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Effect of Quercetin on Retention and Retrieval of Memory in Young and Aged Mice.

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ABSTRCT

Learning ability and memory are among the outstanding features of human beings. The increasing number of patients with learning disabilities and memory disorders has motivated many researchers to study the discovery of new medicines which can improve memory, learning ability and prevent its relevant disorders. Since some of the memory disorders are caused by free radicals and oxidative stress ,a good solution to prevent such disorders is to use antioxidants. The aim of this research was to investigate the effect of Quercetin on retention and retrieval of memory in young and aged mice. Animals were divided into groups (n = 8) as follows: test groups received electric shock plus quercetin (12.5,25,50mg/kg, i. P.), control group received electric shock plus normal saline and blank group received only electric shock. In all groups, step-down latency for both retention and retrieval test of memory was measured. quercetin was administered immediately after receiving electric shock in the retention test, but quercetin was administered 23.5 hours after receiving electric shock in the retrieval test. The best dose of quercetin in retention test of the young group was found 50 mg/kg, And the best Response was attained with 25mg/kg of quercetin in retention test of the aged group and retrieval test of young and the aged groups. Receiving quercetin may improve the retention and retrieval of memory in aged and young mice.

Keywords: quercetin; Memory; Retention; Retrieval; Mice

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INTRODUCTION

Learning ability and memory are among the outstanding features of human beings which are unavoidable for their survival and scientific developments. The increasing number of patients with learning disabilities and memory disorders has motivated many researchers to study the discovery of new medicines which can improve memory, learning ability and prevent its relevant disorders [1].

Memory and learning ability are composed of several and separate processes. Learning is a process in which new information is collected from the surrounding environment, whereas memory refers to the ability to retention and retrieve information [2].

In recent years, using medical plants to improve memory and treat amnesia has been the subject of many studies in medical sciences.

Very different medicinal plants have been used to improve memory and to treat amnesia, such as: saffron [3], Ginkobiloba [4], and Senna [5]. As studies indicated, Quercetin has positive effects on the physiological processes such as inhibiting growth of cancer cells [6, 7], inhibiting platelet aggregation and treating coronary artery diseases [8, 9], treating neurodegenerative diseases [9, 10], treating osteoarthritis [11, 12], treating diabetes [13] and treating eye disorders [14].

Quercetin is a bioflavonoid which is found frequently in onions, apples, tea, strawberries, cabbages, and so on [15]. According to the studies, both quercetin and polyphenols, as antioxidants, protect cells from oxidative stress. Quercetin also stimulates cell proliferation and increases the total antioxidant capacity of the cells [16].

Since some of the memory disorders are caused by free radicals and oxidative stress [17], a good solution to prevent such disorders is to use antioxidants [16].

According to the studies, polyphenols improve the memory performance in the aged rats [18, 19]. Previous studies showed that as the age increases and when synthesis of reactive oxygen species (ROS) and oxidative stress condition are maximized, brain starts to experience abnormal activities [17]. Since quercetin is a bioflavonoid, [15] which has shown considerable antioxidant features in many studies, strengthening antioxidant condition, decreasing free radicals have ideal effects on memory and learning ability, [4] and aggregation of antioxidant substances in the nervous tissue is effective in treating disorders caused by the oxidative stress [20], in present study investigated the effect of quercetin on the retention and retrieval of memory in both aged and young mice.

Objectives

The aim of this research was to investigate the effect of Quercetin on retention and retrieval of memory in young and aged mice.

MATERIALS AND METHODS

Animals

Young (aged 3 months) and old (aged 15 months) male N-Mari mice were used during the study. The animals were purchased from the animal house of Jundishapur University of Medical Sciences, Ahvaz, Iran. They were kept in a clean holding room on a 12-hour light and dark cycle with relative humidity of 45-55% and temperature of 23 ± 2°C. During the experimentation, all mice were fed with concentrated food pellets (Pars Khurakdam Shushtar, Iran) and tap water ad libitum(21).

The Experiments

In this study, two groups of young adult and aged mice were used. Each group divided into five sub groups (n = 8) subsequently. The test groups received Quercetin 12.5, 25 and 50 mg/kg. The Control group received normal saline (10 mL/1Kg) and the blank group was untreated.

