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EFFECTS OF AQUEOUS SEED EXTRACT OF SOYBEANS (*Glycine max*) ON MERCURY CHLORIDE-INDUCED TOXICITY ON THE CEREBRUM OF ADULT WISTAR RATS.

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ABSTRACT

Mercury chloride ($HgCl_2$) is a heavy metal known to cause adverse effects on biological systems, particularly the central nervous system. The cerebrum, which is responsible for cognitive functions, has been reported to be vulnerable to mercury toxicity. Numerous studies have demonstrated that plants and their phytochemicals possess therapeutic potentials. Hence, there is increased attention towards the therapeutic potential of herbal extracts. Soybean (Glycine max), a legume known for its high protein content and rich source of bioactive phytochemicals has been reported to possess antioxidant, anti-inflammatory, estrogenic, anti-diabetic, and neuroprotective properties. Accordingly, this study investigated the neuroprotective effects of aqueous seed extract of soybeans on mercury chloride-induced toxicity in adult Wistar rats. Twenty-four rats were divided into four groups (n=6): Group A (control) received 1ml distilled water, Group B received 4 mg/kg body weight of $HgCl_2$, Group C received 1000 mg/kg body weight of aqueous seed extract of soybeans, and Group D received 1000 mg/kg body weight of aqueous seed extract of soybeans 1 hour before 4 mg/kg $HgCl_2$. All administration via orogastric tube lasted for 28 days. At the end of the experimental period, the rats were weighed and Y-maze test was used to evaluate spontaneous alternation of the experimental rats. Following sacrifice, the cerebrum was harvested for histological assessment. Results obtained shows a significant decrease ($p<0.05$) in the body weight change of experimental animals in Group B when compared to group A (control) while Groups C and D showed significant increases ($p<0.05$) in the body weight change when compared to Group B. No significant differences were observed in relative brain and cerebral weights across experimental groups. In the Y-maze test, Group B exhibited a significant decrease ($p<0.05$) in spontaneous alternation when compared to group A whereas Groups C and D showed significant increase ($p<0.05$) in spontaneous alternation when compared to Group B. Photomicrographs obtained revealed shrunken neuronal cells with pyknotic nuclei and irregular pia mater in group B when compared to group A. Group C showed fewer dark, shrunken neuronal cells while Group D, several normal pyramidal cells were observed when compared to group B. These findings suggest that aqueous seed extract of soybean possess the potential to mitigate mercury chloride-induced neurotoxicity. Further research is needed to understanding the mechanism of action involved in the neuroprotective potentials exhibited by aqueous seed extract of soybeans.

Keywords: *Glycinemax*, Neurobehavioural, Cerebrum, Wistar rat

INTRODUCTION

Soybean (*Glycine max*) has been reported to be a vital crop for thousands of years, with research focused on genetic improvements like yield, disease resistance, and nutritional quality (Concibido*et al.,* 2004). Soy beans are one of the richest and cheapest sources of protein for humans and animal feed. Traditionally, soybeans have been a staple in Asian diets, consumed as tofu, soy sauce, and miso (Alghamdi *et al.,* 2018). As plant-based diets become more popular, soybeans are increasingly used as an alternative protein source (Singh *et al.,* 2013). Soy beans contain significant amount of oligosaccharide, dietary fibers, phytic acid, minerals and vitamins (Bansal and Parle, 2010). Phytochemically, soy beans contain several bioactive phytochemicals which include phenolic acid, flavonoid, isoflavones, saponins, phytosterols and sphingolipids (Lee *et al.,* 2008), eugenols, terpenoids and alkaloids (Ali *et al.,* 2022). The reported pharmacological properties of soy beans include antioxidant, estrogenic, antidiabetic, antihypercholesterolemic, antihyperlipidermic, antiobesity, antihypertensive, anticancer, antimutagenic, hepatoprotective, antiviral, anti-inflammatory, immunomodulatory, neuroprotective, wound healing effects (Wang *et al.,* 2018; Hughes *et al.,* 2011). The pharmacological benefits of soy beans to a large extent have been attributed to the presence of isoflavones in soy beans (Messina, 2010). According to Bansal and Parle (2010), consumption of soy bean in diet may not only improve memory but also significantly reversed alprazolam-induced amnesia in a dose-dependent manner, owing to its multifarious activities. Clinical studies have demonstrated that soy isoflavones increased the cognitive function of postmenopausal women and had beneficial effect on cognition in aged adults, especially those with Alzheimer's disease (Gleason *et al.,* 2015). Report in literature suggests that soy isoflavones may improve verbal and non-verbal memory in men and women (Zhao and Briton, 2007).

