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Tree nuts supplementation instigates the oxidative status and improves brain performance in male rats

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Abstract: Exposure to cadmium has been extensively increased due to its usage in modern daily life. Inside the human body it induces deteriorating effects in every vital organ including brain. Oxidative stress has been widely implicated in neurotoxicity induced by cadmium exposure. Consumption of dietary source of exogenous antioxidants is one of the recommended ways to extenuate heavy metal-induced oxidative stress. The potential of nuts against heavy-metal induced neurotoxicity has not been investigated earlier. This study was, therefore, conducted to find out the antioxidant ability of almond and walnut in the prevention of cadmium-induced oxidative stress. Rats were treated with nuts (400 mg/kg) daily for 28 days whereas, cadmium (50 mg/kg) was given once in a week. Brain function was monitored in terms of memory performance using Morris water maze and elevated plus maze. Moreover, oxidative stress status was also evaluated. Results showed that weekly exposure of cadmium significantly reduced %memory retention, increased lipid per oxidation and inhibited antioxidant enzymes activity. When nuts supplemented rats were monitored for these parameters, it was observed that almond and walnut have a great potential to reduce cadmium-induced neurotoxicity as evident by decreased oxidative stress and improved memory function in cadmium intoxicated rats.

Keywords: Almond, cadmium, memory retention, oxidative stress, walnut.

INTRODUCTION

The group of heavy metals comprise of those metals having a density greater than 5g/cm^3. These heavy metals are considerably present in environment naturally or due to different activities of human population. Heavy metals including zinc, copper, cobalt, selenium and manganese are required at very low concentration to maintain various biochemical and physiological functions of living body (Ali *et al*., 2019). However, toxic and deleterious heavy metals such as cadmium have no known physiological functions and regarded as environmental pollutants and threat for living individuals (Jaishankar *et al*., 2014). Cadmium is being leaked into environment due to increased industrialization and human activities. The human population experience cadmium exposure by the ingestion of contaminated food (Rafati Rahimzadeh *et al*., 2017). Tobacco smoke is also considered as the major source of cadmium exposure (WHO, 2010). Accumulation of cadmium occurs due to its daily environmental exposure. It can stay inside of living body for many years due to long biological half life and low excretion through kidney. The toxic effects of cadmium affect every organ of body where it accumulates (Zhang *et al*., 2019). It can also increase permeability of blood brain barrier and enter into nervous system to induce neurotoxicity. Cadmium has been reported to cause neuronal apoptosis by oxidative stress and DNA destruction (Branca *et al*., 2020). Deposition of cadmium in brain leads to development of various neurological disorders such as hyperactivity, memory dysfunction and learning disabilities (Branca *et al*., 2018b). Alterations in visuomotor and psychomotor functioning, and speed in workers exposed to cadmium has also been reported earlier (Wang and Du, 2013). Moreover, increased aggression and anxiety-like behaviors have also been reported in cadmium-exposed rats (Terçariol *et al*., 2011). At cellular level, the mechanism of cadmium toxicity includes the hindrance in calcium homeostasis and imbalance in excitation-inhibition synaptic neurotransmission (Wang and Du, 2013). Oxidative stress is also widely implicated as a deleterious outcome of cadmium toxicity. The difference in the brain levels of oxidants and endogenous antioxidants due to cadmium intoxication leads to impaired neurogenesis, neuronal differentiation and neuronal cell death which ultimately results in neurobehavioral deficits (Branca *et al*., 2018b).

Oxidative stress occurs as a result of accumulation of reactive species comprising hydroxyl radicals (OH-), superoxide anion radicals (O2), nitrate radicals (NO-), and lipid peroxyl radicals (LOO-) (Halliwell, 2007).