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The step-down apparatus used to test passive avoidance, consisted of a box 25 × 25 × 20 cm in diameter with an electrifiable grid floor. There was a round plastic which could be enclosed by a 20-cm long hollow plastic cylinder with an inner diameter of 10 cm. On the first day, groups of four animals were given access to learning apparatus for three minutes to be familiarized with the new environment. On the second day, mice were individually placed on the platform inside the cylinder and after 10 seconds the cylinder was removed and the step-down latency was measured. Animals with latencies longer than 30 seconds were excluded from the study. On the third day, the same procedure was followed as the second day, except that a one-second foot shock (1 mA) was administered as soon as the animals left the platform with all four legs. Drugs were injected to animals immediately after foot shock, to study the effects on retention of memory. After 23.5 hours of shock, the same drug was injected to study the effect of retrieval of memory. On the fourth day, step-down latency of the mice was recorded. Each animal was used only once. All drugs were administered intraperitoneally (21).

Statistical Analysis

Results were expressed as means ± SEM. The data was analyzed using Student T-test and One-way ANOVA followed by LSD test. $P < 0.05$ was considered statistically significant.

RESULTS

The mean of step-down latency on day four was higher compared to day two ($P < 0.05$) in retention and retrieval of memory in all young and aged groups of mice (Figures 1 - 4).

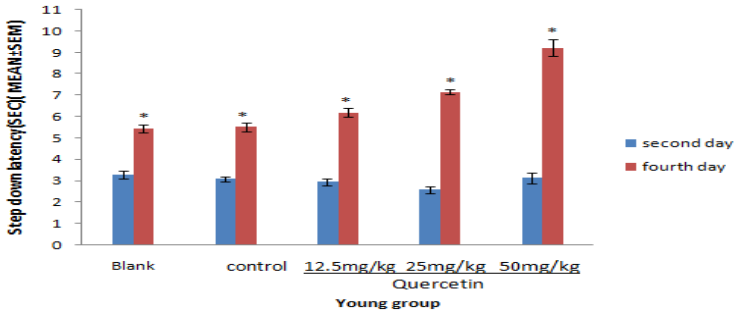

Figure 1: Comparison of the Step-down Latency in Young Mice (n = 8) That Received (Blank) No Injection, (Control) Normal Saline (10 mL/kg), (Test) 12.5 , 25, 50 mg/kg quercetin in MemoryRetention Test in the Second and Fourth Days of Study.

Significant differences between the second and fourth days are shown as *P < 0.05. Data was analyzed using Student's T-test and One-way ANOVA followed by LSD test

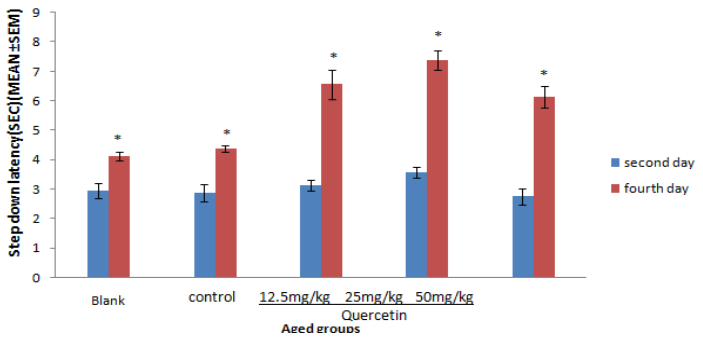

Figure 2: Comparison of the Step-down Latency in Aged Mice (n = 8) That Received (Blank) No Injection, (Control) Normal Saline (10 mL/kg), (Test) 12.5 , 25, 50 mg/kg quercetin in Memory Retention Test in the Second and Fourth Days of Study.

Significant differences between the second and fourth days are shown as *P < 0.05. Data wasanalyzed using Student's T-test and One-way ANOVA followed by LSD test.

