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Comparative Study of Aqueous and Ethanolic *Artocarpus heterophyllus* Extracts Against Mercuric Chloride Induced Neurobehavioral Toxicity

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ABSTRACT

In rodents, oxidative stress from mercuric chloride poisoning damages many organs, including the brain. The purpose of this study was to determine whether jackfruit may protect rat brains from the oxidative stress caused by mercuric chloride ($HgCl_2$). After acclimatization, thirty-two adult male rats weighing between 160 and 200 grams were randomly assigned to eight groups of four rats each. These groups were as follows: A: Tap water as the control; B: $HgCl_2$ (0.5 mg/kg body wt.); C and D: Jackfruit ethanolic and aqueous extract (200 mg/kg body wt.); E and F: $HgCl_2$ + Jackfruit ethanolic and aqueous extract (200 mg/kg body wt.); G and H: $HgCl_2$ + Jackfruit ethanolic and aqueous extract (400 mg/kg body wt.) respectively. Every therapy involved oral gastric gavage and a 14-day duration. On the fifteenth day, rats underwent behavioral testing; the same day, they were put to death by cervical dislocation. All groups underwent the following analyses: behavioral investigations, phytochemical and proximate analysis of plant extracts, antioxidant measures, and histology of the rat cerebellum with respect to micro-anatomical parameters. In comparison to the control, mercuric chloride ($HgCl_2$) significantly ($p<0.05$) increased the MDA level, CAT and SOD activity, decreased GSH and GPx level, and impaired motor performance. Additionally, it changed the microanatomy of these brain areas by reducing Purkinje cells. However, concurrent treatment of *Artocarpus heterophyllus* extract with $HgCl_2$ caused a reversal of these parameters relative to control. Consequently, the rat cerebellum's histoarchitecture showed protective effects from $HgCl_2$-induced oxidative, neurobehavioral, and histological alterations when *Artocarpus heterophyllus* was administered both aqueously and ethanolically.

Keywords: Oxidative stress; mercuric chloride poisoning; ethanolic artocarpus heterophyllus.

INTRODUCTION

At a time when life expectancy is rising globally, it is declining in Nigeria. At a time when other countries, particularly those in Africa, experienced an increase of five years, Nigeria's has decreased to 54.5 years [1]. According to [2,47,48,49,54,55], heavy metals and chemicals are dangerous environmental pollutants linked to a number of illnesses affecting human health, including cognitive dysfunctions. According to Grandjean and Landrigan [3] and Tolins et al. [4], mercury (Hg) is an environmental neurotoxicant that has been connected to detrimental effects on memory as well as the possibility of emotional and learning impairments in both people and mice. It can cause apoptosis and reduce the number of neurons and astrocytes in the motor cortex, which can lead to motor impairments even though it has a weak ability to overcome biological barriers [5]. Mercuric chloride ($HgCl_2$) after consumption has been linked to tissue damage from oxidative stress induced by the generation of highly reactive hydroxyl radicals (OH) and other intermediate intermediates that encourage lipid peroxidation. This could cause harm to biomembranes and change their function, which would then lead to the emergence of various disease processes [6,7, 44]. Additionally, free radicals generated by mercuric ions have the ability to inactivate a