The cerebrum is made up of right and left hemisphere constituting the largest portion of the brain (Raichle, 2010). It lies in the anterior and middle cranial fossae of the skull (Snell, 2010) and is made up of the cerebral cortex (two cerebral hemisphere), and subcortical structures, including the hippocampus, basal ganglia, and olfactory bulb. (Bhuiyan *et al*., 2018). On its surface are convolutions and folds, with the ridges between the convolution known as gyri and the shallow grooves between the gyri called sulci (Raichle, 2010; Gomez-Ramirez and Gonzalez-Rosa, 2022). Both cerebral hemispheres are made up of an outer layer of gray matter and an inner subcortical white matter (Raichle, 2010; Jawabri and Sharma, 2019). The cerebrum is the largest and most important part of the brain responsible for functions such as cognition, memory, and learning. Mercury, a heavy metal has been reported to induce toxicity in the cerebrum that can lead to significant impairment of its functions (Wang *et al*., 2012). Mercury exposure has also been shown to cause neuronal damage, impairing dendrite and synapse morphology, which impacts cognitive functions (Yasutake *et al.,* 2018; Abbott & Fikru, 2021). Mercury chloride ($HgCl_2$) is particularly harmful, but research indicates that soybeans extract might mitigate these effects. Ayinde *et al.,* (2010) reported that soybean extract reduced mercury concentration and oxidative stress in the brain tissues of rats exposed to mercury chloride. Similarly, Ibrahim *et al.,* (2021) reported that soybean extract reduced mercury-induced oxidative stress, inflammation, and neuronal damage in the cerebrum of adult Wistar rats. Hence, this study investigated the neuroprotective potential of aqueous seed extract of soybean (*Glycine max*) on mercury

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chloride- induced neurotoxicity in adult Wistar rats.

MATERIALS AND METHOD

Animals and Management

In this study, 24 adult Wistar rats were used for this study with body weight ranging from 200g-230g. The rats were bred in the animal house of the department of anatomy, University of Benin, Benin City. They were housed in plastic cages at room temperature and given water and Grower's mash every day, which was produced by Premier feed Mills Co LTD, a division of Flour Mills of Nigeria Plc and water *ad libitum*. The procedures for this investigation followed the recommendations for the care and use of experimental animals.

Plant Material

Soybeans (*Glycine max* (L) Merr.) were obtained from a local market (Lagos street market) in Benin City, Edo state, Nigeria. It was authenticated in the herbarium unit of the Department of Plant Biology and Biotechnology, University of Benin, Benin City, Nigeria, with a herbarium specimen deposited and a Voucher number UBH- G470 given.

Acute toxicity Study

This study was carried out as previously reported Lorke (1983).Three groups (1,2 and 3) with three (3) rats respectively, given single doses of 10, 100 and 1000mg/kg body weight of aqueous *Glycine max* seed extract, were observed for 72 hours for behavioural changes and death. Afterwards, three new groups (4,5 and 6), with three (3) rats respectively, given single doses of 1600mg/kg, 2900mg/kg and 5000mg/kg body weight of aqueous *Glycine max* seed extract. They were further monitored for 72 hours for likely mortality and behavioural alterations.

Experimental Design

A total of twenty-four (24) adult Wistar rats were used in this study, they were randomly divided into four (4) groups of six (6) rats each, after acclimatization to animal house conditions for two weeks with free access to feed and water, the administration was carried out for twenty-eight (28) days and done orally using orogastric tube. Group A, (control) received 1 ml of distilled water daily. Group B received a daily dose of 4 mg/kg body weight of mercury chloride. Group C was treated with 1000 mg/kg body weight of soybean extract daily. Lastly, Group D received a 1000 mg/kg soybean extract 1 hour before 4 mg/kg mercury chloride daily. All administration via an orogastric tube lasted for 28 days.

