to the difference in vinegar composition, which is the result of many different variables in the production process (Morgan and Mosawy, 2016).

Conclusion

In this study, commercial and home-made apple vinegars in native and neutralized form showed antiproliferative effect on myeloma cells in a dose-dependent manner. The activity may be attributed to their bioactive components that have anticancer activity.

Conflict of Interest

The authors declare that there is no conflict of interest.

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