Food and Chemical Toxicology 133 (2019) 110755

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

Aqueous *Coriandrum sativum* L. extract promotes neuroprotection against motor changes and oxidative damage in rat progeny after maternal exposure to methylmercury

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ARTICLE INFO

Keywords:
Coriandrum sativum
Methylmercury
Rat offspring
Behavioral parameters
Oxidative stress

ABSTRACT

This study aimed to investigate the effects of *Coriandrum* sativum aqueous extract (CSAE) on the rat progeny of mothers exposed to methylmercury (MeHg). The presence of bioactive compounds and CSAE's antioxidant capacity been evaluated, and the offspring were assessed for their total mercury levels, motor behavioral parameters and oxidative stress in the cerebellum. The analysis of the bioactive compounds revealed significant amounts of polyphenols, flavonoids, and anthocyanins, as well as a variety of minerals. A DPPH test showed the CSAE had important antioxidant activity. The MeHg + CSAE group performed significantly better spontaneous locomotor activity, palmar grip strength, balance, and motor coordination in behavioral tests compared the MeHg group, as well as in the parameters of oxidative stress, with similar results to those of the control group. The MeHg + CSAE group also had significantly reduced mercury levels in comparison to the MeHg group. Based on the behavioral tests, which detected large locomotor, balance, and coordination improvements, as well as a reduction in oxidative stress, we conclude that CSAE had positive functional results in the offspring of rats exposed to MeHg.

1. Introduction

Mercury is an extremely toxic heavy metal widely distributed in the environment, and in its organic form of methylmercury (MeHg), capable of biomagnification (Bisi et al., 2012; Boudou and Ribeyre, 1997; Coelho et al., 2013). It is important to note that 80%–90% of human

Abbreviations: ATP, Adenosine triphosphate; BDNF, derived neurotrophic factor; Ca, Calcium; CAT, Catalase; CNS, Central Nervous System; CSAE, *Coriandrum sativum* aqueous extract; Cu, Copper; DNA, deoxyribonucleic acid; DPPH, 2,2 diphenyl-1-picrylhydrazyl; DTNB, 5,5′-dithiobis-2-nitrobenzoic acid; Fe, Iron; H_2O_2, hydrogen peroxide; H_2SO_4, Sulfuric acid; $HClO_4$, Perchloric Acid; HNO_3, Nitric acid; $KMnO_4$, Potassium permanganate; MeHg, methylmercury; Mg, Magnesium; Mn, Manganese; NBT, Nitroblue Tetrazolium; NO, Nitric oxide; $O2^{\cdot}$, Reactive oxygen; PBS, Phosphate buffered saline; ROS, Reactive oxygen species; $SnCl_2$, Tin chloride; SOD, Superoxide dismutase; TBARS, Thiobarbituric acid reactive substances; TNB, 5-thio-2-nitrobenzoic acid; Zn, Zinc

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https://doi.org/10.1016/j.fct.2019.110755
Received 3 May 2019; Received in revised form 3 August 2019; Accepted 8 August 2019
Available online 10 August 2019

exposure occurs through the ingestion of contaminated fish or water, which, due to the bioaccumulation phenomenon, can result in high organic mercury levels in human populations (Buchanan et al., 2015; Liu et al., 2018; McDowell et al., 2004; Pinheiro et al., 2000; Vieira et al., 2015). Most (95%) ingested MeHg is readily absorbed in the gastrointestinal tract and assimilated, leading to protein complexes containing thiol groups with high mobility through bodily tissues and barriers such as the placental and blood-brain barriers (Amonpatumrat et al., 2008; Aschner and Clarkson, 1989; Balthasar et al., 2017; Roos et al., 2010). Methylmercury accumulates mostly in the central nervous system (CNS), with the cerebellum being one of the most affected areas (Cheng et al., 2015; Heimfarth et al., 2018; Mancini et al., 2009; Ruszkiewicz et al., 2016). This leads to neurotoxicity, especially after fetal and neonatal exposure during the early stages of neural development, which are characterized by an immature blood-brain barrier and the rapid growth, proliferation, and differentiation of brain tissue (Ballester et al., 2018; Murcia et al., 2016; Sakamoto et al., 2017).

Methylmercury-induced toxicity contributes to epigenetic alterations that change the expression of important enzymes such as glutathione peroxidase and tyrosine hydroxylase and growth factors such as brain-derived neurotrophic factor (Go et al., 2018; Onishchenko et al., 2008; Usuki et al., 2011). In addition, MeHg leads to alterations in glutamatergic transmission (Deng et al., 2014; Feng et al., 2014; Gutierrez et al., 2018; Liu et al., 2016; Xu et al., 2012), calcium homeostasis (Shao et al., 2015; Shen et al., 2016), and oxidative stress (Al-Osaimi et al., 2018; Dos Santos et al., 2018; Fujimura and Usuki, 2018). All these effects can lead to neurological dysfunction and severe motor disorders (Fujimura et al., 2012; Tavares et al., 2005; Yamamoto et al., 2019; Zimmermann et al., 2014).

Research on various florae to prevent the negative effects of xenobiotic poisoning has significantly increased in the last decade (Fujimura et al., 2012; Kopec et al., 2016; Mzid et al., 2017; Ola-Mudathir and Suru, 2015; Tavares et al., 2005; Yamamoto et al., 2019; Zimmermann et al., 2014). Plant extracts have been extensively investigated in both *in vivo* and *in vitro* models, yielding several interesting positive results (Akhter et al., 2013; Dewanjee et al., 2017; Kujawska et al., 2016; Nazima et al., 2016; Olaleye et al., 2010).

Coriandrum sativum L. (Umbelliferae), a species native to Europe and Asia and known popularly as coriander, is commonly used as a condiment in the northern and northeastern regions of Brazil (Al-Mofleh et al., 2006; Bhuiyan et al., 2009; Cavalcante et al., 2016; Melo et al., 2003; Msaada et al., 2014). The species has numerous reported biological activities (Aissaoui et al., 2008, 2011; Bogavac et al., 2015; Hosseinzadeh et al., 2016; Jabeen et al., 2009; Kazempor et al., 2015; Paarakh et al., 2016), including effects on the CNS such as anxiolytic activity (Emamghoreishi and Heidari-Hamedani, 2006; Emamghoreishi et al., 2005; Mahendra and Bisht, 2011; Pathan et al., 2011) and both *in vitro* and *in vivo* antioxidant activity (Anaeigoudari et al., 2016; Chithra and Leelamma, 1999; Harsha and Anilakumar, 2014; Hwang et al., 2014; Kozlowska et al., 2016; Pellegrini et al., 2018; Sreelatha and Inbavalli, 2012; Wangensteen et al., 2004). These activities may be related to coriander's reported chemical composition, which has shown high levels of total phenolic compounds and flavonoids that can attenuate oxidative damage (Justesen and Knuthsen, 2001; Melo et al., 2003. 2005; Pereira and Tavano, 2014).