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These accumulated reactive species cause oxidation of endogenous biomolecules including DNA, proteins, and lipids resulting in impairment of neuronal function and synaptic plasticity which may reflect in impaired memory function of the affected individual (Di *et al*., 2016). One of the effective ways to overcome oxidative stress-induced brain malfunctioning is the consumption of antioxidant rich dietary supplements. Such supplements provide surplus amount of different exogenous antioxidants which aid in scavenging of free radicals and thus provide protection against oxidative stress (Bjørklund and Chirumbolo, 2017). An ample amount of research has demonstrated that the consumption of plant-based supplements is useful to insulate the brain from oxidative reactive species produced by the exposure of heavy metals (Gupta *et al*., 2015). For example, administration of diet rich in, onion tomato, soybean, green tea, ginger, garlic, grapes, and curry leaf has shown to ameliorate cadmium-induced toxicity in different animal models (Zhai *et al*, 2015). Almonds and walnuts are amongst the natural sources of essential macro- and micro-nutrients including minerals, vitamins and antioxidant polyphenols (Alasalvar and Shahidi, 2009). These nuts have shown significant antioxidant capacity which can help to reduce oxidative stress induced by metal toxicity. Previously, long-term administration of these nuts has shown to ameliorate cadmium-induced neurobehavioral deficits by normalizing the neurotransmitters derangements (Batool *et al*., 2017; Batool *et al*., 2019). The current study was planned to further extend the previous findings to determine the effectiveness of antioxidant capacity of these nuts against cadmium-induced oxidative stress. Brain function was examined in terms of %memory retention while oxidative status was determined by the estimation of lipid peroxidation and activity of antioxidant enzymes in brain of cadmium-intoxicated rats which were supplemented with almond or walnut.

MATERIALS AND METHODS

Albino Wistar rats weighing 180-200g were procured from Dow University of Health Sciences, OJHA campus, Karachi, Pakistan. Animals were kept individually with free access to standard rodent diet and tap water under 12:12h light/dark cycle (lights on at 7:00 am) at controlled room temperature (24±2°C). All experiments were carried out in a balanced design to avoid influence of order and time. The experimental procedures were approved by the institutional Advanced Studies and Research Board (ASRB/03009/Sc) and performed in strict accordance with Guide for the Care and Use of Laboratory Animals published by the National Institutes of Health (NIH Publication no. 85-23, revised 2011).

Experimental protocol

Experiments for almond and walnut were performed on two separate set of rats. For each set of experiment, 24 rats were taken and divided into four groups. For first experimental groups were named as control, cadmium, almond and cadmium +almond, while second experimental rats were divided into control, cadmium, walnut and cadmium +walnut. Rats were intoxicated with cadmium by administering $CdCl_2$ orally at the dose of 50mg/kg/week (Kaoud *et al*., 2010; Batool *et al*., 2019). Shelled almonds and walnuts were purchased from local super market which were then peeled and finely crushed into fine powder. Each nut suspension was freshly prepared daily and administered at the dose of 400mg/kg/day (Batool *et al*., 2019). The whole treatment was continued for 4 weeks followed by behavioral assessment to determine the memory retention using Morris water maze (MWM) and elevated plus maze (EPM) tests. After behavioral analysis, rats were decapitated to collect the brain samples which were stored at -20^{o}C until biochemical analyses.

Behavioral test

EPM and MWM paradigm were used to assess memory function at the end of experiment. The apparatus and experimental procedures were same as described previously (Itoh *et al*., 1990; Batool *et al*., 2019).

Brain biochemical analyses

The whole brains were removed, rinsed in isotonic saline, and weighed. A 10% (w/v) tissue homogenate was prepared with 0.1 M phosphate buffer (pH 7.4) and centrifuged at 10,000 × g for 10 min at 4^{o}C. The supernatant was used for the estimation of lipid peroxidation (Chow and Tappel 1971), superoxide dismutase (SOD) (Chidambara *et al*. 2002), catalase (CAT) (Sinha 1972) and glutathione peroxidase (GPx) (Flohe and Gunzler 1984) activity.

STATISTICAL ANALYSIS

Data from both set of experiments were analyzed by two-way ANOVA with Tukey's post-hoc test using SPSS version 20. Values are presented as mean±SD (n=6) and p values less than 0.05 were considered as significant.