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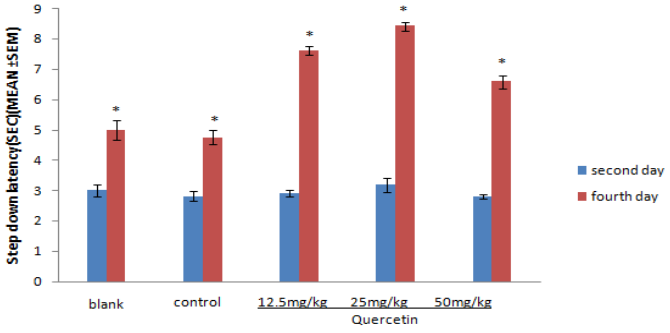

Figure 3: Comparison of the Step-down Latency in Young Mice (n = 8) That Received (Blank) No Injection, (Control) Normal Saline (10 mL/kg), (Test) 12.5 , 25, 50 mg/kg quercetin in Memory Retrieval Test in the Second and Fourth Days of Study.

Significant differences between the second and fourth days are shown as *P < 0.05. Data wasanalyzed usingStudent's-test and One-way ANOVA followed by LSD test.

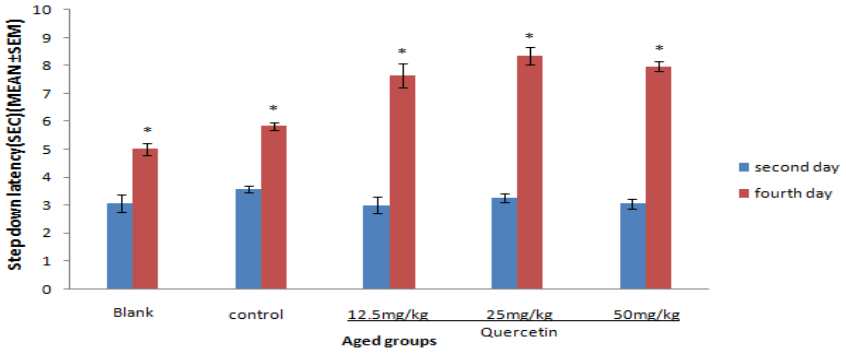

Figure 4: Comparison of the Step-down Latency in Aged Mice (n = 8) That Received (Blank) No Injection, (Control) Normal Saline (10 mL/kg), (Test) 12.5 , 25, 50 mg/kg quercetin in Memory Retrieval Test in the Second and Fourth Days of Study.

Significant differences between the second and fourth days are shown as *P < 0.05. Data was analyzed using Student's T-test and One-way ANOVA followed by LSD test.

Comparing The mean of step-down latency on day four of various test groups of young mice(received 12.5 mg/kg, 25 mg/kg and 50 mg/kg, Quercetin, IP) in retention of memory test, with the blank and control groups showed that the mean of step-down latency for three test groups was significantly more than that of blank group (P < 0.05). However, The mean of step-down latency in two doses of 25 and 50 mg/kg Quercetin was significantly more than that in control group (P < 0.05), Also The mean of step-down latency in two doses of 25 and 50 mg/kg Quercetin was significantly more than that in 12.5 mg/kg Quercetin (P < 0.05) (Figure 5).

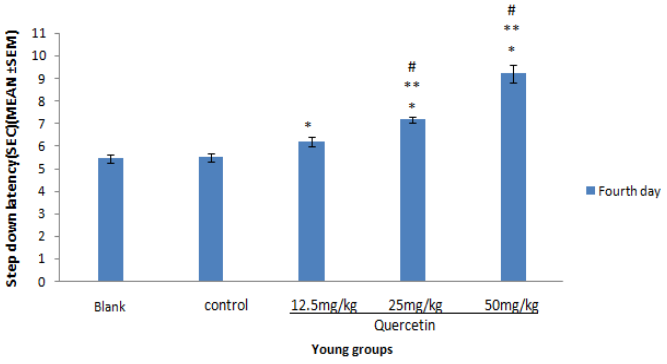

Figure 5: Comparison of the Step-down Latency in Young Mice (n = 8) That Received (Blank) No Injection, (Control) Normal Saline (10 mL/kg), (Test) 12.5 , 25, 50 mg/kg quercetin in Memory Retention Test in Fourth Day of Study.

Data was analyzed using one-way ANOVA followed by LSD test. *P<0.05 as compared with the blank group. ** P < 0.05 as compared with the control group.# P<0.05 as compared with the 12.5mg/kg group.