Previous reports have shown the capacity of aqueous *C. sativum* extracts to remove inorganic mercury and MeHg from plants (Karunasagar et al., 2005). Considering this species can decrease mercury levels, and that high systemic levels of this metal can cause oxidative damage and induce motor dysfunction, we hypothesized that a *C. sativum* aqueous extract (CSAE) would reduce MeHg levels, and consequently, reduce lipid peroxidation and improve motor function. Therefore, this study aimed to evaluate the effects of CSAE on the oxidative damage and behavioral and motor parameters in progeny rats after maternal exposure to MeHg.

2. Materials and methods

2.1. Preparation of the Coriandrum sativum aqueous extract

Coriandrum sativum leaves and stalks were obtained in São Francisco do Pará-Pa (01°10′03″ S, 47°47′45″ W). The specimen was identified by Dr. Antônio Elielson Rocha, and a voucher specimen was deposited in the Museum Paraense Emílio Goeldi herbarium (MG: 228890). After collection, the fresh material was washed under running water, rinsed in distilled water, then frozen for later lyophilization in a vacuum chamber at −20 °C for 24 h. After lyophilization, the material was pulverized in a Willye-type mill (Star FT 50/1; 620 rpm) coupled to 60-mesh sieves, weighed, vacuum packed in polyethylene bags, and stored at −20 °C until use. The extract was prepared by adding 13.5 g of ground material to 300 mL deionized water and homogenizing at room temperature for 1 h for a final concentration of 45 mg/mL (Kansal et al., 2011).

2.2. Mineral and phytochemical content of the Coriandrum sativum extract

2.2.1. Mineral content determination

The mineral content was determined as described by Amarante et al. (2010). After transferring 500 mg of coriander dry mass to a digester tube, a HNO_3:$HClO_4$ solution (3:1) was added for cold and hot digestions performed in triplicate. The digests were then quantitated in an atomic absorption spectrophotometer (Thermo, ICE3000). The calcium (Ca), magnesium (Mg), copper (Cu), iron (Fe), zinc (Zn), and manganese (Mn) results were compared to their respective standard curves to determine their concentrations, which are expressed in mg/L.

2.2.2. Phytochemical composition of the Coriandrum sativum extract

To identify any secondary metabolites with antioxidant activity in the CSAE, the total phenolic (Singleton and Rossi JR, 1965), flavonoid (Quettier-Deleu et al., 2000), and anthocyanin (Askar and Treptow, 1993) contents were determined. The tests were performed in triplicate, and the results are expressed as mg·100 g^{-1} dry matter.

2.3. Antioxidant capacity of the Coriandrum sativum extract

The antioxidant capacity of the CSAE was assessed using the DPPH (2,2-diphenyl-1-picryl-hydrazyl) method (Frankel and Meyer, 2000; Vicentino and Menezes, 2007). Standard solutions were prepared with the extract and ascorbic acid at concentrations of 0.176–21 μg/mL, which were then incubated with a 21 μg/mL solution of DPPH at room temperature in the dark for 30 min. The reaction product was measured in a spectrophotometer at a wavelength of 515 nm (BIO-RAD Model 450 Microplate Reader). The EC50 calculation is the concentration of extract that provides a 50% response (Sridhar and Charles, 2019). This experiment was performed in triplicate.

2.4. Animals

Fifty six primiparous female rats (*Rattus norvegicus*, Wistar strain) weighing ≅ 250 g and in the first trimester of gestation were obtained from the Federal University of Pará breeding facilities and kept in individuals cages. The environment had a controlled room temperature (22 ± 2 °C) and a light-dark cycle of 12 h. Water and food were provided *ad libitum* (periodically measured for assessment). The study followed the *NIH Guide for the Care and Use of Laboratory Animals*, and the Ethics Committee on Animal Use in Research at the Federal University of Pará, Brazil (CEPAE-UFPA 243–14) approved the experimental protocols.

2.5. Experimental design

After 7 days of acclimatization, pregnant rats were divided into 4

groups composed of 14 animals each (n = 14): Control; CSAE; MeHg; and MeHg + CSAE.

The control and CSAE groups received filtered water, while the MeHg and MeHg + CSAE groups received mercury at a concentration of 40 μg/mL diluted in drinking water (Andersen and Andersen, 1993; Farina et al., 2005). The CSAE and MeHg + CSAE groups received the CSAE treatments by gavage with CSAE extract (360 mg/kg day), from 14th of pregnancy to 14th day of lactation (corresponding 21 days of treatment) (Gandhi et al., 2014). The control and MeHg groups were treated by gavage with filtered water over the same test period. After birth, 8 animals per mother were retained to normalize the number of animals per group. For the behavioral assays in pups at 30 days postnatal, a single male was randomly selected from each litter for a total of 14 animals per group. This was done to reduce gender-related assay distortions. For the biochemical assessments, a pool from each mother's litter was used, making a total of 14 pools per group (EPA, 1998).

2.6. Behavioral assays

When the progeny were 30-days old, they were subjected to behavioral tests after acclimatizing in a test room with attenuated light and sound for 1 h. All behavioral tests (open-field, grip, beam-walking, and rotarod) were performed between 10:00 a.m. and 6:00 p.m.

2.6.1. Open-field test

Open-field tests were performed to evaluate spontaneous locomotor activity (von Horsten et al., 1998). The apparatus consisted of an acrylic arena (100 × 100 × 40 cm) divided into 25 quadrants (20 × 20 cm each), 9 central and 16 peripheral. Each animal was placed at the center of the apparatus and assessed for their exploratory behavior for 5 min. The number of crossings between quadrants, the total number of quadrants, and the distance crossed (measured in meters) were determined for each animal (Fernandes et al., 2018a, 2018b). The tests were recorded via a camera coupled to a computer, and the images were analyzed with Any-Maze® software (Stoelinf Co., Wood Dale, IL, USA).