RESULTS

Memory retention

Memory retention was determined to find out the degree of deleterious effects of cadmium intoxication on brain function. EPM and MWM activity were monitored during training and testing sessions. Data analysis for EPM memory retention showed significant effects of almond ($F_{1,20}$ =86.27, p<0.01), cadmium ($F_{1,20}$ =13.02, p<0.01) and almond × cadmium interaction ($F_{1,20}$ =19.09, p<0.01) (fig. 1a). Almond supplementation significantly improved memory function of rats as evident by increased %memory retention in almond group as compared to control rats (p<0.01). Cadmium administration caused significant impairment of memory in cadmium group as

compared to controls (p<0.01). On the other hand almond supplementation in combination with cadmium significantly improved memory retention as compared to that of control (p<0.01) and cadmium (p<0.01) groups. Similar results were observed in MWM paradigm (fig. 2a). There were significant effects of almond ($F_{1,20}$ = 55.46, p<0.01), cadmium ($F_{1,20}$ =13.67, p<0.01) and almond × cadmium interaction ($F_{1,20}$ =10.08, p<0.01) on %memory retention. Tukeys's test showed significantly improved memory performance in rats supplemented with almond as compared to controls (p<0.05). The rats treated with cadmium showed markedly impaired memory retention as compared to control animals (p<0.01). However, almond supplementation significantly attenuated cadmium-induced memory impairment as shown by increased %memory retention in almond and cadmium co-administered group as compared to that of cadmium (p<0.01) group.

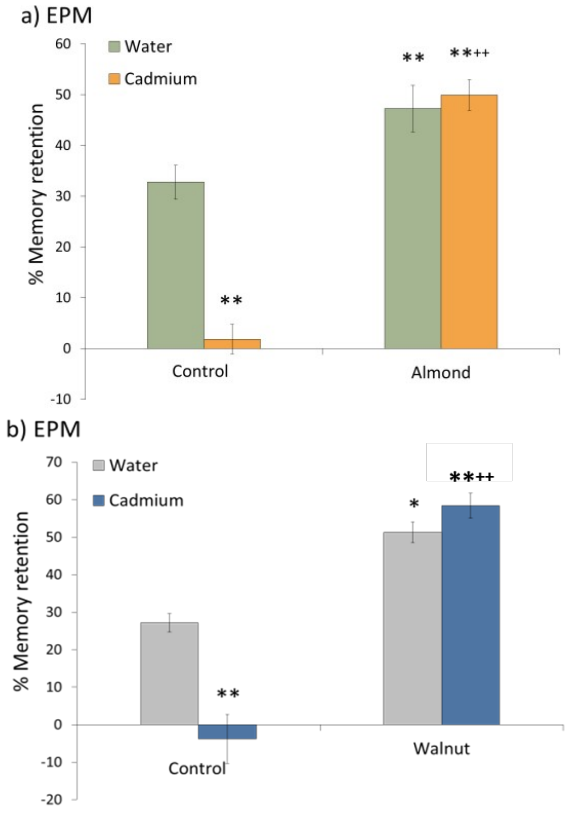

Fig. 1: Effects of a) almond and b) walnut supplementation on memory retention assessed by EPM in cadmium intoxicated rats. Values are mean ± SD (n=6). Significant differences were obtained by Tukey's test. *p<0.05, **p<0.01 versus water treated controls; ++p<0.01 versus cadmium treated rats.