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wide range of enzymes by adhering to sulfhydryl groups in binding or catalytic domains, inhibiting their functional locations. High levels of reactive oxygen species (ROS) and oxidative stress indicate mercury's toxicity to the central nervous system [8,9]. This alters the brain's, cerebellum's, and medulla oblongata's morphology and functioning. Mello-Carpes et al. [10] also observed recognition memory impairments in adult rats after extended low-level mercury exposure, which is similar to occupational exposure in humans. It is highly likely that these effects were partially or entirely related to the oxidative stress that was observed in several tissues and organs in this experimental paradigm and others [11,12]. According to Arago et al. [13], organic mercury is absorbed by human body cells derived from the central nervous system and then changes into inorganic mercury. The etiology of Niigata Minamata sickness and Hunter-Russell syndrome is methyl mercury, which is produced as a byproduct of acetaldehyde production [14]. According to Genchi et al. [15], exposure to mercury has been associated with serious health problems affecting the kidney, skin, eyes, lungs, and brain in addition to the immunological, neurological, and digestive systems. Clinical signs of methyl chloride intoxication include cerebellar ataxia, constriction of visual fields, and abnormalities in sensory and auditory perception, depending on the location of the lesions [14]. Mercury exposure is associated with a variety of ailments, such as odd behavior, fatigue, tremors, headaches, cognitive decline, hallucinations, incoordination, and mortality [15]. Health problems associated with exposure to mercury contribute to the global and local burden of disease. The burden of mercury exposure is disproportionately felt by the developing countries [16]. The fruit tree known as jackfruit (*Artocarpus heterophyllus*) is a member of the Moraceae family [17,18]. This tropical plant is primarily seen growing in southern Asia [17]. It yields what is essentially the largest fruit on the planet, a very huge fruit. Many of the jackfruit's pharmacological properties are attributed to its abundance of phytochemicals in the leaves. The leaves of *A. heterophyllus* have been shown to contain plant compounds such as flavonoids, tannins, βsitosterol, cycloartenol, and sapogenins [19,20]. The flavonoid concentration of *A. heterophyllus* leaf extract in vitro has been related to the antioxidant activities of jack fruit leaves, as well as its reduced lipid peroxidation, diphenylpicrylhydrazyl radical scavenging, and Fe+2 chelating activities [19]. According to ethnopharmacological claims, jackfruit leaves are used to cure skin conditions, boils, wounds, diabetes, hypertension, and fever [17]. According to research on animals, *A. heterophyllus* leaves have a variety of pharmacological properties, such as anticonvulsant, antiulcer, antidiabetic, and antilipidemic properties [19,21,22]. For this reason, we wish to compare, under the same experimental conditions, the extract of Jackfruit that provides greater neuroprotection against free radicals between aqueous and ethanolic for the first time going beyond routine basic phytochemical analysis. The objective of the study was to ascertain the neuroprotective qualities of ethanolic and aqueous extracts of *Artocarpus heterophyllus*, or "Jack Fruit," on the cerebellum of male Wister rats that had been inebriated with mercuric chloride.

MATERIALS AND METHODS

Preparation of Plant Materials

The fruits were obtained from Abia State University, Nigeria and verified by a plant taxonomist, of the Department of Plant Science and Biotechnology. They were washed and dried at room temperature. Dried samples were then ground into powder mechanically, using manual grinder and were put away in a fridge before use [53].

Extraction Procedure

For the aqueous extraction, 500g of the macerated plant powder was soaked in 1000ml of distilled water and kept in a container for 24 hours, while for ethanolic extraction, 500g of the macerated plant powder was soaked in 1000ml of absolute alcohol and kept in a container for 24 hours The mixtures were then vigorously shaken intermittently for additional 2 hours, to allow complete extraction. The resulting mixture was rapidly filtered through Whatman no 1 filter paper to obtain a homogenous filtrate. This filtrate was then concentrated in a vacuum at a low temperature (37-40°c) to about one-tenth the original volume using a rotary evaporator. The concentrates were allowed to open in a water bath (40°c) for complete dryness yielding 200g of dark brown and light brown gummy substances respectively. The extract was later reconstituted in distilled water at a concentration of 1g/ml before administration. The extract was then refrigerated until use.

Experimental Animals and design

Thirty-two (32) Wistar rats weighing between 160-200g were used for this study. The animals were purchased from the animal house of Abia State University. They were housed in standard cages and left to acclimatize for 14 days under natural conditions in the animal house before the commencement of the experiment. They were fed rat chow and tap water ad libitum. The rats were divided into 8 groups A, B, C, D, E, F, G, and H of 4 rats each. Rats in group A received only food and water. All rats in group B were injected with mercury chloride ($HgCl_2$) at 0.5mg/kg/bw intraperitoneally two times a week for 2 weeks. Rats in groups C received aqueous *Artocarpus heterophyllus* extract while D received ethanolic respectively, groups E to H were injected with mercury chloride ($HgCl_2$) at 0.5mg/kg/bw intraperitoneally two times a week for 2 weeks according to the method reported in NTP, 1993 and concurrent administration of aqueous and ethanolic extract of *Artocarpus heterophyllus* respectively. All *Artocarpus heterophyllus* administration was done orally using a gavage. Groups E and G received 200mg/kg per body weight

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of aqueous and ethanolic leaf extracts of *Artocarpus heterophyllus* respectively and also, F and H received 400mg/kg per body weight of aqueous and ethanolic leaf extracts of *Artocarpus heterophyllus* respectively.