2.6.2. Grip-strength test

This method assesses muscular strength and takes advantage of the natural behavior of rats to cling to horizontal surfaces when supported by the tail. For the test, the animals were allowed to grasp a mounted dynamometer bar while being firmly held by the tail and slowly pulled back by an inspector. The peak pull force was recorded and expressed in grams (g). The tests were performed in triplicate, and the results represent the mean of the 3 values (Takeshita et al., 2017).

2.6.3. Rotarod test

A motor coordination assay was performed with a rotating cylinder test on an apparatus consisting of a 20 cm high, 8 cm diameter transversal rod that rotated at variable speeds. The animals were tested on the rotating bar at speeds of 16, 20, 25, 28, and 37 rpm. The latency time until a fall occurred (recorded for a maximum 120 s) and the number of falls were recorded for each animal (da Silva et al., 2018; Slamberova et al., 2006).

2.6.4. Beam-walking test

Motor coordination and balance were also assessed by a beam-walking test (Stanley et al., 2005). The apparatus consisted of two supports holding a 1 m wooden beam suspended 50 cm off the floor. The serial beams had 2 types of cross sections: square (12 and 5 mm) and circular (17 and 11 mm). Each apparatus had a platform with a safe box (20 cm^2) at one end. The animals were placed at the starting point and had 60 s to cross the beam to reach the safe box, with 2 attempts per beam. We counted the number of times that at least one of the hind legs slipped. If two legs slipped at the same time, it was counted as two slips (Carter et al., 2001).

2.7. Tissue samples

When they were 30-days old, the progeny rats were anesthetized with ketamine hydrochloride (50 mg/kg) and xylazine hydrochloride (5 mg/kg) before perfusing with cold phosphate buffered saline (PBS; pH 7.4). Approximately 1 g of hair was collected and stored in a polypropylene bag until the mercury testing. The cerebellum was dissected and homogenized in PBS (1:1 w/v) with an Ultra-Turrax homogenizer (IKA-Werke GmbH & Co.). The samples were centrifuged for 10 min at 5000 rpm at 4 °C, and the supernatant was collected and frozen at −80 °C until the biochemical analysis.

2.8. Biochemical analysis

2.8.1. Oxidative damage assessment

The thiobarbituric acid-reactive substances (TBARS) were determined as described by Ohkawa et al. (1978). This test indicates the presence of products derived from lipid peroxidation, mainly malonaldehyde. Proteins were recovered with 15% trichloroacetic acid, and the supernatant was incubated with 10 mM thiobarbituric acid and heated at 80 °C for 45 min. The resulting lightly pink-colored product was placed in a 96-well microplate for spectrophotometer quantification at 535 nm (BIO-RAD Model 450 Microplate Reader). The results are expressed in nmol TBARS/mg protein.

In high amounts, nitric oxide (NO) can lead to oxidative stress. Therefore, the samples were incubated with Griess reagent (Moncada, 1992; Nims et al., 1995), placed in a 96-well microplate, and measured in a spectrophotometer at 550 nm (BIO-RAD Model 450 Microplate Reader). The amount of NO is expressed as μmol/mg protein based on a standard curve for sodium nitrite.

The superoxide anion was quantified with a nitroblue tetrazolium (NBT) assay. This test detects NBT oxidation by intracellular reactive oxygen (O_2^-), which generates formazan crystals that can be quantified by spectrophotometry using a 620 nm filter (BIO-RAD Model 450 Microplate Reader). The results are expressed as absorbance intensity/mg protein (Baehner et al., 1976; Meerovich et al., 2014).

2.8.2. Evaluating total glutathione

Total glutathione levels (Foyer and Shigeoka, 2011; Tietze, 1969) were determined by the detection of recycled enzyme after a glutathione reductase treatment in which glutathione's sulfhydryl group reacts with 1 mM 5,5′-dithiobis-(2-nitrobenzoic acid) to form 5-thio-2-nitrobenzoic acid, which has a yellow color. The absorbance was immediately measured by spectrophotometry, once per minute for 5 min, at the 412 nm wavelength (BIO-RAD Model 450 Microplate Reader). Results are expressed in pmol/μg protein.

2.8.3. Enzymatic antioxidant activities

Superoxide dismutase (SOD) was estimated through a reaction of the samples with hypoxanthine and NBT (Maier and Chan, 2002). The absorbance was measured at the 470 nm wavelength (BIO-RAD Model 450 Microplate Reader), and the results are expressed as units of SOD activity per milligram protein.

Catalase enzyme activity was measured after reacting a sample with hydrogen peroxide (H_2O_2) to form formaldehyde, which is revealed by treating with 34.2 mM Purpald® reagent (4-amino-3-hydrazino-5-mercapto-l, 2, 4-triazole). The results are expressed as μM formaldehyde/min/mg protein, determined by comparing the absorbance at 540 nm (BIO-RAD Model 450 Microplate Reader) with a standard curve for 4.25 μM formaldehyde (Johansson and Borg, 1988; Wheeler et al., 1990).

2.9. Protein quantification

The Bradford (1976) method was utilized to quantify the protein level. A standard curve was generated with solutions containing known

concentrations of bovine serum albumin, and the results are expressed in mg/mL.

2.10. Total mercury dosage (total Hg)

The procedure to extract total mercury was based on a modified method by Costa et al. (2017). Atomic fluorescence spectrometry was used to detect the amount of Hg in 100 mg of animal hair digested in HNO_3/H_2SO_4 (1:1) and fixed in 5% (m/v) potassium permanganate ($KMnO_4$). The mercury sample was reduced with 20% (m/v) tin chloride ($SnCl_2$) and quantified with a Quick Trace M-7500 Mercury Analyzer (Teledyne CETAC Technologies), which has a detection limit of 1 ng g^{-1} (Costa et al., 2017).

2.11. Statistical analyses

The statistical analyses were performed with GraphPad Prism ® 6.0. software (GraphPad Software, San Diego, CA, EUA). All results are expressed as the mean ± standard deviation (SD). Data normality was assessed with the Shapiro-Wilk test, after which, a two-way ANOVA followed by a Tukey post-test was applied. Each experimental group comprised a total of 14 animals, and p values < 0.05 were considered statistically significant.

