

Psychiatry and Clinical Psychopharmacology

ISSN: 2475-0573 (Print) 2475-0581 (Online) Journal homepage: https://www.tandfonline.com/loi/tbcp21

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To cite this article: Derya Guliz Mert, Nergiz Hacer Turgut, Emre Arslanbas, Huseyin Gungor & Haki Kara (2019) The influence of quercetin on recognition memory and brain oxidative damage in a ketamine model of schizophrenia, Psychiatry and Clinical Psychopharmacology, 29:1, 1-7, DOI: 10.1080/24750573.2018.1442670

To link to this article: https://doi.org/10.1080/24750573.2018.1442670

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Published online: 03 Mar 2018.

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PSYCHIATRY AND CLINICAL PSYCHOPHARMACOLOGY
2019, VOL. 29, NO. 1, 1–7
https://doi.org/10.1080/24750573.2018.1442670

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The influence of quercetin on recognition memory and brain oxidative damage in a ketamine model of schizophrenia

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ABSTRACT

OBJECTIVE: The aims of this study were to investigate the protective effect of quercetin on changes in recognition memory as assessed by the novel object recognition (NOR) test, as well as on changes in the oxidative stress levels in the hippocampus and prefrontal cortex, produced in a model of memory impairment in schizophrenia induced by administration of a subanesthetic dose of ketamine.

METHODS: A total of 40 Balb-C mice were randomly divided into five groups (Corn oil + Saline, Quercetin 50 + Saline, Corn oil + Ketamine, Quercetin 25 + Ketamine, Quercetin 50 + Ketamine). Corn oil and Quercetin (25 or 50 mg/kg/day) was given by orogastric gavage once daily for 21 days. Corn oil was chosen as the vehicle and administered at the same volume as quercetin. Ketamine was injected at a dose of 25 mg/kg intraperitoneally (i.p.) for a period of 7 days starting from the 15th day. Behavioural responses were evaluated with the NOR test. The activity levels of antioxidant enzymes and levels of malondialdehyde (MDA) were assayed in the prefrontal cortex and hippocampus.

RESULTS: The time of exploration of the novel object was longer than T_F (time to explore the familiar object) in the Corn oil + Saline and Quercetin 50 + Saline groups in NOR Test-1 ($p < .05$). The discrimination ratios of the Quercetin 50 + Ketamine and Corn oil + Ketamine groups were significantly lower than that of the Quercetin 50 + Saline group ($p < .05$). The discrimination ratios of the Quercetin 50 + Ketamine and Corn oil + Saline groups were significantly lower than that of the Quercetin 50 + Saline group ($p < .05$). The time of exploration of the novel object was longer than T_F in the Corn oil + Saline and Quercetin 50 + Ketamine groups in NOR Test-2 ($p < .05$). The discrimination ratios of the Corn oil + Ketamine and Quercetin 25 + Ketamine groups were significantly lower than those of the Quercetin 50 + Ketamine group ($p < .05$). Quercetin at 50 mg/kg reduced the MDA levels and elevated the SOD and GPx activity compared to the Corn oil + Ketamine group.

CONCLUSION: These results show that quercetin has the potential to improve cognitive deficits in mice and that quercetin may be useful for treating the symptoms of schizophrenia, partially due to its ability to scavenge free radicals and its high antioxidant capacity.

ARTICLE HISTORY
Received 21 December 2017
Accepted 25 January 2018

KEYWORDS
Quercetin; schizophrenia; recognition memory; ketamine; antioxidant

Introduction

Schizophrenia is a serious mental disorder that affects 1% of the world's population. The impaired cognitive function observed in this disorder is among its leading symptoms and is the most important symptom that adversely affects the social function of patients [1]. The etiology of schizophrenia is multifactorial. There are various genetic and environmental risk factors, such as drug and alcohol abuse, prenatal infections and malnutrition [2]. In addition to the heterogenity of risk factors, oxidative stress may be associated with the underlying biological mechanisms [3] because the central nervous system, compared to other organs of the body, is more sensitive to the toxic effects of reactive species. This sensitivity may be attributed to the brain's high oxidative metabolic activity, increased oxygen consumption, low levels of antioxidant production and larger membrane surface than cytoplasmic volume. Additionally, the presence of oxidizable membrane polyunsaturated fatty acids leads to a condition of being more easily affected by oxidative stress [4].