Neurobehavioural tests

On the 15th day of the experiment, the forelimb grip strength test were carried out.

Table 1:Experimental protocol

GROUP	ADMINISTRATION	NO. OF RATS	DURATION
A (Normal control)	Food and Water	4	14 days
B (Negative control)	HgCl2 at 0.5mg/kg/bw only intraperitoneally	4	Twice a week for 2wks
C (Ethanolic extract)	HgCl2 at 0.5mg/kg/bw + 200mg/kg/bw of Ethanolic extract of *A. Heterophyllus*	4	14 days
D (Aqueous extract)	HgCl2 at 0.5mg/kg/bw + 200mg/kg/bw of Aqueous extract of *A. Heterophyllus*	4	14 days
E (Low dose group)	HgCl2 at 0.5mg/kg/bw + 200mg/kg/bw of Ethanolic extract of *A. Heterophyllus*	4	14 days
F (Low dose group)	HgCl2 at 0.5mg/kg/bw + 200mg/kg/bw of Aqueous extract of *A. Heterophyllus*	4	14 days
G (High dose group)	HgCl2 at 0.5mg/kg/bw + 400mg/kg/bw of Ethanolic extract of *A. Heterophyllus.*	4	14 days
H (High dose group)	HgCl2 at 0.5mg/kg/bw + 400mg/kg/bw of Aqueous extract of *A. Heterophyllus*	4	14 days

The forelimb grip strength test

This is a test of muscular strength in the forelimbs [23, 42, 43]. In this test, the forepaws were placed on a horizontally suspended metal wire 2 mm in diameter, 1 m in length and placed 1 m above a landing area filled with soft bedding. The length of time each rat was able to stay suspended before falling off the wire was recorded; a maximum of 2 minutes was given to each rat. Each animal was given two trials with a period of rest interval. This test assessed muscle strength and balance.

Sacrifice and Sample Collection

The administration of *Artocarpus heterophyllus* lasted daily for 14 days. On the 15th day the rats were subjected to the neurobehavioral tests (forelimb grip strength test), after which they were sacrificed by cervical dislocation.
According to the technique of [50], blood sample of the rats were collected into a plain tube. They were then centrifuged to obtain the serum antioxidant parameters considered include lipid peroxidation (MDA), superoxide dismutase (SOD), reduced glutathione (GSH), Glutathione peroxidase (GPx) and catalase (CAT). The brains from each group were harvested and fixed in 10% formal saline for histological studies using H&E procedure.

Statistical Analysis

Data will be presented as the Means ± Standard Error of Mean and analysed using one-way analysis of variance (ANOVA) followed by post-test using computer based fitting program (IBM SPSS) version 20. Statistical significance was set at $p<0.05$. INITIAL and FINAL for each group was compared using students T test and differences between means were regarded significant at $P < 0.05$.

RESULTS

Preliminary Phytochemical and Proximate analysis of *Artocarpus heterophyllus*

The result of the preliminary phytochemical analysis is presented in Table 2 (quantitative analysis). Results of the preliminary qualitative analysis show the presence of important phytochemicals like saponins, tannins, steroids, flavonoids, and alkaloids in the fruit of Jackfruit. Flavonoid and Saponin are the highest in Quantitative phytochemical analysis which is highly significant compared to other parameters. Alkaloid and tannin showed minimal quantitative phytochemical analysis. For the qualitative analysis of *Artocarpus heterophyllus*, carbohydrate is seen at a high level, which serves above 50%, and protein content is seen as the top content, the presence of high fiber showed the moisture content (Table 2).