3. Results

3.1. Minerals and phytochemicals in the Coriandrum sativum extract

A wide array of minerals was present in the CSAE (Table 1), with Ca (11,024.5 ± 944 mg/L) and Mg (3041 ± 121 mg/L) being the most abundant, followed by Fe (110.7 ± 9.18 mg/L), Zn (72.4 ± 1.21 mg/L), Mn (34.5 ± 0.174 mg/L), and Cu (13.6 ± 0.173 mg/L). The phytochemical analysis revealed that polyphenols (14 ± 2.42 mg/g) were the most abundant secondary metabolites in the CSAE, followed by anthocyanins (9.8 ± 0.174 mg/g) and flavonoids (5.1 ± 0.174 mg/g).

3.2. Antioxidant and free radical scavenging activities of the Coriandrum sativum extract

The CSAE inhibited the DPPH radical in a concentration-dependent manner. The EC50 was 13.4 ± 2.3 µg/mL, a capacity to donate hydrogen similar to that of ascorbic acid (EC50 14.6 ± 3.8 µg/mL; Fig. 1).

3.3. Total mercury in the progeny's hair

The total mercury in the progeny's hair was assessed after 21 days of treating the progenitor with MeHg (MeHg and MeHg + CSAE groups; Fig. 2). Compared to the control group (0.019 ± 0.004 µg/g), the MeHg group had significantly higher mercury levels (0,693 ± 0.148 µg/g; p < 0.05), while the CSAE group (0.020 ± 0.010 µg/g) had levels similar to those of the control group. The MeHg + CSAE group (0.068 ± 0.032 µg/g) had higher mercury levels than the control group, but compared to the MeHg group, they had significantly less total mercury in their hair.

Table 1
Minerals (mg/mL) and phytochemical constituents (mg/g) of the *Coriandrum sativum* aqueous extract. Data are shown as the mean ± SD of 3 independent experiments.

Components	Values
Minerals	
Calcium (Ca)	11,024.5 ± 944
Magnesium (Mg)	3041.2 ± 121
Copper (Cu)	13.6 ± 0.173
Iron (Fe)	110.7 ± 9.18
Zinc (Zn)	72.48 ± 1.21
Manganese (Mn)	34.6 ± 0.174
Secondary metabolites	
Total polyphenols	14.01 ± 2.42
Total flavonoids	5.1 ± 0.174
Anthocyanins	9.8 ± 0.174

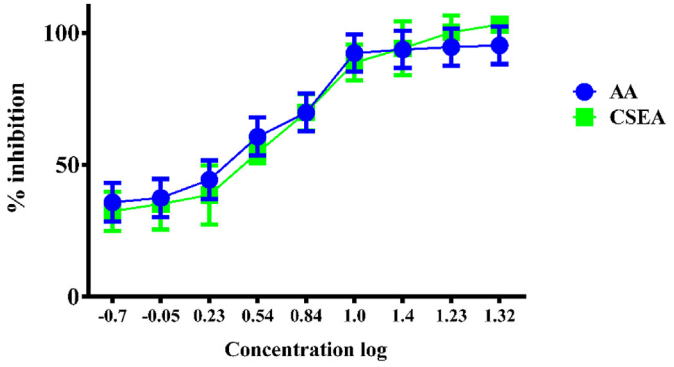

Fig. 1. Logarithmic curve of the effect of concentration on the DPPH inhibition capacity of the *Coriandrum sativum* aqueous extract (CSAE) compared to that of ascorbic acid in µg/mL. Data are shown as the mean ± SD of 3 independent experiments; p values < 0.05 were considered statistically significant. Abbreviation: DPPH, 2,2-diphenil-1-picrilhidrazil; AA, ascorbic acid.

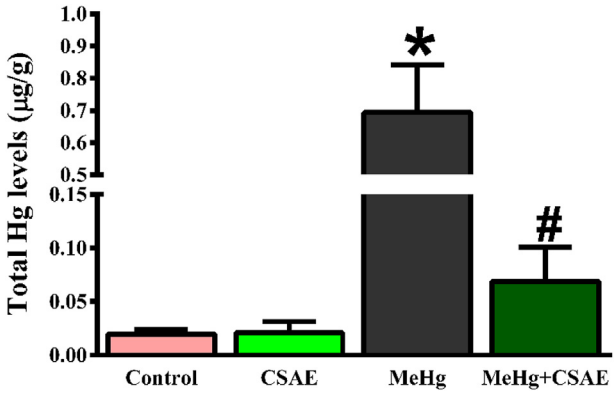

Fig. 2. Mercury levels (µg/L) in the progeny's hair after intoxicated the progenitors with methylmercury (MeHg) and treating with a *Coriandrum sativum* aqueous extract (CSAE). Data are shown as the mean ± SD (n = 14/group). *, p < 0.05 compared to the control group; #, p < 0.05 compared to the MeHg-treated group (two-way ANOVA and Tukey test).

3.4. Treatment with CSAE ameliorated the motor deficits induced by methylmercury

To assess the effects of mercury on spontaneous locomotor activity and the effectiveness of the CSAE treatment, the progeny were subjected to an open-field test. The total and central distances covered were reduced in the MeHg group, with means of 14.35 ± 2.948 m and 0.38 ± 0.093 m, respectively, versus 19.43 ± 4.349 m (p < 0.05) and 2.03 ± 0.676 m (p < 0.05) for the control group. The distances for the CSAE (21.92 ± 3.680 m; 1.84 ± 0.732 m) and MeHg + CSAE (20.47 ± 2.731 m; 1.49 ± 0.615 m) groups did not significantly differ from the control group. Importantly, when the MeHg and MeHg + CSAE groups were compared, the intoxicated animals treated with CSAE performed better than the untreated intoxicated animals, reaching distances similar to those of the control group (Fig. 3A and B). It is noteworthy that the reduction in central distance traveled qualifies the spontaneous locomotion as anxiogenic.