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Comparing the mean of step-down latency on day four of various test groups in young mice (12.5 mg/kg, 25 mg/kg, and 50 mg/kg quercetin,IP), in retrieval of memory test, with control and blank groups showed that the mean of step-down latency in all test groups was significantly more than that in control and blank groups($p<0.05$). Also a significant increase ($p<0.05$) was seen in dose of 25 mg/kg in compared to other groups (Figure 6).

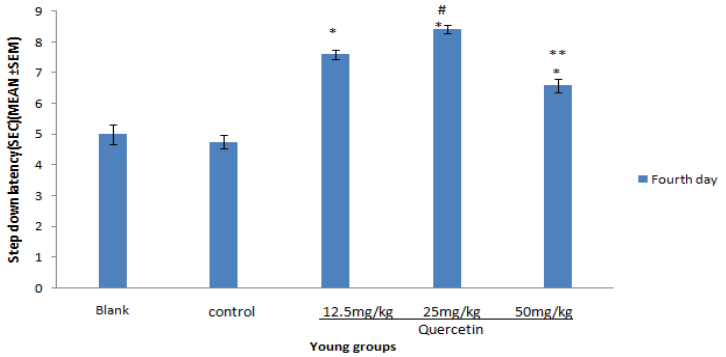

Figure 6. Comparison of the Step-down Latency in young Mice (n = 8) That Received (Blank) No Injection, (Control) Normal Saline (10 mL/kg), (Test) 12.5 , 25, 50 mg/kg quercetin in Memory Retrieval Test in Fourth Day of Study.
Data wasanalyzed usingOne-way ANOVA followed by LSD test. *P < 0.05 as compared with the blank and control group. **P < 0.05 as compared with the 12.5 and 25 mg/kg group. # P < 0.05 as compared with the 12.5 mg/kg group.

Comparing the mean of step-down latency on day four of various test groups in aged mice (12.5 mg/kg, 25 mg/kg, and 50 mg/kg quercetin,IP) in retention of memory test, with control and blank groups indicated that the mean of step-down latency in all test groups is significantly ($P<0.05$) more than that in blank and control groups. The mean of step-down latency which recieved 50 Mg/kg quercetin in compared to 25 mg/kg quercetin was decreased significantly ($P<0.05$)(Figure 7).

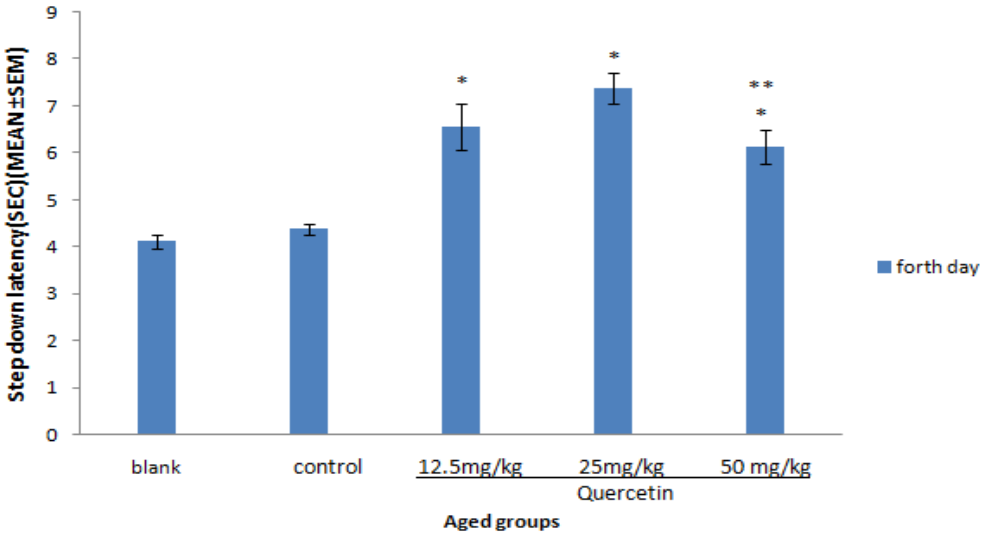

Figure 7: Comparison of the Step-down Latency in aged Mice (n = 8) That Received (Blank) No Injection, (Control) Normal Saline (10 mL/kg), (Test) 12.5 , 25, 50 mg/kg quercetin in Memory Retention Test in Fourth Day of Study.
Data was analyzed using One-way ANOVA followed by LSD test. *P < 0.05 as compared with the blank and control group. **P < 0.05 as compared with the 25 mg/kg group.