Neurobehavioral Tests (Y-maze test)

The Y-maze test, widely used to assess spatial memory and learning in rodents, involves placing a rat at the center of a Y-shaped apparatus with three arms. The rats were allowed to explore freely, and the sequence of arm entries were recorded to calculate the percentage of spontaneous alternation, which reflects spatial working memory. An alternation is defined as visiting each arm consecutively without returning to the same arm (Deacon, 2006; Monte *et al.,* 2013). The apparatus, with arms measuring 33 cm long, 11 cm wide, and 12 cm high, was cleaned with70% ethanol after each session (Dalligna*et al.,* 2007).

Histological Procedures

After 28 days, the rats were sacrificed via cervical dislocation, the skulls were opened, and the brain extracted. The brains of rats in control and experimental groups were fixed in 10% buffered formal saline fir 72 h. the tissues were processed and stained using the methods for histological examination (Drury & Wallington, 1980). Sections were examined using a digital camera (Leica CC50) coupled to a Leica DM750 research microscope. Photomicrograph of the tissue sections was taken using a scale bar of 25µm.

Statistical Analysis

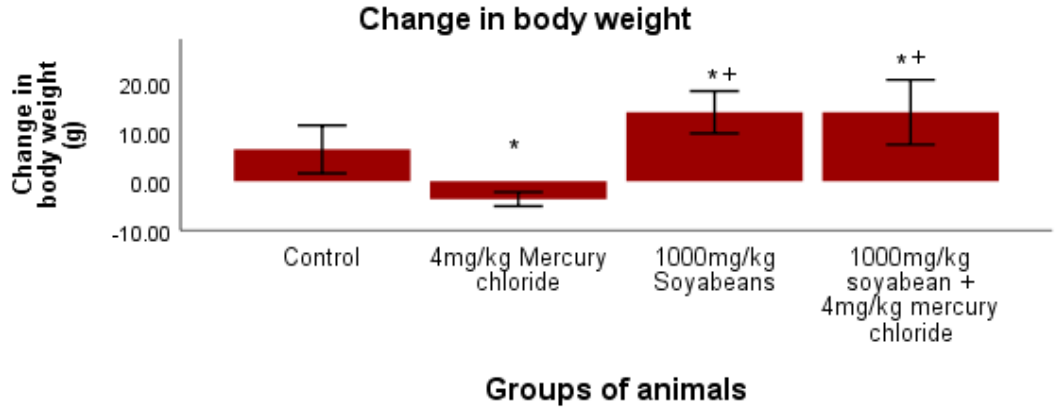
All values in this study were provided as mean ±standard error of the mean for all groups. One way analysis of variance (ANOVA) was used to examine the significance of variations in the means of all parameters. All statistical analyses were performed using the International Business Machine Corporation's (IBM) statistical program for social sciences (SPSS) in Armonk, New York.

RESULTS

No behavioral changes or mortality were noted in any of the experimental groups following the administration of aqueous seed extract *Glycine max* at doses ranging from10 to5000 mg/kg body weight. This suggests that the extract was safe for the experimental rats in the study.

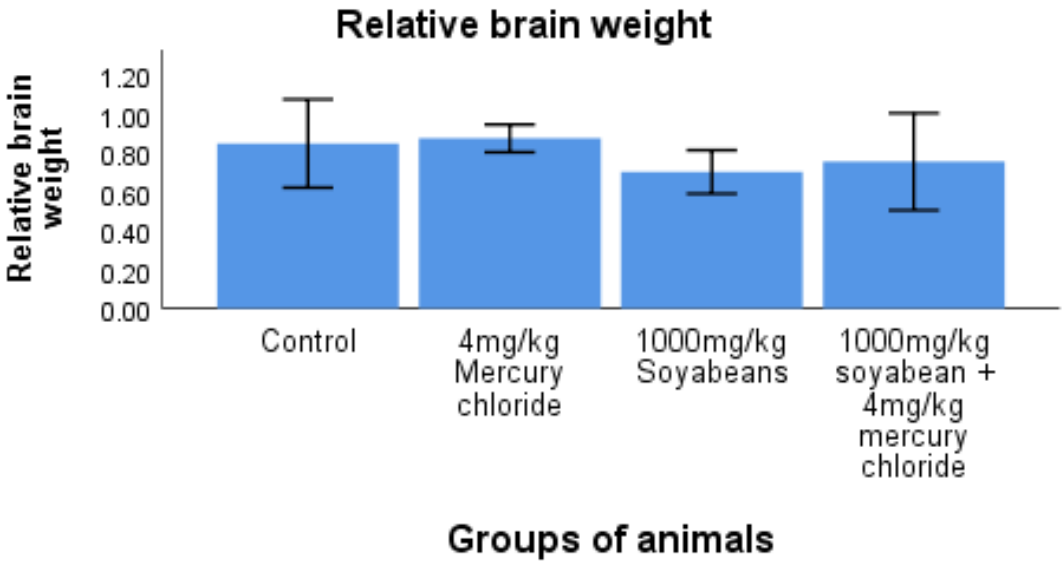
Effect of *Glycine max* on body weight, relative brain weight, and cerebral weight