Cerebellar damage is accompanied by reduced muscle strength. Hence, we utilized a grip strength test. The MeHg group

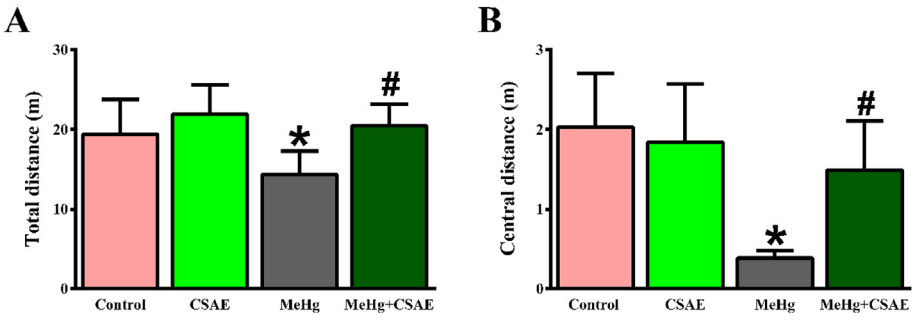

Fig. 3. Methylmercury (MeHg) intoxication and *Coriandrum sativum* aqueous extract (CSAE) treatment effects on neonate rats' spontaneous locomotor activity. (A) Total distance; (B) Central distance. Data are the mean ± SD of the total number of quadrants crossed after 300 s (n = 14/group). *, $p < 0.05$ compared to the control group; #, $p < 0.05$ compared to the MeHg group (two-way ANOVA and Tukey test).

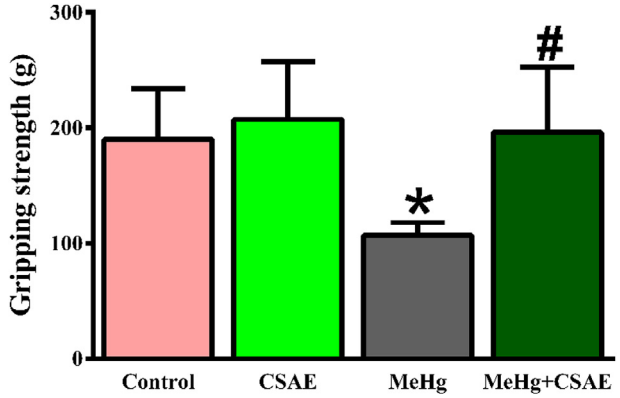

Fig. 4. Methylmercury (MeHg) intoxication and *Coriandrum sativum* aqueous extract (CSAE) treatment effects on paw grip strength. Data are shown as the mean ± SD of 3 test sequences with 14 animals per group. *, $p < 0.05$ compared to the control group; #, $p < 0.05$ compared to the MeHg group (two-way ANOVA and Tukey test).

(106 ± 11.32 g) showed a reduced grip strength relative to the control group (189 ± 43.81 g; $p < 0.05$), whereas the CSAE (207 ± 50.26 g) and MeHg + CSAE (196 ± 56.59 g) groups did not significantly differ. Comparing the MeHg and MeHg + CSAE groups, the positive effects of the CSAE treatment on the intoxicated animals was shown by their increased muscle strength (Fig. 4).

A rotarod test was utilized to assess motor coordination and balance, with the latency and number of slips evaluated at rotational speeds of 16, 20, 25, 28, and 37 rpm. The latency times for the MeHg group (83.3 ± 49.4, 81.7 ± 31.5, 53.3 ± 22.6, 43 ± 23.0, and 16.6 ± 9.2 s, respectively) were shorter in comparison to the control group (126.6 ± 30.4, 157.9 ± 19.1, 153.6 ± 18.6, 145.0 ± 21.0, and 127.6 ± 48.0 s, respectively), while those for the CSAE group did not differ from the control group. In comparison to the control group, the MeHg + CSAE group (159.1 ± 16.1, 154.3 ± 16.0, 142.5 ± 20.8, 137.1 ± 26.4, and 123.9 ± 18.8 s, respectively) had no significantly differences, whereas in comparison with the MeHg group, they had significantly longer latency times on all rotational speeds (Fig. 5A).

When the number of falls was assessed (Fig. 5B), the MeHg group (2.5 ± 1.4, 5.1 ± 1.4, 7.5 ± 3.4, 10.2 ± 1.3, and 9.5 ± 3.7) had significantly more than the control group (1.2 ± 1.0, 1.7 ± 1.3, 2.7 ± 1.3, 3.9 ± 2.2, and 4.0 ± 2.2; $p < 0.05$) at all rotational speeds. In contrast, the numbers of falls for the CSAE (1.3 ± 1.0, 1.0 ± 1.4, 3.2 ± 1.7, 3.5 ± 2.2, and 3.2 ± 2.2) and MeHg + CSAE (1.2 ± 0.8, 1.4 ± 1.2, 2.4 ± 2.2, 3.5 ± 1.7, and 3.4 ± 1.7) groups did not statistically differ from those of the control group. Comparing the MeHg + CSAE and MeHg groups, a significant improvement was seen in the balance quality of the MeHg + CSAE group (Fig. 5B).

The beam walk test was used as a second assay to evaluate balance. Again, the MeHg group (4.85 ± 1.2, 5.2 ± 2.6, 4.6 ± 1.9, and 12.5 ± 4.3) had significantly more slips than the control group (2.5 ± 0.9, 2.7 ± 1.4, 2.1 ± 1.2, and 5.3 ± 2.0; $p < 0.05$), while the CSAE (2.2 ± 1.0, 3.0 ± 1.4, 2.2 ± 1.0, and 4.7 ± 2.5) and MeHg + CSAE (2.3 ± 1.0, 3.3 ± 1.7, 2.4 ± 1.0, and 5.7 ± 2.0) groups showed no significant differences. The MeHg + CSAE group had significantly fewer slips than the MeHg group, suggesting the CSAE treatment improved their balance (Fig. 6).

3.5. Treatment with CSAE decreased the oxidative damage in the progeny induced by MeHg

A TBARS assay was performed to assess for possible oxidative damage after the intrauterine and lactation mercury exposure and whether the CSAE treatment ameliorated lipid peroxidation in the neonate animals. Lipid peroxidation was significantly higher in the MeHg group (1.4 ± 0.2 pg/mg protein; $p < 0.05$) than in the control group (0.6 ± 0.1 pg/mg protein), while that of the CSAE (0.5 ± 0.1 pg/mg protein) and MeHg + CSAE (0.7 ± 0.1 pg/mg protein) groups remained similar to the control group value. Compared to the MeHg group, the MeHg + CSAE group showed reduced levels of lipid peroxidation, demonstrating an attenuated oxidative pattern (Fig. 7).