Table 2: Quantitative phytochemical analysis of jack fruit

PARAMETER	Jack Fruit
Alkaloid	3.76
Flavonoid	17.91
Saponin	16.28
Steroid	4.53
Tannin	3.98

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Table 3:Proximate analysis of jack fruit

PARAMETER	Jack Fruit (%)
Ash	12.48
Moisture content	8.73
Crude Lipid	0.38
Crude Fiber	9.21
Crude Protein	14.79
Carbohydrate	54.41

Body weight

Table 3 shows the mean ± S.E.M of 8 groups. Increase in body weight gain was seen following *Artocarpus heterophyllus* administration though was statistically insignificant.

Table 4:Effect on body weight of adult male wistar rat following mercury-chloride induction and *Artocarpus heterophyllus* administration

Groups	Initial Body weight (g)	Final Body weight (g)	P-Value
Normal control	105.20±1.85	137.80±3.13	0.23
HgCl2	129.40±3.14	123.40±3.32	0.81
Ethanolic extract	124.60±2.03	124.40±3.14	0.93
Aqueous extract	121.40±1.86	141.20±3.84	0.26
Low dose Ethanolic extract	116.00±1.87	105.20±5.61	0.08
Low dose Aqueous extract	119.60±3.26	131.60±4.41	0.00
High dose Ethanolic extract	125.00±3.53	112.00±2.54	0.33
High dose Aqueous extract	122.00±1.22	140.20±3.05	0.45

Data is presented as Mean ± S.E of 4 animals each per group

Biochemical parameters

Table 5: Effects of *Artocarpus heterophyllus* administration and HgCl2 treatment on biochemical parameters of rat blood

Groups	MDA (µmol/mg)	GSH (ug/ml/mg)	GPX (units/mg)	SOD (units/mg)	CAT (Units/mL)
Normal	0.55 ±0.02	2.04 ±0.02	0.89 ±0.002	0.23 ±0.02	4.42 ±0.015
HgCl2	0.91 ±0.27	0.74 ±0.29	0.03 ±0.001	0.31 ±0.25	4.53±0.085
Ethanolic extract	0.51±0.02	0.63±0.02	0.03±0.003	0.21±0.01	3.64±0.051*
Aqueous extract	0.56±0.07	1.22±0.30	0.05±0.013	0.22±0.08	3.94±0.419
Low dose Ethanolic extract	0.64±0.03	0.67±0.06	0.03±0.003	0.12±0.02	3.35±0.040*
Low dose Aqueous extract	0.56±0.03	1.05±0.03**	0.05±0.003****	0.17±0.02	3.73±0.749***
High dose Ethanolic extract	0.63±0.04	1.82±0.04	0.081±0.003*	0.12±0.02	3.83±0.043
High dose Aqueous extract	0.56±0.04	0.67±0.02	0.032±0.001	0.17±0.03	4.48±0.961****

MDA: malondialdehyde, SOD: Superoxide dismutase, CAT: Catalase, GSH: Reduced Glutathione and GPX. *Indicates statistical significance at P≤0.05 *Artocarpus heterophyllus* aqueous and ethanolic extract, HgCl2 –Mercury chloride. *P< 0.05 versus Control, **P< 0.05 versus HgCl2, ***P< 0.05 versus aqueous extract, ****P< 0.05 versus ethanolic extract

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Behavioral Studies

Table 6:Effects of *Artocarpus heterophyllus* administration and HgCl2 treatment on animal behavior

Groups	Basal forelimb grip (Sec)	Treatment forelimb grip (Sec)
Normal	4.38 ± 1.65	5.05 ± 0.40
HgCl2	5.08 ± 1.05	1.36 ± 0.25
Ethanolic extract	4.23 ± 0.57	2.21 ± 0.32
Aqueous extract	4.43 ± 0.36	4.51 ± 0.24
Low dose Ethanolic extract	4.19 ± 0.36	1.14 ± 0.11
Low dose Aqueous extract	4.43 ± 1.15	3.45 ± 0.46
High dose Ethanolic extract	5.10 ± 1.08	2.23 ± 0.62
High dose Aqueous extract	5.05 ± 1.10	4.02 ± 0.13