Figure 1-3 shows a significant decrease ($P<0.05$) in body weight of rats in group B (4mg/kg mercury chloride) when compared to the control, while groups C (1000 mg/kg soybeans) and D (1000 mg/kg soybeans + 4 mg/kg mercury chloride) showed significant increases ($P<0.05$) when compared to group B. However, there were no significant changes ($P>0.05$) in relative brain weight and cerebral weight among experimental groups.



* compares B versus A

\+ compares group C and D versus B



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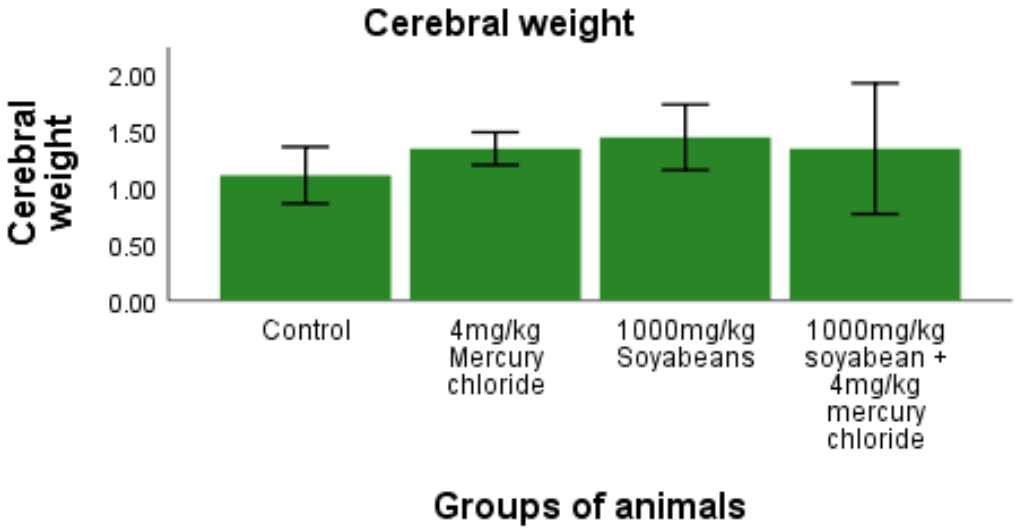

Figures1–3shows changes in body weight, relative brain weight, and cerebral weight in control rats and rats administered with 4 mg/kg mercury chloride, 1000 mg/kg soybeans, and 1000 mg/kg soybeans plus 4 mg/kg mercury chloride for 28days, with values presented as mean± SEM for each group (n=4/group), where*indicates control versus mercury chloride group and + indicates mercury chloride versus soybeans treated group and soybeans plus mercury chloride treated group.

Effect of *Glycine max* on Spontaneous Alternation

Results obtained shows a significant decrease ($p<0.05$) in the spontaneous alternation of rats in group B (4mg/kg body weight of mercury chloride) when compared to control. A significant increase ($p<0.05$) was observed in the spontaneous alternation of rats in groups C and D when compared to group B