There was significant increase ($P<0.05$) in the mean of step-down latency on they four regarding retrieval of memory in aged mice test group(12.5mg/kg, 25 mg/kg, and 50 mg/kg quercetin,IP) compared to control and blank groups. However, no significant difference was seen between none of quercetin receiver groups(Figure8).

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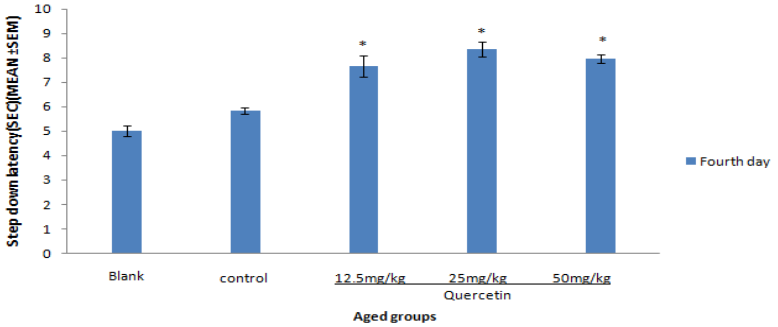

Figure 8: Comparison of the Step-down Latency in Aged Mice (n = 8) That Received (Blank) No Injection, (Control) Normal Saline (10 mL/kg), (Test) 12.5 , 25, 50 mg/kg quercetin in Memory Retrieval Test in Fourth Day of Study.

No significant difference between the groups. Data wasanalyzed using One-way ANOVA followed by LSD test. *P < 0.05 as compared with the blank and control group.

In memory retention test, the mean of step-down latency on day four of young mice groups that received 50 mg/kg Quercetin, blank and control groups were higher (P<0.05) than aged mice whereas in group that received 12.5 and 25 mg/kg quercetin, no significant difference was seen(Figure 9).

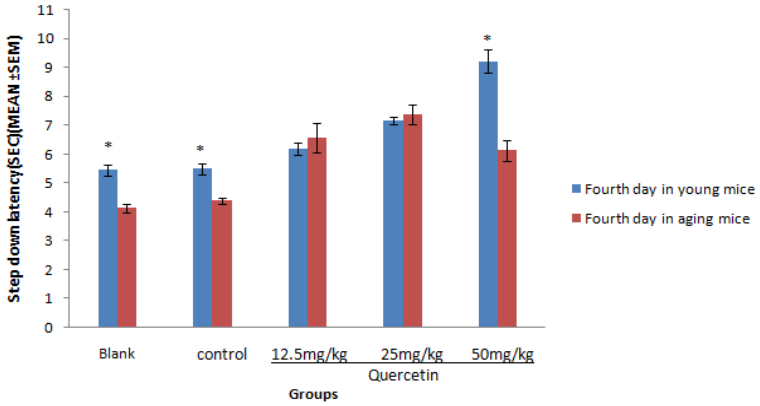

Figure 9. Comparison of the Step-down Latency inYoung and Aged Mice (n = 8) That Received (Blank)No Injection, (Control) Normal Saline (10 mL/kg), (test) 12.5 , 25, 50 mg/kg quercetin in Memory Retention Test in Fourth Day of Study.

Significant difference between young and aged groups are shown as*P < 0.05. Data was analyzed using Student's T-test and One-way ANOVA followed by LSD test.

In memory retrieval test, the mean of step-down latency on day four of aged mice groups that received 50 mg/kg Quercetin and control groups were higher (P<0.05) than young mice whereas in groups that received 12.5 mg/kg, 25 mg/kg quercetin and blank group, no significant difference was seen(Figure10).