Data is presented as Mean ± Standard deviation of 4 rats in each group

Data presented in Table 5 shows that HgCl2 elevated MDA and reduced GSH and GPX levels significantly ($p<0.05$) relative to control. Similarly, it increased the activity of the enzymes SOD and CAT relative to control. However, in rats co-treated with aqueous and ethanolic extract of *Artocarpus heterophyllus* (Jack fruit), all the induced changes were significantly ($p<0.05$) reversed to near control values when compared with HgCl2 treated animals and statistically significant difference seen within groups at $P < 0.05$. As displayed in Table 6, HgCl2 administration decreased the forelimb grip relative to control, while the aqueous extract of *Artocarpus heterophyllus* administration increased in forelimb grip compared to control and basal. However, concomitant administration of *Artocarpus heterophyllus* with HgCl2 significantly increased forelimb grips relative to HgCl2 and control.

DISCUSSION

In this study, we presented data showing that rats given 0.5 mg/kg of mercuric chloride (HgCl2) for 14 days experienced alterations in oxidative, behavioral, and histological parameters. These alterations were lessened in these rats when 200 and 400 mg/kg of an ethanolic and aqueous extract of *Artocarpus heterophyllus* were given concurrently with HgCl2. Although the fact that neurotoxicity caused by mercury chloride (HgCl2) is a well-documented phenomenon, there are currently no viable treatments for mercury poisoning. Actually, because of their unfavorable side effects, chelating agent treatments to remove mercury from the tissues are not very effective. According to research published in the literature in recent years, oxidative stress is the primary mechanism via which mercury (Hg) causes harm to the central nervous system (CNS) [24]. The protective effect of *Artocarpus heterophyllus* against Hg-induced neurotoxicity in vivo has been demonstrated for the first time in this work; our results also support further research on *Artocarpus heterophyllus* advantageous effects on oxidative stress and behavioral changes. In the present investigation, we observed that *Artocarpus heterophyllus* protects against neurotoxicity caused by mercury. There is evidence that mercury damages the cerebellum, which in turn affects the motor system [25,26]. We conducted a rotarod experiment in this regard to observe motor deficiency, memory, and recognition. In HgCl2, we saw a motor deficit. This study assessed the nutritional contents of boiled jackfruit. The results of the study's quantitative phytochemical analysis of the boiled jackfruit showed that it had significant concentrations of tannins, steroids, saponins, flavonoids, and alkaloids (Table 1). The antioxidant flavonoid helps to avoid oxidative damage. It is well known that flavonoids and phenols, or tannins, have strong antioxidant activity [27,46,54]. The result of quantitative phytochemical analysis of boiled jack fruit used in the study revealed that it possesses good antioxidant activity and therefore suggests that its diets could be useful in scavenging free radicals in the body. This is consistent with the findings of Phukan et al. [28], who suggested that the diet could be used to cure anemia because of the high iron concentration of jackfruit seeds. Antioxidant phytochemicals and antioxidant mineral components are thus present in boiled jack fruit. This implies that consuming boiled jackfruit may help the body scavenge free radicals and stave off oxidative stress.

Furthermore, the study's proximate analysis of the boiled jackfruit revealed that it had a moderate protein percentage and a high carbohydrate content. The study's proximate composition of jackfruit agrees with Isinenyi and Nwaka's [29] report, which also found that jackfruit seeds had a significant amount of fat and protein and approximately 42% carbohydrates. Table 2 indicates that the high carbohydrate and protein content of jackfruit makes it a potential source of energy when digested. Its composition, which is abundant in protein, may help to strengthen the body system [30].