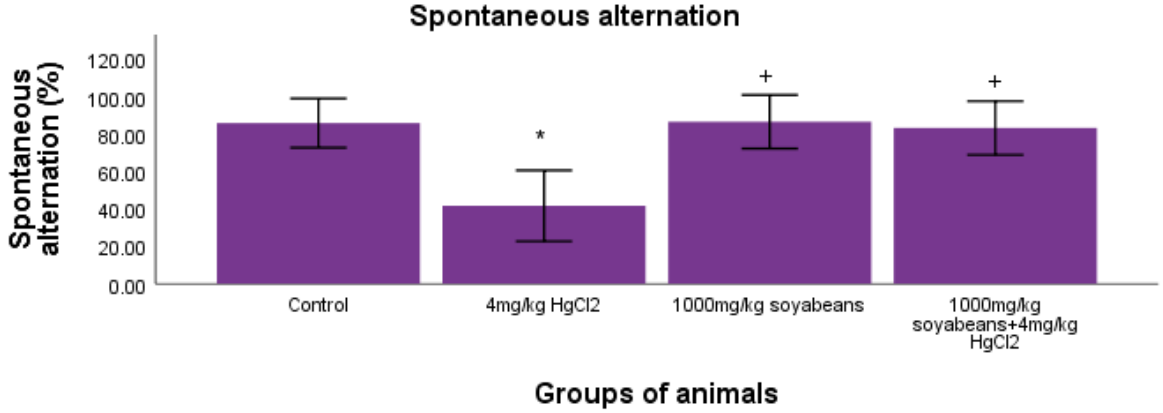

Figure 4: Spontaneous alternation across experimental groups after 28 days in control rats and rats administered with 4 mg/kg mercury chloride, 1000 mg/kg soybeans, and 1000 mg/kg soybeans plus 4mg/kg mercury chloride for 28 days, with values presented as mean± SEM for each group (n=4/group), where* indicates control versus mercury chloride treated group and + indicates mercury chloride versus soybeans treated group and soybeans plus mercury chloride treated group.

Effect of *Glycine max* on the histology of the prefrontal cortex

Photomicrographs of histological sections of the prefrontal cortex (inner pyramidal layer, V) showing normal pyramidal cells (P) of control group (Plate A). Photomicrograph of cerebral cortex (inner pyramidal layer , V) of rats treated with 4 mg/kg body weight mercury chloride showing dark shrunken neuronal cell bodies with deeply stained pyknotic nuclei appearing with pointed end and

pericellular haloes (thick arrows) ; deeply stained glial nuclei can be noticed in the vacuolated neuropil (V) . Normal pyramidal cells (P) are hardly seen (Plate B). Photomicrograph of cerebral cortex (inner pyramidal layer, V) of rats treated with 1000 mg/kg body weight of aqueous extract of soybeans showing several normal pyramidal cells (P) (Plate C). Photomicrograph of cerebral cortex (inner pyramidal layer, V) of rats treated with 1000 mg/kg body weight of aqueous extract of soybeans + 4mg/kg mercury chloride showing several normal pyramidal cells (P).