Schizophrenia features compromised neurocognitive function, which involves the speed of processing, memory, attention, processing, learning, social cognition and executive functioning [5–9]. In this regard, as a memory type, recognition memory is impaired in patients with schizophrenia [10–12]. This memory is dependent on organized brain regions, including the hippocampus, frontal lobe and parietal cortices, visual ventral stream, and medial temporal lobe structures [13,14]. The hippocampus and prefrontal cortex are important brain regions that need to be addressed

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for recognition memory [14–16]. There is widespread recognition concerning the presence and effect of deficits in cognition in schizophrenic individuals. Nevertheless, the neurobiological mechanisms that are behind this condition have not been discovered in all cases. However, many studies have recently shown that oxidative stress could negatively affect cognitive abilities, particularly memory in schizophrenia [17,18].

It was found that ketamine induces behaviours in humans that are reminiscent of schizophrenia [19], and ketamine treatment in animals involving subanesthetic doses appears to be a pharmacological model of schizophrenia [20]. Moreover, it was shown that oxidative stress in the rodent brain is increased by administering ketamine in subanesthetic doses [21–24]. Quercetin, commonly found in many fruits and vegetables, is one of the most abundant flavonoids in the human diet [25]. Quercetin has a number of activities, including antioxidant, anticancer, cardioprotective, antiulcer, antiallergic, antiinflammatory, antiviral and antiproliferative activities, and has been reported to have many beneficial effects on human health [25–27].This bioflavonoid is a potent free radical scavenger and a metal chelator that has the ability to inhibit lipid peroxidation in in vitro and in vivo systems [27]. As quercetin has high antioxidant effects and the underlying pathology of schizophrenia can be attributed to increased oxidative stress, these findings indicate that this flavonoid might decrease oxidative stress in schizophrenia and thereby prevent the cognitive destruction that occurs in this disease.

The aims of this study were to investigate the protective effect of quercetin on the change in recognition memory as assessed by the novel object recognition (NOR) test, as well as on the change of the level of oxidative stress in the hippocampus and prefrontal cortex produced by a model of memory impairment in schizophrenia induced by administration of a subanesthetic dose of ketamine.

Materials and methods

Chemical reagents and drugs

Sigma Chemical Co. (St. Louis, MO, USA) supplied quercetin and ketamine hydrochloride. We purchased commercial kits from Cayman Chemical Company, USA and used them to specify glutathione peroxidase (GPx), malondialdehyde (MDA) and superoxide dismutase (SOD). The purity of all of the chemical reagents was not less than analytical grade. The dose concentration selection for quercetin and ketamine was based on the literature [28–31].

Animals and experimental design

Eight-week-old male BALB/c mice ($n = 40$) were used. All experiments were conducted at Cumhuriyet University. Eight mice were housed per cage under standardized conditions (12-h light/dark cycle, 24 ± 2°C, 35–60% humidity) and provided a commercial standard mouse diet and water ad libitum. The experiments were performed in accordance with the Guide for the Care and Use of Laboratory Animals [National Academy Press publication, Washington, DC 20055, USA, 1996]. The study protocol was approved by the Animal Ethical Committee (date: 07/16/2014, number: 65202830/131) of Cumhuriyet University (Turkey). After one week of adaptation, the mice were randomly divided into five groups ($n = 8$ in each group): Corn oil + Saline, Quercetin 50 + Saline, Corn oil + Ketamine, Quercetin 25 + Ketamine and Quercetin 50 + Ketamine. A ketamine injection was applied in physiological saline at 1 ml/100 g volume [32,33] and oral administration of quercetin was applied in corn oil at 1 ml/100 g volume [29,31]. Corn oil and quercetin (25 or 50 mg/kg/day) were given by orogastric gavage once a day for 21 days. Corn oil was chosen as the vehicle and administered at same volume as quercetin. Ketamine was injected at a dose of 25 mg/kg intraperitoneally for a period of 7 days starting on the 15th day. Ketamine was dissolved in physiological saline. Ketamine was used for an animal model of schizophrenia. Once the period of drug administration ended, biochemical analysis and behavioural testing were conducted.