After identifying the ability of CSAE to lower lipid peroxidation levels, we evaluated the nitrite and superoxide anion levels to see if they also varied after the CSAE treatment. The nitrite levels were significantly higher in the MeHg group (8.2 ± 1.1 μmol/mg protein; $p < 0.05$) than in the control group (4.1 ± 1.3 μmol/mg protein), while the levels in the CSAE (4.5 ± 1.2 μmol/mg protein) and MeHg + CSAE (4.6 ± 0.9 μmol/mg protein) groups remained similar to the control group. However, there was a significant difference between the MeHg and MeHg + CSAE groups (Fig. 8A).

The superoxide anion levels were also significantly higher in the MeHg group (0.2 ± 0.03 U/mg protein; $p < 0.05$) than in the control group (0.1 ± 0.02 U/mg protein), while the CSAE (0.1 ± 0.02 U/mg protein) and MeHg + CSAE (0.17 ± 0.02 U/mg protein) groups had levels comparable to those in the control group. The MeHg + CSAE group had lower superoxide anion levels than the MeHg group (Fig. 8B).

After assessing the reactive oxygen species (ROS) levels, the antioxidant systems were investigated. A reduction in the total glutathione levels was observed in the MeHg group (8.5 ± 1.5 pmol/μg protein) relative to the control group (13.2 ± 2.6 pmol/μg protein; $p < 0.05$), while the levels in the CSAE (13.3 ± 2.0 pmol/μg protein) and MeHg + CSAE (12.7 ± 2.4 pmol/μg protein) groups were comparable to the control group. The MeHg + CSAE group had significantly higher total glutathione levels than the MeHg group (Fig. 9).

Relative to the control group (14.4 ± 1.3 nmol/min/mg protein), less catalase activity was seen in the MeHg group (6.5 ± 0.9 nmol/min/mg protein; $p < 0.05$). The enzyme activity was preserved in the CSAE (13.9 ± 1.5 nmol/min/mg protein) and MeHg + CSAE (13.7 ± 2.0 nmol/min/mg protein) groups, with levels comparable to those of the control group. Importantly, the MeHg + CSAE group had significantly higher catalase activity than the MeHg group (Fig. 10A).

Superoxide dismutase activity was also significantly lower in the MeHg group (25.2 ± 8.4 U/mg protein; $p < 0.05$) than in the control

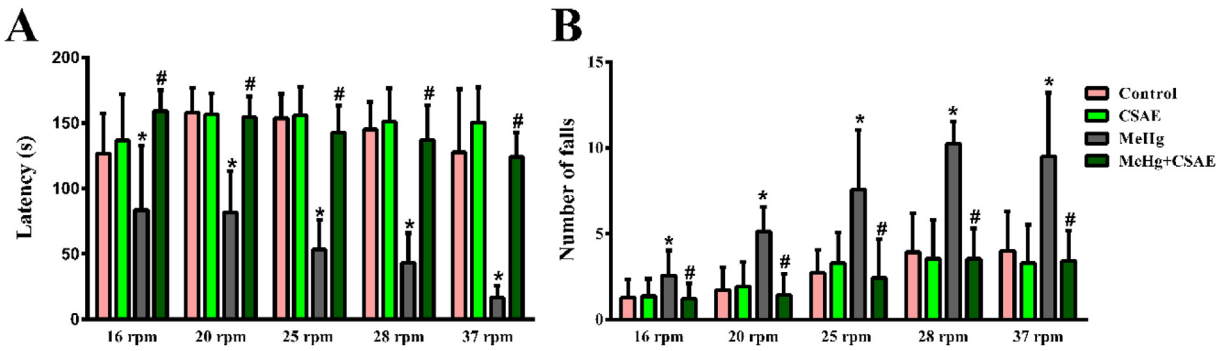

Fig. 5. Methylmercury (MeHg) intoxication and *Coriandrum sativum* aqueous extract (CSAE) treatment effects on neonates' balance and motor coordination. (A) Latency; (B) Number of falls. Data are shown as the mean ± SD (n = 14/group). *, $p < 0.05$ compared to the control group; #, $p < 0.05$ compared to MeHg group (two-way ANOVA with repeated measures and Tukey test).

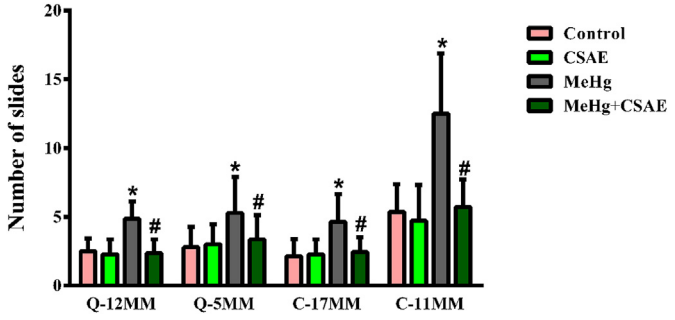

Fig. 6. Methylmercury (MeHg) intoxication and *Coriandrum sativum* aqueous extract (CSAE) treatment effects on neonates' balance. Data are shown as the mean ± SD (n = 14/group). *, $p < 0.05$ compared to the control group; #, $p < 0.05$ compared to the CSAE-treated group (two-way ANOVA with repeated measures and Tukey test); BWT/Q-12MM, 12 mm wide quadrangular pole; BWT/Q-5MM, 5 mm wide quadrangular pole; BWT/C-17MM, 17 mm diameter circular pole; BWT/C-11MM, 11 mm diameter circular pole.

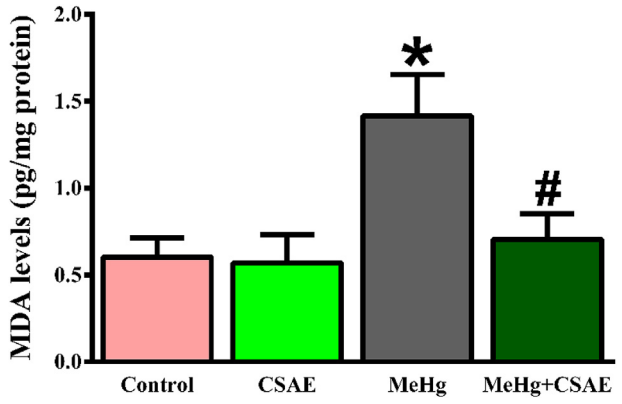

Fig. 7. Malondialdehyde (MDA) levels in the offspring. Results are expressed in pg/mg protein. Data are shown as the mean ± SD (n = 14/group). *, $p < 0.05$ compared to the control group; #, $p < 0.05$ compared to the CSAE-treated group (two-way ANOVA and Tukey test); CSAE, *Coriandrum sativum* aqueous extract; MeHg, methylmercury.

group (38.9 ± 12.0 U/mg protein), while the CSAE (39.0 ± 10.8 U/mg protein) and MeHg + CSAE (39.3 ± 8.0 U/mg protein) groups had enzyme activities similar to that of the control group. Significantly higher superoxide dismutase activity was observed in the MeHg + CSAE group than in the MeHg group (Fig. 10B).