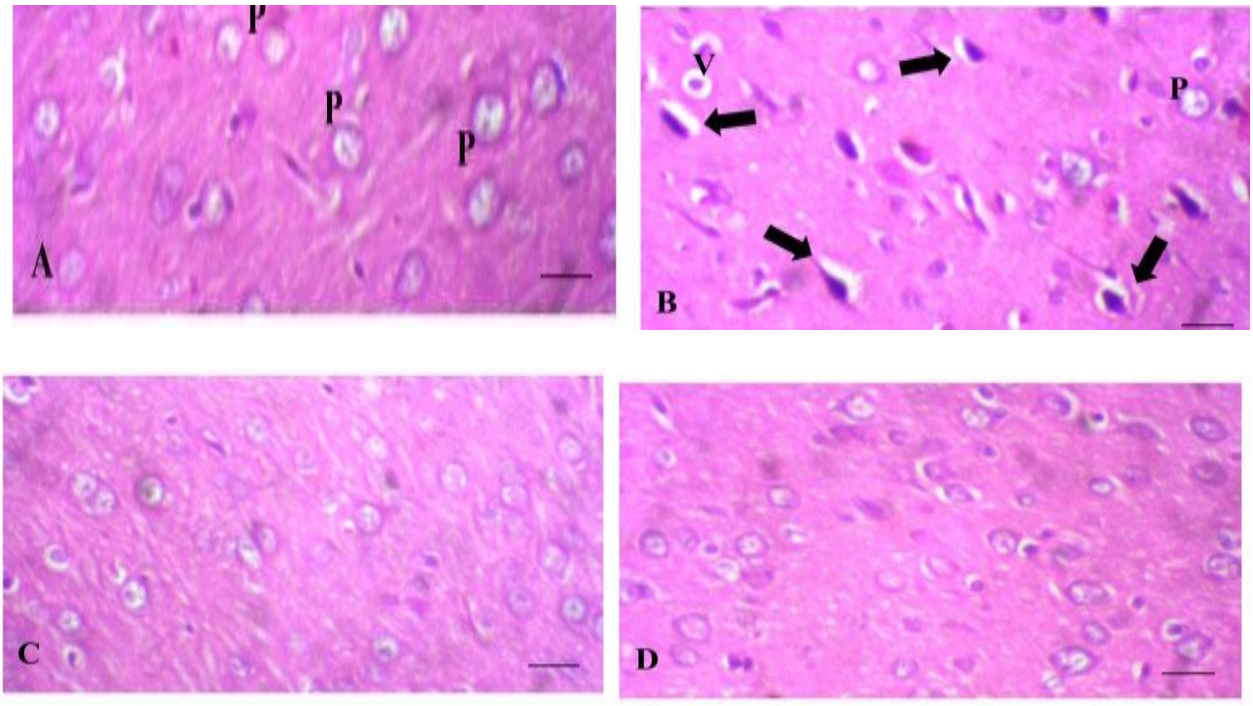

Plate 1: Representative Photomicrographs of the prefrontal cortex across experimental groups (A) Control (B) 4 mg/kg mercury chloride (C) 1000 mg/kg soybeans extract (D) 1000 mg/kg soybeans extract + 4 mg/kg mercury chloride. Scale bar: 25µm

DISCUSSION

In this study, a significant decrease in body weight ($P<0.05$) was observed in rats administered with 4 mg/kg mercury chloride (Group B) when compared to the control. This finding aligns with Aschner *et al.*, (2019), who also reported weight loss associated with mercury chloride exposure due to its accumulation in brain tissues, disrupting cellular processes and impacting appetite and metabolism. These effects have been further confirmed by Aragão *et al.*, (2023), who demonstrated how mercury exposure leads to significant alterations in neural homeostasis, metabolism, and appetite regulation in rats. Conversely, rats treated with 1000 mg/kg soybeans (group C) showed a significant body weight increase when compared to group B. Findings is in agreement with Messina *et al.*, (2019), who attributed this weight increase to the high-quality proteins and essential nutrients in soybeans, as reported by Valin *et al.*, (2023). Rats in group D (treated with1000mg/kgsoybeansand4mg/kg mercury chloride) showed a significant weight increase which aligns with the findings of Penumetcha *et al*. (2013), who associated this with soybeans' energy content offsetting mercury chloride's toxicity. Recent studies reveal that soybean extract has a modest effect on lipid metabolism, without significantly altering brain weight. Soybeans been rich in proteins, unsaturated fatty acids, and bioactive compounds like isoflavones has contributed to its effect on lipid regulation (Yang *et al.*, 2021).No significant difference was observed

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in the relative brain weight and cerebral weight, aligning with the observations of Messina *et al.,* (2019), where soybeans prevented cerebral weight loss from mercury chloride exposure due to its antioxidant property as reported by Jiang *et al.,* (2018).A significant decrease in spontaneous alternation ($P<0.05$)was observed in group B when compared to the control, which is in line with (Thimm *et al.,* 2012; UAH study, 2023). This decrease in spontaneous alternation could possibly be due to neurotoxicity and cognitive disruptions from mercury chloride, as reported by Farina *et al.* (2018). Groups C and D showed a significant increase ($P<0.05$) in spontaneous alterations when compared to group B which align with the findings of Yang *et al.,* (2021), who reported improved spontaneous alternation and reduced anxiety-like behaviors following administration of soybeans and this was attributed to the neuroprotective property of soybeans' as reported by Sharma *et al*. (2020).

Histological analysis of group B revealed neuronal damage, including shrunken neuronal bodies and pyknotic nuclei in the prefrontal cortex. These findings agree with previous studies that reported alterations and degenerative changes in the architecture of the cerebrum following mercury exposure (Owoeye *et al.,* 2018; Said *et al.,* 2021). However, HgCl2-exposed rats pretreated with *Glycine max* showed significant protection against the altered histological architecture of the cerebral cortex thus suggesting a potential attenuation of HgCl2-induced neurotoxicity. This finding is in agreement with the report of Abbasabadi and Tadjalli (2016), where soy milk diet protected the cerebrum against mercury chloride toxicity.

CONCLUSION

In conclusion, the aqueous seed extract of soybeans demonstrated significant protective effect against mercury chloride- induced neurotoxicity in Wistar rats. These effects are likely mediated through its antioxidant properties. Further research is required to fully understand the mechanisms involved and translate these findings to clinical applications. Our study suggests that soybeans extract may be a promising natural remedy for individuals exposed to mercury toxicity.

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