One of the organs most severely impacted by mercury poisoning is the nervous system, which can result in a variety of neuropathologies and cognitive impairments. The Hg-induced group had higher levels of TBARS (thiobarbituric acid-reactive compounds) in the cerebellum. It serves as a lipid peroxidation marker. In the current investigation, we found that the administration of HgCl2 markedly increased the generation of ROS in the cerebellum and

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proposed that this metal's promotion of oxidative stress is linked to the observed motor impairment. Compared to the control group, the induction of mercuric chloride resulted in a significant increase in oxidative stress due to the decrease of antioxidants such as SOD, catalase, GPx, and GSH, as well as an increase in MDA. Consistent with the current investigation, an earlier study examined the protective effects of vitamin E and Lactobacillus plantarum against the neurotoxicity caused by mercuric chloride. According to Fadda et al. [24], mercuric chloride was found to have a considerable negative impact on both GSH levels and SOD activity, suggesting heightened oxidative stress. In another study, the administration of methyl mercury decreased the levels of enzymatic and nonenzymatic antioxidants, such as SOD and GSP, which led to oxidative damage to proteins, lipids, and DNA. It also improved the restriction of lipid metabolism in animal brains, influencing the metabolism of triglycerides, cholesterol, and total lipids, resulting in an imbalance between the synthesis and breakdown of lipids. Mercuric chloride produces reactive oxygen species (ROS) in tissues and raises MDA levels, which suggests that unsaturated fatty acids are being oxidized in the brain. This alteration in the anti-oxidative defense system occurs in both humans and experimental animals. [31,5,45]. When comparing the cerebellum of rats exposed to HgCl2 to the control group, the activity of glutathione peroxidase (GPx) was considerably reduced. GPx uses up GSH in the process of reducing hydrogen peroxide, phospholipid hydroperoxide, and other organic hydroperoxides. As the primary cytosolic antioxidant, GSH is essential for preserving the intracellular redox state and for scavenging reactive oxygen species (ROS) through the enzyme GPX. In the cerebellum of the HgCl2-induced group, GSH levels were lower. Antioxidants that produce conditions related to oxidative stress, such as SOD and CAT, are involved in reducing damage caused by free radicals. In the HgCl2-induced group, SOD and CAT activity were found to be considerably lower. We concluded from our data that there was a decline in SOD and CAT activity.

Interestingly, the biochemical changes were eliminated when HgCl2 was given concurrently with *Artocarpus heterophyllus*, indicating a possible connection between the two, much like oxidative stress in the cerebellum. Both high and low dosages of ethanolic and aqueous *Artocarpus heterophyllus* intake were able to stop the rise in ROS production caused by HgCl2 exposure in the brain, demonstrating antioxidant activity in vivo and a statistically significant difference from rats that were not treated with HgCl2. Some peptides have redox characteristics that enable them to function as reducing agents, hydrogen donors, and singlet oxygen quenchers. These characteristics are primarily responsible for their antioxidant activity. Furthermore, according to Ding et al. (2015), they possess a metal chelation capability. The ability of flavonoids and tannins to scavenge free radicals is linked to their abundance [32,51,52]. Also, MDA was reduced and GSH, GPx, SOD, and CAT activities were increased after treatment with ethanol and an aqueous extract of *A. heterophyllus*. The plant's high levels of phytochemicals can be linked to this decrease. This suggests that there are plant chemicals in the ethanol and aqueous extract of *A. heterophyllus* that may be able to lower the increased MDA levels. We propose that the antioxidant effect of *A. heterophyllus* on the oxidative stress observed in the brain in this study is likely due to its metal chelating and subsequent free radical scavenging activity, taking into account that the main components of the extract are flavonoids, saponins, steroids, alkaloids, and tannins. The decreased MDA value observed in the Mercuric chloride treated group could confirm the chelating activity of *A. heterophyllus*. This technique is based on the power of the sample to donate electrons to reduce ferric chloride added to the medium and indicates the antioxidant capacity of the sample as a reducing agent. The decreased values in the group that received both treatments indicate a possible bond between HgCl2 and *A. heterophyllous* present in the sample, avoiding the donation of electrons to the ferric ion.