The beneficial effects of nuts supplementation were also emphasized from experimental results of walnut and cadmium protocol. The EPM data analyzed by two-way

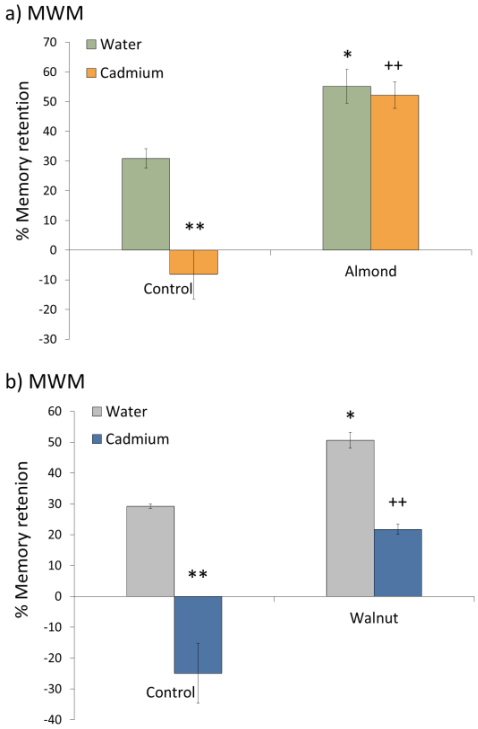

Fig. 2: Effects of a) almond and b) walnut supplementation on memory retention assessed by MWM in cadmium intoxicated rats. Values are mean ± SD (n=6). Significant differences were obtained by Tukey's test. *p<0.05, **p<0.01 versus water treated controls; ++p<0.01 versus cadmium treated rats.

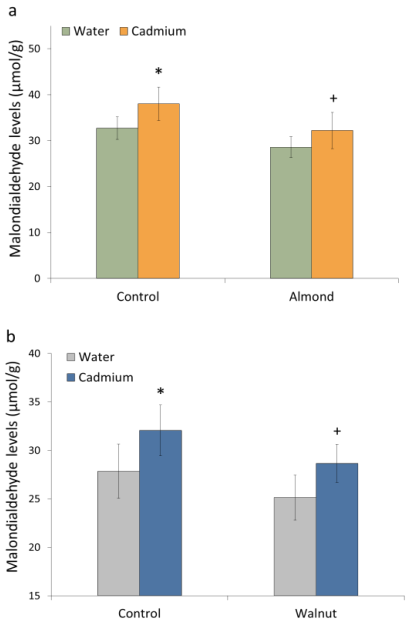

Fig. 3: Effects of a) almond and b) walnut supplementation on brain MDA levels in cadmium intoxicated rats. Values are mean ± SD (n=6). Significant differences were obtained by Tukey's test. *p<0.05, versus water treated controls; +p<0.05 versus cadmium treated rats.

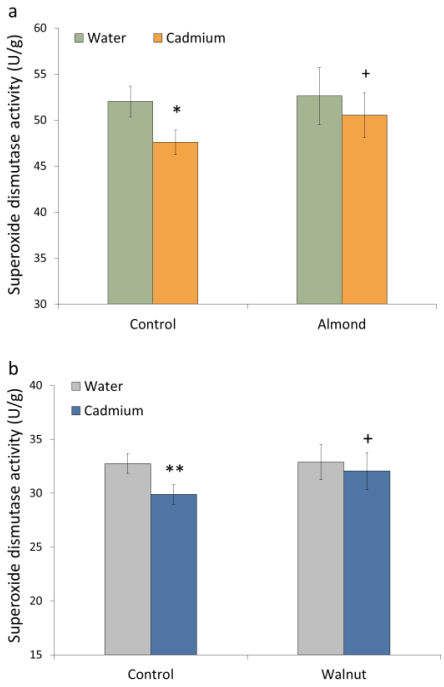

Fig. 4: Effects of a) almond and b) walnut supplementation on SOD activity in cadmium intoxicated rats. Values are mean ± SD (n=6). Significant differences were obtained by Tukey's test. *p<0.05, **p<0.01 versus water treated controls; +p<0.05 versus cadmium treated rats.