4. Discussion

The results show that the progeny of mothers subjected to MeHg intoxication and treated with CSAE had functional motor improvements during spontaneous (Fig. 3A and B, and 6) and forced locomotion (Fig. 5A and B) assessments. The progeny also showed increased grip strength (Fig. 4). Both outcomes may be linked to a reduction in total mercury levels in the CSAE-treated group.

The harmful effects of MeHg on motor performance have been described previously. Su and Okita (1976) were pioneers in investigating the effects of a single dose of MeHg on Day 10 of gestation. They observed reduced spontaneous locomotor activity in the offspring, which reverted as the specimens grew older. In another study with a similar animal model, Ghizoni et al. (2018) utilized polyunsaturated fatty acids as a treatment for MeHg intoxication, but the test subjects showed no improvement in their behavioral parameters, had compromised motor coordination, and had an accumulation of MeHg in their cerebellar tissue. We hypothesized that the bioactive compounds with intense antioxidant activity present in *C. sativum* might ameliorate the motor-function damage that results from MeHg poisoning during neurodevelopment. Thus, we investigated several parameters related to motor function: spontaneous and forced ambulation, balance and equilibrium through two paradigms, and grip strength.

The mercury reduction seen in the MeHg + CSAE group might be associated with the extract's antioxidant activity (Fig. 1). The antioxidant properties observed in this study have also been seen in other studies that utilized *C. sativum* extracts (Abbassi et al., 2018; Dias et al., 2011; Harsha and Anilakumar, 2014; Pereira and Tavano, 2014; Sreelatha and Inbavalli, 2012). An aqueous extract was preferred, because it has been shown to contain greater amounts of polyphenols (Melo et al., 2003) with high antioxidant capacities such as caffeic acid and glycitin (Melo et al., 2005). Our results demonstrated that the utilized CSAE had high antioxidant activity, free-radical scavenging capacity, and total phenolic content.

An increase in mercury level promotes oxidative stress, with cell membranes and organelle phospholipids as the primary targets (Nath et al., 1996), which leads to higher ROS production, lipid peroxidation, protein synthesis disturbance, and enzyme disruption, all of which contribute to reduced antioxidant enzyme activity (Abdel-Salam et al., 2018; Olguin et al., 2018; Wilson et al., 2005). Methylmercury also leads to neurotoxicity in humans and in animal models, but to date, there is no efficient treatment available for mercury poisoning (Cao et al., 2011; Nielsen and Andersen, 1991; Schutzmeier et al., 2018).

This is the first time the protective properties of CSAE against mercury-induced neurotoxicity have been demonstrated in an *in vivo* model, where the behavioral parameters improved after treatment, likely due to a decrease in oxidative stress. *Coriandrum sativum* has already been shown to have protective effects against oxidative damage in rat brains after lead poisoning at doses of 250 and 500 mg/kg (Vekaria et al., 2012; Velaga et al., 2014). Other extracts have also been investigated to assess their effects on heavy metal poisoning. A *Polygala paniculata* extract prevented lipid peroxidation in the rat cerebellum

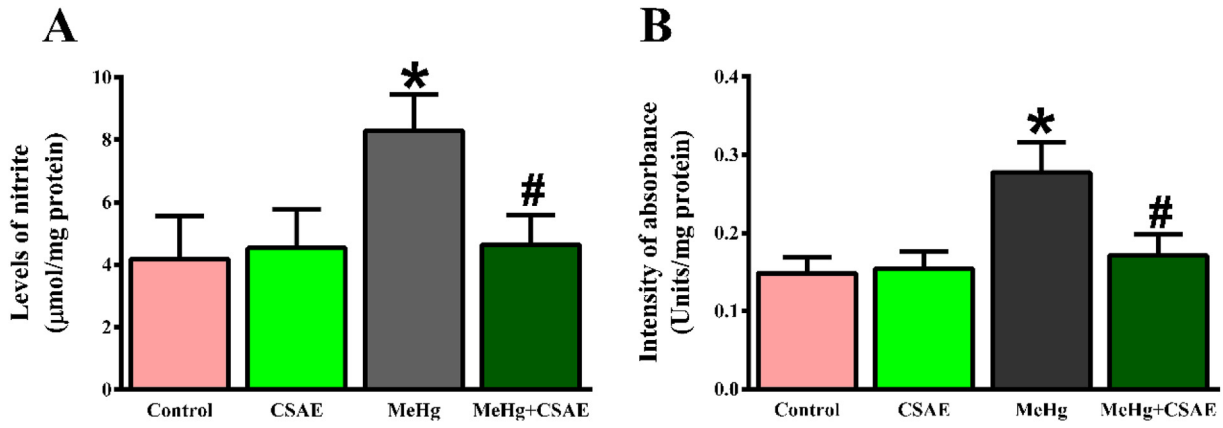

Fig. 8. Reactive oxygen species assessment in the offspring. (A) Nitrite levels expressed in µmol/mg protein; (B) Superoxide anion intensity expressed in absorbance/mg protein. Data are shown as the mean ± SD (n = 14/group). *, $p < 0.05$ compared to the control group; #, $p < 0.05$ compared to the CSAE-treated group (two-way ANOVA and Tukey test); CSAE, *Coriandrum sativum* aqueous extract; MeHg, methylmercury.