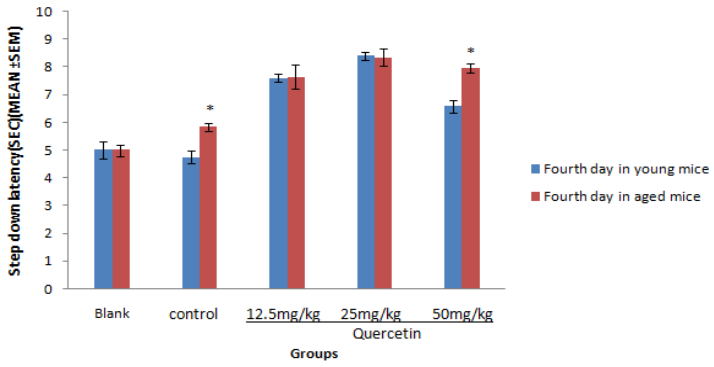

Figure 10. Comparison of the Step-down Latency in Young and Aged Mice (n = 8) That Received (Blank) No Injection, (Control) Normal Saline (10 mL/kg), (Test) 12.5 , 25, 50 mg/kg quercetin in Memory Retrieval Test in Fourth Day of Study.

Significant difference between young and aged groups are shown as*P < 0.05. Data was analyzed using Student's T-test and One-way ANOVA followed by LSD test.

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DISCUSSION AND CONCLUSION

Using chemical drugs to improve learning and memory ability is usually associated with several side effects; thus, today most researchers have returned to medicinal plants and natural medicines. So if their scientific function, in terms of selection, consumption level and consumption procedure, is demonstrated positively, they will be very helpful because of their very low, and even sometimes negligible, side effects [22].

Since a part of memory disorders is caused by free radicals and oxidative stress [17], a good solution to prevent such disorders is to use antioxidants [16]. Since quercetin has shown considerable antioxidant features in many studies, its effect on retention and retrieval of memory in both the aged and young mice was studied.

In aging time, the oxidative stress is considered as a risk factor in increasing the oxidized lipids and proteins in the central nervous system which in turn finally will result in cell damages [23].

Studies have shown that more ROS was produced in different parts of the brain of aged mice in compared to young ones [24].

In this study, the effect of quercetin on retention and retrieval of memory in the aged and young male mice was examined. The results showed that receiving quercetin resulted in improving the retention and retrieval of memory in aged and young mice. The best dose in retention test for the young test group was found 50 mg/kg, whereas the best dose in retention test of the aged mice and retrieval of young and the aged mice was reported to be 25 mg/kg of quercetin

Rinwa *et al.* (2013) showed that piperine improved the neuro-protective effect of quercetin against oxidative stress caused by chronic unpredictable stress (CUS), neuro-inflammation and memory disorders [25].

Administration of quercetin for rats with Parkinson helped them protect CNS neurons against toxicity of 6-OHDA (6- hydroxydopamine) [26].

Singh *et al.* (2003) observed that administration of quercetin (10, 25 and 50 mg/kg)for 30 days or co-administration with ethanol (2 g/kg, 15% w/v per orally) for 24 days reversed cognitive dificit in aged and ethanol-intoxicated mice. This effect was due to antioxidant feature of quercetin [27].

Kumar *et al.* (2008) observed that After chronic treatment with quercetin (20 and 40 mg/kg po) twice daily for a period of 25 days beginning 4 days prior to colchicine injection (15 µg/rat,icv), significantly improved the colchicines-induced cognitive impairment and also decrease the lipid peroxidation [28].

Ansari *et al.* (2009) suggested that quercetin showed protective effects against Aβ(1–42) toxicity by modulating oxidative stress at lower doses, but higher doses were not only non-neuroprotective but also toxic [29].

Jamshidzadeh *et al.* (2010) observed that invitro administration of quercetin declined oxidative stress and decreased Malondialdehyde [30].

According to the studies,both quercetin and polyphenols, as antioxidants, protected the cells from oxidative stress. Low concentration of quercetin also stimulates proliferation and increased the total antioxidant capacity of the cell [16].

Quercetin is a natural antioxidant which implements its antioxidant effect through inhibiting lipids peroxidation, blocking xanthine oxidase, chelating iron, hydrogenising the free radicals or removing them [32,31].

Regarding the role of quercetin in removing free radicals and oxidative stress, it appears that quercetin, as an antioxidant, can be considered a proper treatment to alleviate oxidative stress in the central nervous system. It is necessary to mention that guaranteeing such useful effects of quercetin needs further studies on various animal models and finally on human model through observing current standards and rules.

ACKNOWLEDGEMENTS

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