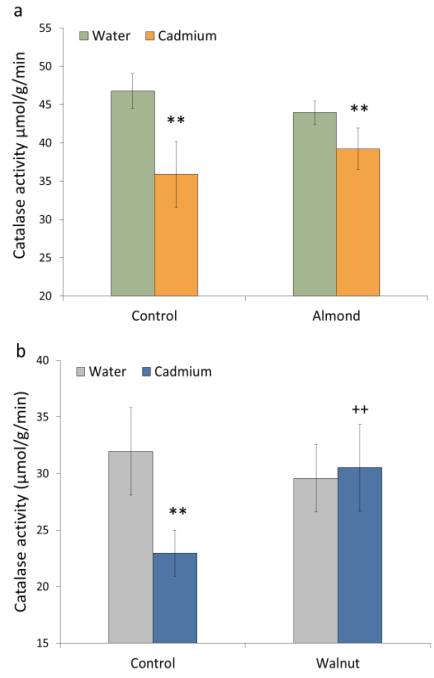

Fig. 5: Effects of a) almond and b) walnut supplementation on CAT activity in cadmium intoxicated rats. Values are mean ± SD (n=6). Significant differences were obtained by Tukey's test. **p<0.01 versus water treated controls; ++p<0.01 versus cadmium treated rats.

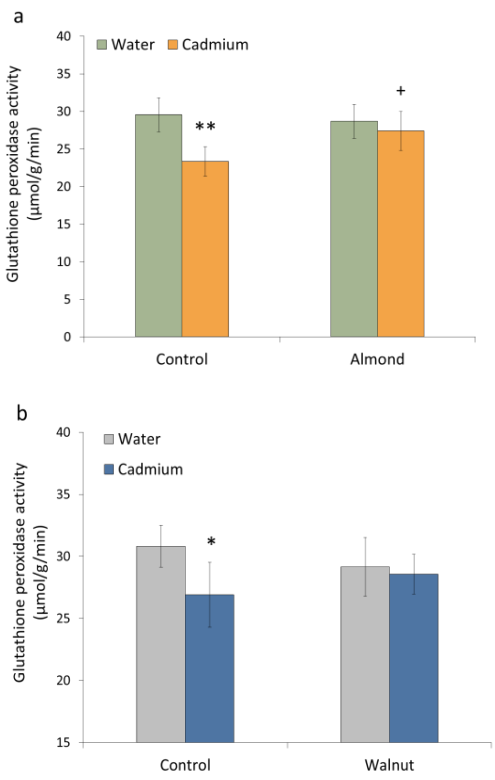

Fig. 6: Effects of a) almond and b) walnut supplementation on GPx activity in cadmium intoxicated rats. Values are mean ± SD (n=6). Significant differences were obtained by Tukey's test. *p<0.05, **p<0.01 versus water treated controls; +p<0.05 versus cadmium treated rats.

ANOVA showed significant effects of walnut ($F_{1,20}$ = 96.9, p<0.01), cadmium ($F_{1,20}$ =12.7, p<0.01) and walnut × cadmium interaction ($F_{1,20}$ =28.05, p<0.01) on %memory retention (fig. 1b). Supplementation of walnut showed significantly increased memory function in walnut group as compared to control rats (p<0.05). Cadmium treated rats were unable to find out the closed arm during test session on EPM paradigm resulting in significantly impaired memory retention as compared to controls (p<0.01). However, walnut and cadmium co-administered rats located the closed arm in given specific time and they showed improved memory function as compared to control and cadmium groups (p<0.01). These results were also validated from the data of MWM protocol. %Memory retention was significantly affected by walnut ($F_{1,20}$ = 49.09, p<0.01), cadmium ($F_{1,20}$ =63.89, p<0.01) and walnut × cadmium interaction ($F_{1,20}$ =4.39, p<0.05) (fig. 2b). Rats treated with walnut suspension effectively located the hidden platform in MWM in short duration of time as compared to control animals (p<0.05). Cadmium intoxicated rats consistently showed impaired ability to retain the learnt task in MWM as compared to controls (p<0.01). Likewise, walnut supplementation co-administered with cadmium attenuated the cadmium-

induced impairment in memory retention as compared to cadmium group (p<0.01).