NOR test

The NOR test is extensively used to test recognition memory in a non-spatial manner. It was demonstrated that the NOR performance is interrupted in pharmacological animal models of schizophrenia [34]. Additionally, it is an efficient tool for screening the cognitive effects of new antipsychotics. The NOR test was conducted in an open field box with dimensions of 40 cm × 40 cm × 40 cm. Mice were habituated to the empty box 10 min per day for two days. Twenty-four hours after habituation, the training started by placing each mouse in the box for 10 min. Two similar objects (Lego toys) were placed symmetrically on adjacent corners of the box, and the objects were 10 cm away from the wall. An hour after training, a short-term memory (STM) test (NOR Test-1) was conducted. In this test, a novel toy and a familiar toy were placed. The size of the novel toy was identical, but its colour and shape were different. The mouse explored the environment for 5 min. After each experiment, the toy and the box were washed with 70% ethanol. At 24 h after the training session, a long-term memory (LTM) test was conducted **(NOR Test-2).** The same mouse was allowed to explore the site for 5 min in the presence of the familiar object and another novel object. Every smell and touch meant exploring the objects. Straightening of the nose toward an object from a 2-cm or shorter distance or touching the nose to an object was considered to be exploration. Rotating around the object or sitting on

it was not accepted as exploration. In each session, mice were recorded and a discrimination index was calculated for each mouse.

The discrimination index [35] was calculated as follows:

$$T_N/(T_F + T_N),$$

where T_N is the time to explore the novel object; T_F is the time to explore the familiar object.

Biochemical assessment

Biochemical tests were performed 24 h after the behavioural test. The mice were sacrificed, and their prefrontal cortices and hippocampi were excised immediately in an ice cold condition, blotted free of blood and tissue fluids, and weighed and rapidly stored at −80°C for further analysis.

Assay of MDA levels

Lipid peroxidation was monitored in terms of MDA by the method of Ohkawa et al. [36] MDA levels were determined by thiobarbituric acid reactive substances (TBARS) in brain tissue homogenate, based on the reaction between MDA and thiobarbituric acid. Thiobarbituric acid, when allowed to react with MDA aerobically, forms a coloured complex [MDA-(TBA) 2 complex], which was measured by a spectrophotometer (Shimadzu UV-1700, Japan) at 532 nm. The MDA concentrations (measured as TBARS) were calculated as "nmol/ml" for serum and "nmol/mg protein" for brain and liver tissues. The absorbance values were compared with those of a series of standard solutions of 1, 1, 3, 3-tetraethoxypropane (TEP).

Measurement of SOD activity

SOD activity was determined by using a commercially available standard enzymatic kit (Cayman Chemical Company, USA) that utilizes a tetrazolium salt for the detection of superoxide radicals generated by xanthine oxidase and hypoxanthine. The SOD assay measures all three types of SOD (CU/Zn, Mn and Fe SOD). One unit of SOD activity is defined as the amount of enzyme needed to exhibit 50% dismutation of the superoxide radical. The absorbance was read at 440–460 nm using a plate reader (Thermo, Multiskan GO Microplate, USA). The SOD activity was expressed as "U/ml" for serum and "U/mg protein" for brain and liver tissues.

Measurement of GPx activity

A commercially available kit (Cayman chemical, USA) was used to measure GPx activity. The levels of GPx activity were expressed as "nmol/min/ml" for serum and "nmol/min/mg protein" for brain and liver tissues. GPx activity was measured relying on the acceptance of a coupled reaction with glutathione reductase (GR) in principle. The oxidized glutathione formed after the reduction of hydroperoxide by GPx is recycled to its reduced state by GR in the presence of NADPH and is accompanied by a decrease in absorbance at 340 nm. The quantity of enzyme that catalyzes the oxidation of 1 nmol of NADPH per minute at 25°C defines one unit of GPx activity. Absorbance was read once every minute at 340 nm using a plate reader to obtain at least 5 time points.

Estimation of total protein content

The total protein content was estimated by the method of Bradford [37] Bovine serum albumin was used as a standard.

Statistical analysis

Data were analysed by using SPSS for Windows, Version 15 (SPSS Inc., Chicago, IL, USA). The results were expressed as the means ± standard deviation (SD). The normality of the data distributions was tested with Kolmogorov–Smirnov tests. Normally distributed data were analysed by parametric tests. Nonparametric tests were used for data that were not normally distributed. For the data obtained from the NOR test, one-way analysis of variance (ANOVA) was conducted to compare the exploration times of the objects in a training session between the five groups. Within-group differences concerning the time of exploration of the novel and familiar objects were analysed by means of Wilcoxon tests in NOR Test-1 and Test-2, respectively. Discrimination ratios of the five groups in NOR test 1 and 2 were analysed by the Kruskal–Wallis test, followed by a *post hoc* Mann–Whitney U-test. The data obtained from biochemical tests were analysed with one-way ANOVA, followed by Newman–Keuls or Tukey–Kramer multiple comparison tests as *post hoc* tests. A value of $p < .05$, $p < .01$ or $p < .001$ was regarded as significant.