The hanging wire test was employed in this study to examine fine motor coordination, and the time it took the mice. The present showed that the administration of HgCl2 was neurotoxic and affected motor coordination among the test animals, as indicated by the decrease in the time taken in the grip strength test; this could be attributed to a cortical impact lesion. Similarly, since is the focal neuron of the cerebellum, Purkinje cell death will inevitably affect the coordinating role of the cerebellum as regards movement of voluntary skeletal muscle, posture, and gait leading to such features as muscular hypotonia, intentional tremor, and nystagmus. The decrease in forelimb strength in rats treated with HgCl2 was consistent with the findings of Owoeye and Farombi [33], who also reported a decline in a similar study. However, all of the treatment groups showed an improvement in coordination when *A. heterophyllus* was administered. This discovery could corroborate the earlier study on the potential anti-inflammatory benefits, reduced anxiety, free radical scavenging, and inhibition of oxidative generation linked to mercury [34, 44]. The damage to the histoarchitecture caused by the toxicity of HgCl2 is evident in the degeneration of Purkinje cells and the total loss of neurons found in the cerebellum after treatment (fig. 1). Purkinje cell depletion is consistent with other studies [35,33]. Exposure to HgCl2 was linked to degenerative changes in the cerebellar cortex's Purkinje layer, as evidenced by the population of Purkinje cells declining and the emergence of pyknotic Purkinje cells. The results could corroborate earlier research by Ayuba et al. [36,35] which found that exposure to aluminum chloride caused degenerative and necrotic alterations in the Purkinje cells of the cerebellar cortex's Purkinje cell layer. Cerebellar injuries frequently impact changes in fine motor function, balance, posture, and motor learning. Learning and fine motor function can be hindered by damage to the Purkinje cells in the cerebellum. This damage may have resulted from chromatin condensation, which kills cells. Due to the blood-brain barrier (BBB) in the

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cerebellum's vulnerability to mercury toxicity [14]. Similar to this, Purkinje cell death will unavoidably impact the cerebellum's coordinating function with regard to voluntary skeletal muscle movement, posture, and gait, resulting in characteristics like purposeful tremor, nystagmus, and muscular hypotonia (Snell, 2006). This is because is the cerebellum's focal neuron. Mercuric chloride has the potential to cause damage to the BBB through the production of RECA-1 and extravasation of endogenous IgG [14]. Our findings are in line with those of Olivier et al., (2021), who found glial cell multiplication and granular cell loss beneath the Purkinje cell layer.

Rats were concurrently exposed to HgCl2 and given 200 and 400 mg/kg of ethanolic and aqueous extract orally to evaluate the protective therapeutic potential of *A. heterophyllus* extract. The cerebellar cortex's histoarchitecture showed normal histoarchitecture in comparison to the control group. Hussain et al. [37] investigated the role of plant-derived alkaloids and their mechanisms in neurodegenerative disorders and found that plants containing these compounds have potential therapeutic effects against a range of neurodegenerative diseases. The proven medicinal potential of *A. heterophyllus* may be explained by the presence of phytochemicals such as alkaloids, flavonoids, polyphenols, and steroids that are present in the plant. This indicates that the observed cell recovery may be caused by the presence of such phytochemicals. Comparing group E-H (fig. 1) to the control group, concurrent administration of HgCl2 and *A. heterophyllous* extract demonstrated normal histoarchitecture of the cerebral cortex, hippocampus, and cerebellar cortex.

CONCLUSION

The study revealed that rats exposed to HgCl2 in the cerebellum experienced decreased Purkinje cell, loss of neuromuscular function, imbalance, and impaired coordination. Nonetheless, adult male rats treated with *A. heterophyllus* showed therapeutic benefit in preventing HgCl2-induced neurotoxicity. Moreover, the ameliorative changes observed in biochemical and histologically studies across all the groups concurrently treated with *A. heterophyllus* and HgCl2 suggests the potency of the antioxidant potential of *A. heterophyllus* to reduce most of the above implications in the rats affected. It would be beneficial to separate the phytoconstituents of *Artocarpus heterophyllus* and assess their potential for use as a treatment in the control of neuroprotection.

CONSENT

It is not applicable.

ETHICAL APPROVAL

Animal Ethic committee approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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