Lipid peroxidation

Two-way ANOVA for the effects of almond supplementation on lipid peroxidation in cadmium intoxicated rats showed significant effects of almond ($F_{1,20}$ =14.84, p<0.01) and cadmium ($F_{1,20}$=11.98, p<0.01). Tukey's post-hoc test revealed that cadmium intoxication caused increase in lipid peroxidation as evident by increased MDA levels in cadmium group (p<0.05) as compared to control animals. Co-administration of almond, however, significantly reduced lipid peroxidation in cadmium intoxicated rats (p<0.05) as compared to cadmium group (fig. 3a).

Walnut supplementation also altered the levels of lipid peroxidation in cadmium intoxicated rats (fig. 3b). There was significant effect of walnut ($F_{1,20}$ =10.96, p<0.01) and cadmium ($F_{1,20}$ =13.79, p<0.01) administration on MDA levels. Cadmium rats showed significantly increased MDA levels (p<0.05) as compared to control rats which was normalized by walnut supplementation in walnut and cadmium co-administered group (p<0.05).

Superoxide dismutase activity

Antioxidant enzymes activity was also determined to get insight of the antioxidant effects of nuts supplementation in cadmium intoxicated rats. Almond ($F_{1,20}$ =5.92, p<0.05) and cadmium ($F_{1,20}$ =9.54, p<0.01) administration significantly affected the activity of SOD. Cadmium group exhibited reduced activity of SOD as compared to controls (p<0.05) which was significantly attenuated by almond supplementation in almond and cadmium co-administered group (p<0.05) (fig. 4a).

There were significant effects of walnut ($F_{1,20}$ =4.401, p<0.05) and cadmium ($F_{1,20}$ =11.37, p<0.01) administration on SOD activity (fig. 4b). In this set of experiment, cadmium intoxication also significantly reduced SOD activity as compared to control animals (p<0.01) and walnut supplementation co-administered with cadmium normalized SOD activity when compared with that of cadmium group (p<0.05).

Catalase activity

There were significant effects of cadmium administration ($F_{1,20}$ =44.25, p<0.01) and almond × cadmium interaction ($F_{1,20}$ =6.84, p<0.05) on catalase activity (fig. 5a). Cadmium intoxication significantly reduced CAT activity in rat brain as compared to control animals (p<0.01). The reduced CAT activity was not significantly attenuated by almond supplementation in almond and cadmium co-administered group (p<0.01) as compared to controls.

Catalase activity was also affected in walnut and cadmium phase of experiment (fig. 5b). There were significant effects of cadmium administration ($F_{1,20}$ =8.76, p<0.01) and walnut × cadmium interaction ($F_{1,20}$ =14.47, p<0.01) on catalase activity. Post-hoc analysis showed significant reduction of CAT activity in cadmium group as compared to controls (p<0.01) which was significantly attenuated by walnut co-administered with cadmium as compared to cadmium intoxicated rats (p<0.01).

Glutathione peroxidase activity

Data analysis of GPx activity revealed significant effects of cadmium ($F_{1,20}$ =16.13, p<0.01) and almond ×cadmium interaction ($F_{1,20}$ = 6.93, p<0.05) (fig. 6a). GPx activity was significantly reduced by cadmium intoxicated rats as compared to control rats (p<0.01) whereas, almond supplementation increased the GPx activity in almond and cadmium co-administered group as compared to that of cadmium group (p<0.05).

In walnut and cadmium phase of experiment, GPx activity was also significantly altered by cadmium administration ($F_{1,20}$ = 6.72, p<0.05) (fig. 6b). Post-hoc analysis showed significantly reduced GPx activity in cadmium group as compared to control animals (p<0.05). While in walnut and cadmium co-administered group the GPx activity became comparable to controls due to walnut supplementation.