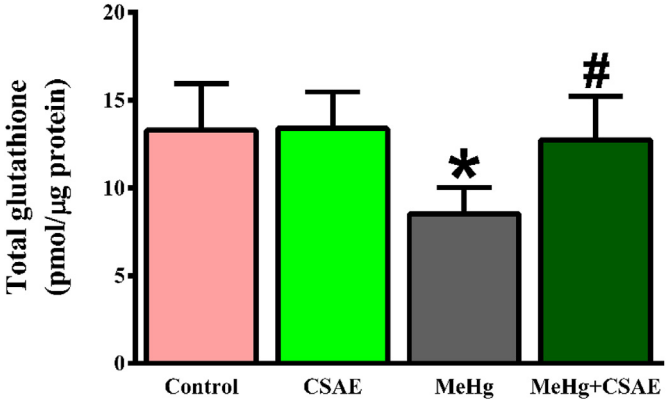

Fig. 9. Total glutathione levels in the offspring. Results are expressed in pmol/µg protein. Data are shown as the mean ± SD (n = 14/group). *, $p < 0.05$ compared to the control group; #, $p < 0.05$ compared to the CSAE-treated group (two-way ANOVA and Tukey test); CSAE, *Coriandrum sativum* aqueous extract; MeHg, methylmercury.

and ameliorated motor damage in an *in vivo* model similar to the one utilized in this study (Farina et al., 2005).

The groups treated with CSAE showed normal ROS levels in the cerebellum, protection against anion superoxide and nitrite damage, and reduced lipid peroxidation. These effects can be attributed to the extract's chemical composition (Table 1), which is rich in flavonoids such as quercetin-3-glucuronide, isoquercetin, and rutin (Kunzemann and Herrmann, 1977; Nagata et al., 1999), phenolic compounds, and anthocyanins. It is important to note that these compounds are linked to higher antioxidant enzyme production and protective properties against ROS (Dai et al., 2012; Kozlowska et al., 2016; Rashid et al., 2014).

Yang et al. (2012) stimulated protein expression related to neuroplasticity and antioxidant activity in rat brains by administering an anthocyanin extract that provided neuroprotection and increased functional performance. This result was similar to those obtained in our study, where the offspring showed increased functional performance after treating with CSAE.

We identified several minerals in CSAE that can contribute to both antioxidant enzyme synthesis and redox balance modulation, properties involved in the reduced oxidative patterns and improved behavioral performance seen in the treated offspring. Micronutrients and macronutrients play a role in CNS homeostasis and the synthesis of antioxidant enzymes and protein structures, but they can also interact with heavy metals (Brose et al., 2014; Lau et al., 2019; Liu et al., 1992). Elements such as Cu and Fe are redox-active elements and act as cofactors to enzymes in various metabolic reactions, free-radical scavenging, and the biosynthesis of neurotransmitters (Lebovitz et al., 1996; Salama et al., 2009; Strange et al., 2003). A dysfunction in the balance of these minerals can lead to neural changes and maladies such as Parkinson disease (Ji et al., 2017; Mischley et al., 2017).

Elements such as Mn and Zn are essential for proper enzyme

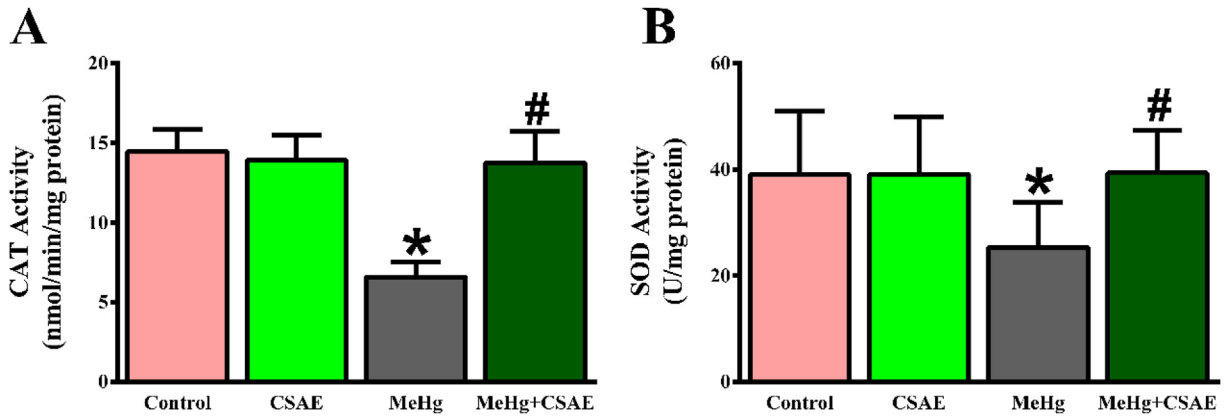

Fig. 10. Antioxidant enzyme activity. (A) Catalase (CAT) and (B) superoxide dismutase (SOD) activities in the progeny of MeHg-poisoned mothers. Results are expressed in nmol formaldehyde/min/mg protein and U/mg protein, respectively. Data are shown as the mean ± SD (n = 14/group). *, $p < 0.05$ compared to the control group; #, $p < 0.05$ compared to the CSAE-treated group (two-way ANOVA and Tukey test); CSAE, *Coriandrum sativum* aqueous extract; MeHg, methylmercury.

functioning (hydrolases, isomerases, ligases, lyases, reductases, and transferases) in various biological systems such as lipid, protein, and carbohydrate metabolism, ATP production, redox homeostasis (SOD2), DNA synthesis, and cellular signaling, where they act as neuromodulators in protein structures with antioxidant properties such as SOD1 (Adebayo et al., 2016; el-Sewedy et al., 1974; Sharma et al., 2010; Sommer et al., 2018). Zinc also acts in glutamatergic synaptic transmission, inhibiting N-methyl-D-aspartate and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor activity, thus modulating neuronal excitability and long-term synaptic plasticity (Takeda et al., 2004). The levels of components such as Zn and Cu are altered in the CNS after heavy metal poisoning due to oxidative stress, but the treatment with CSAE was able to restore the Zn, Cu, and Fe levels to their physiological state (Ren et al., 2009; Velaga et al., 2014).

The results presented in this study support the hypothesis that a CSAE can protect an offspring's cerebellum after its progenitor is poisoned with mercury by reducing oxidative stress, thereby reducing damages to motor function. The total glutathione levels and catalase and SOD antioxidant-enzyme activities returned to their basal levels after treatment with CSAE. Further studies are necessary for a better understanding of the protective effects of CSAE against cerebellar mercury-induced toxicity.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The authors acknowledge CNPq and CAPES for their financial support.

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