Results

Exploration of the objects in the training session

The mean exploration times (s) of the familiar objects in the training session were 61.1 ± 17.9 in the Corn oil + Saline group, 48 ± 16.66 in the Corn oil + Ketamine group, 58.57 ± 10.18 in the Quercetin 25 + Ketamine group, 59.5 ± 22.39 in the Quercetin 50 + Saline group and 71.4 ± 14.76 in the Quercetin 50 + Ketamine group. There was no significant difference between the study groups.

Table 1. Interaction time with the novel and familiar objects and the discrimination ratios in NOR Test-1.

	TN (s) Mean ± SD	TF (s) Mean ± SD	Discrimination ratios** Mean ± SD
Corn + saline	25.7 ± 14.6[a]*	16.4 ± 10.5	0.62 ± 0.08[b]
Corn + ketamine	18 ± 6.6	18.5 ± 12.1	0.52 ± 0.11[b]
Quercetin 25 + ketamine	17.8 ± 6.4	15.7 ± 9.6	0.55 ± 0.14
Quercetin 50 + saline	34.1 ± 13.8[a]*	17.7 ± 9.6	0.67 ± 0.13[c]
Quercetin 50 + ketamine	20.5 ± 9.8	20.9 ± 7.6	0.49 ± 0.12[b]

Notes: TN: Time with novel object, TF: Time with familiar object. Data are presented as the mean ± SD.
[a]$p < .05$ vs. TF.
[b]$p < .05$ vs. [c]Discrimination ratio.
* Wilcoxon signed rank test, TN vs. TF, $p < .05$.
** Kruskal–Wallis test, $p < .05$.

Table 2. Interaction time with the novel and familiar objects and discrimination ratios in NOR Test-2.

	TN (s) Mean ± SD	TF (s) Mean ± SD	Discrimination ratios** Mean ± SD
Corn + saline	27.1 ± 19.1[a]*	19 ± 13.2	0.59 ± 0.09
Corn + ketamine	14.7 ± 7.4	15.4 ± 10.1	0.49 ± 0.14[b]
Quercetin 25 + ketamine	16.3 ± 7.1	19.4 ± 12.1	0.48 ± 0.12[b]
Quercetin 50 + saline	25.7 ± 9.2	18.4 ± 9.2	0.58 ± 0.12
Quercetin 50 + ketamine	32.4 ± 18[a]*	16.7 ± 7.9	0.64 ± 0.09[c]

Notes: TN: Time with novel object; TF: Time with familiar object. Data are presented as the mean ± SD.
[a]$p < .05$ vs. TF.
[b]$p < .05$ vs. [c]Discrimination ratio.
*Wilcoxon signed rank test, TN vs. TF, $p < .05$.
**Kruskal–Wallis test, $p < .05$.

STM performance

The time of exploration of the novel object was longer than T_F in the Corn oil + Saline group and Quercetin 50 + Saline group in NOR Test-1 ($p < .05$). On the other hand, the T_N in the Corn oil + Ketamine, Quercetin 25 + Ketamine and Quercetin 50 + Ketamine groups was not significantly different than T_F ($p > .05$) (Table 1). The discrimination ratios of the Quercetin 50 + Ketamine, and Corn oil + Saline groups were significantly lower than that of the Quercetin 50 + Saline group ($p < .05$) (Table 1).

LTM performance

The time of exploration of the novel object was longer than T_F in the Corn oil + Saline group and Quercetin 50 + Ketamine group in NOR Test-2 ($p < .05$). On the other hand, the T_N in the Corn oil + Ketamine, Quercetin 25 + Ketamine and Quercetin 50 + Saline groups was not significantly different than T_F ($p > .05$) (Table 2). The discrimination ratios of the Corn oil + Ketamine and Quercetin 25 + Ketamine groups were significantly lower than those of the Quercetin 50 + Ketamine group ($p < .05$) (Table 2).

Effect of quercetin on lipid peroxidation levels

The MDA levels significantly increased in ketamine-treated mice compared to the Corn oil + Saline group in both the hippocampus and prefrontal cortex ($p < .001$). Quercetin administration at 50 mg/kg to ketamine-treated mice significantly reduced the MDA levels compared to the Ketamine + Saline group ($p < .001$), whereas 25 mg/kg did not cause a significant change in the MDA levels in either the hippocampus or prefrontal cortex (Figure 1).