DISCUSSION

Since cadmium intoxication results neurobehavioral deficits due to increased oxidative burden. Thus, the present investigation on the administration of cadmium in rats and assessment of brain function in terms of memory retention and oxidative stress represents a significant contribution to understand the cadmium toxicology. We found that exposure to cadmium toxication once in a week significantly induced lipid peroxidation as evident by increased malondialdehyde levels in brain samples. The activity of antioxidant enzymes SOD, CAT and GPx were also significantly reduced in rat brain exposed to cadmium which would have exacerbated the condition of oxidative stress. The consequence of cadmium-induced oxidative stress was observed by decreased %memory retention in cadmium intoxicated rats. The nuts supplementation, however, helped in the attenuation of cadmium-induced memory impairment as the rats which were treated with nuts along with cadmium showed improved %memory retention. These results are concomitant with reduced lipid peroxidation and restoration of activity of antioxidant enzymes, representing antioxidant effects of almond and walnut supplementation.

Exposure to heavy metal has shown to induced mitochondrial damage and generates reactive species. These radicals are involved in the auto-oxidation of lipid bilayer and other cellular vital components (Ercal *et al*., 2001). The hallmark of oxidative stress is lipid

peroxidation. It results from the reaction of free radicals with lipid membrane to produce radical lipid. The radical lipid is strong enough to start the chain reaction resulting in destruction of lipid molecule. Cadmium exposure has shown to induce increased lipid peroxidation (Renugadevi and Prabu, 2010). Moreover, cadmium has inhibitory effects on selenium- and zinc-dependent enzymes including SOD. These enzymes are involved in removal of reactive radicals and resulted in the reduction of oxidative stress (Branca *et al*., 2018a). The increased production of reactive species and reduced activity of antioxidant enzymes can additionally weaken the antioxidant mechanism leading to impaired neuronal activity, apoptosis and ultimately memory dysfunction (Lobo *et al*., 2010; Halliwell, 2001). Oxidative stress has been strongly implicated in neurological diseases such as Parkinson's disease, Alzheimer's disease, depression, and anxiety (Halliwell, 2001). In present study, therefore, the compromised memory function in cadmium intoxicated rats may be in part be due to the inhibition of antioxidant enzymes and resulting oxidative stress in brain.

Antioxidant defense system may provide possible mechanism involved in the attenuation of cadmium-induced neurotoxicity by nuts. Supplementation of exogenous antioxidants is suggested to minimize metal-induced oxidative stress (Gupta *et al*., 2015). Plants-derived flavonoids and antioxidants are reported to reduce cadmium toxicity by scavenging free radicals and/or enhancing antioxidant enzymes activity (Renugadevi and Prabu, 2010). Almonds and walnuts contain considerable amount of flavonoids and antioxidant capacity. Almonds contain potential antioxidant polyphenolic compounds such as quercetin, kaempferol 3-O-rutinoside, quercitrin, morin, isorhamnetin and isorhamnetin-3-O-glucoside which are suggested to have neuroprotective effects (Wijeratne *et al*., 2006). Similarly, walnuts are also rich in tannins and antioxidant phenolic compounds (Fukuda *et al*., 2003). The polyphenolic compounds also act as metal chelators and enhance the removal of heavy metal ions (Scalbert *et al*., 1999). Moreover, it has been shown that natural antioxidants reduce DNA damage, apoptosis and improve cell survival (Heo and Lee, 2005; Tang *et al*., 2019). It has also been reported that reduced dopaminergic and serotonergic turnover following nuts administration may also be responsible to reduce cadmium neurotoxicity (Batool *et al*., 2019). This restoration of biogenic amines may be attributed to the reduced oxidative stress as found in the current study. Thus, in the present study amelioration of cadmium-induced neurotoxicity may result from the antioxidant potential of almonds and walnuts and thus producing memory enhancing effects in cadmium-intoxicated rats.

CONCLUSION

In summary, our study found exposure to cadmium once in a week is sufficient to induce neurotoxicity by inducing oxidative stress and may result in memory dysfunction. However, almond and walnut, being the source of antioxidant nutrients, can provide protection against cadmium-induced oxidative stress. Therefore, these nuts are crucial for maintaining the activities of a healthy brain especially in the individuals exposed to cadmium unavoidably.

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