Effect of quercetin on enzymatic antioxidants

A significant decrease in the levels of GPx was observed in the hippocampus and prefrontal cortex of mice treated with ketamine compared to the mice in the Corn oil + Saline group ($p < .01, p < .001$). Treatment with quercetin (50 mg/kg) in ketamine-administered mice increased the levels of GPx significantly in both the hippocampus and prefrontal cortex compared to the mice the Corn oil + Ketamine group ($p < .05$) (Figure 2).

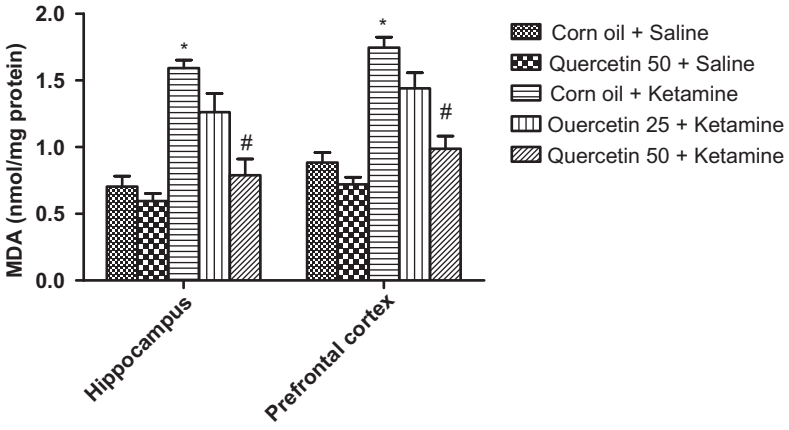


Figure 1. Effect of Quercetin (25 and/or 50 mg/kg) on the levels of malodialdehyde (MDA) in cerebral structures of ketamine-treated rats. Data are expressed as mean ± SD, ($n = 8$ in each group). *$p < .001$, compared with Corn oil + Saline group; #$p < .001$, compared to Corn oil + Ketamine group.

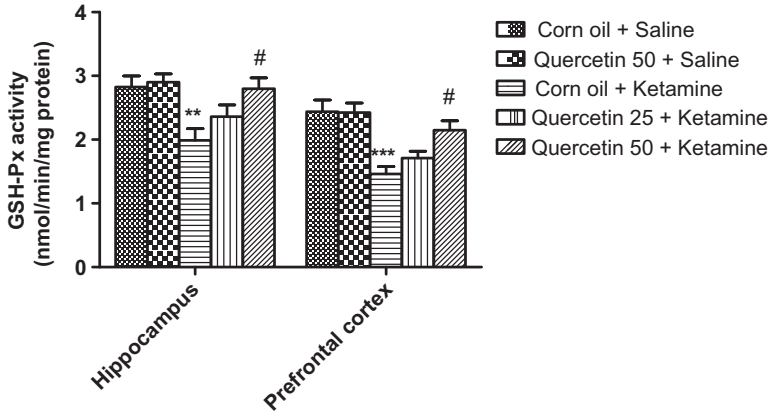


Figure 2. Effect of Quercetin (25 and/or 50 mg/kg) on the activities of glutathione peroxidase (GPx) in cerebral structures of ketamine-treated rats. Data are expressed as mean ± SD, ($n = 8$ in each group). **$p < .01$, ***$p < .001$ compared with Corn oil + Saline group; #$p < .05$, compared to Corn oil + Ketamine group.

A significant decrease in the levels of SOD was noticed in the hippocampus and prefrontal cortex of the mice treated with ketamine compared to the mice in the Corn oil + Saline group ($p < .01$). Treatment with quercetin (50 mg/kg) in ketamine-administered mice increased the levels of SOD in both the hippocampus and prefrontal cortex significantly compared to the mice in the Corn oil + Ketamine group ($p < .05$, $p < .01$) (Figure 3). Quercetin at 25 mg/kg did not cause a significant change in the GPx or SOD levels in either the hippocampus or prefrontal cortex.

Discussion

In the present study, mice were submitted to two different doses of quercetin, which had an antioxidant effect. Afterwards, subanesthetic doses of ketamine, an NMDA antagonist presenting symptoms comparable to those of schizophrenia, were administered, and the STM and LTM NOR test performance was assessed. The LTM NOR test performance in the mice submitted to quercetin 50 mg along with ketamine was not negatively affected. In mice in which the schizophrenia model was created and whose memories were assessed, we then evaluated the effect of the two different doses of quercetin on the parameters of oxidative stress in the prefrontal cortex and hippocampus of the brain. Similarly, it was observed that quercetin 50 mg yielded a protective effect against oxidative stress in both regions of the brain. The pathogenesis of schizophrenia has not been discovered yet. Nevertheless, an association might exist between schizophrenia and oxidative stress, as demonstrated by the evidence [38]

Recognition memory is a subcategory of declarative memory. In line with previous studies conducted with a non-competitive NMDA antagonist, we found that ketamine caused deterioration in the NOR test both in STM and LTM in mice [39–41]. Yet, when quercetin 50 mg plus ketamine was administered, it took longer for the mice to recognize the novel object compared to the familiar object. In other words, it was found that LTM NOR was not deteriorated. Nevertheless, there was deterioration in STM NOR at both doses of quercetin in the mice administered ketamine. These conflicting results regarding the protective effect of quercetin 50 mg on STM and LTM might not be

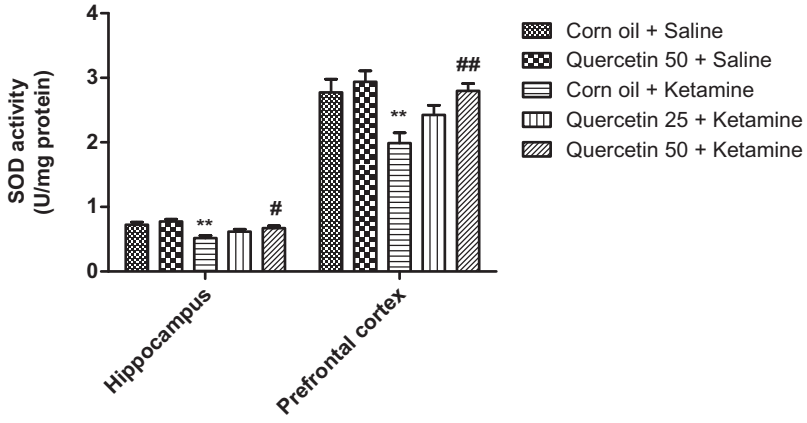


Figure 3. Effect of Quercetin (25 and/or 50 mg/kg) on the activities of superoxide dismutase (SOD) in cerebral structures of ketamine-treated rats. Data are expressed as mean ± SD, ($n = 8$ in each group). **$p < .01$, compared with Corn oil + Saline group; #$p < .05$, ##$p < .01$ compared to Corn oil + Ketamine group.

surprising because the popular concept previously known as "short-term memory is just a passageway to the long-term memory" seems to have changed in the last decade. It has been recently shown that separate subsystems of the brain concern and regulate STM and LTM, and in certain cases, the same or different brain structures [42] contain these subsystems, which include a number of various molecular mechanisms at the receptor and post-receptor level [43].

Increased peroxidation end-products, DNA (and often RNA) base oxidation products and oxidative protein damage are indicative of oxidative stress [22,44]. Although the pathogenesis of schizophrenia is not known, the evidence has noted a possible relationship between oxidative stress and the disease [22,38]. The data available in the literature indicate that patients with all sorts of schizophrenia compared to healthy controls, have decreased activity of the antioxidant enzymes superoxide dismutase (SOD) and glutathione peroxidase, whereas they have increased levels of malondialdehyde [22,45]. Moreover, a relationship of ketamine with oxidative stress has been shown in the literature [22]. The present study also found increased MDA levels and decreased SOD and GPx activity in both the hippocampus and prefrontal cortex of mice administered only ketamine compared to other study groups, yielding support for the association between oxidative stress and schizophrenia. Additionally, our study also found that the Quercetin 50 mg plus ketamine group had significantly decreased MDA levels and increased SOD and GPx activity in both regions of the brain compared to the group administered ketamine only. This might show the protective effect of quercetin 50 mg against oxidative stress in the schizophrenia model. Although the protective effect of quercetin against oxidative stress in various diseases has been discussed in the literature, the present study supports its protective effects in a schizophrenia model for the first time.

Conclusion

A proper understanding of the pathophysiology of schizophrenia is still lacking. Nevertheless, the possible involvement of oxidative stress in the development of schizophrenia is indicated by oxidative protein damage, increased lipid peroxidation, and decreased enzymatic defenses observed in an animal model of induced schizophrenia. The deterioration in the novel recognition test can be explained by such findings. Moreover, the protective effect of quercetin at a 50 mg dose against oxidative stress was shown by contributions appearing both in the NOR test and in the increase of antioxidant enzymes.

Disclosure statement

No potential conflict of interest was reported by the authors.

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