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Effects of Aqueous Extract of *Syzygium aromaticum* (Clove) On Mercury Chloride-Induced Toxicity in The Hippocampus of Adult Wistar Rats

Akporufuoma Racheal Orheruata *, Fredrick Ohiomokhai Tobalu

Department of Anatomy, School of Basic Medical Sciences, College of Medical Sciences, University of Benin, Edo State, Nigeria.

Author for Correspondence*: racheal.orheruata@uniben.edu/+234-706-466-9673.

<https://dx.doi.org/10.4314/sokjmls.v10i1.9>**Abstract**

Mercury is a neurotoxic substance that crosses the blood-brain barrier and disrupts neuronal functions by inducing oxidative stress (OS), impairment of neurotransmission, and neuronal damage, resulting in cognitive and motor dysfunction. Since OS is one of the mechanisms of actions of mercury, reports suggest that antioxidant-rich plants can attenuate its effects. Accordingly, this study investigated the effect of aqueous extract of *Syzygium aromaticum* (AESA) on mercury chloride-induced hippocampal toxicity in adult Wistar rats. Thirty-six (36) rats were randomized into six groups of six rats each. Group A (Control), B [4 mg/kg mercury chloride (HgCl₂)], C (250 mg/kg AESA), D (500 mg/kg AESA), E (4 mg/kg HgCl₂ and 250 mg/kg AESA) and F (4 mg/kg HgCl₂ and 500 mg/kg AESA). All administration was via oral route and lasted for 28 days. At the end of the experimental period, rats were weighed, euthanized via cervical dislocation, brain harvested, weighed and analyzed for biochemical and histological changes. Findings from the study revealed that *Syzygium aromaticum* is a nutrient-rich plant as indicated by its high content of bioactive compounds like glycosides, phenols, flavonoids, alkaloids and eugenols. There was a significant decrease ($p < 0.05$) in body weight, SOD, CAT, GPx activity, as well as a significant increase ($p < 0.05$) in MDA concentration in rats treated with HgCl₂ only when compared to control. A significant increase ($p < 0.05$) in body weight, SOD, CAT, GPx activity as well as a significant decrease ($p < 0.05$) in MDA concentration was

observed in rats treated with AESA when compared to HgCl₂ only group. Histological findings revealed atrophy and vacuolation of the pyramidal cells and astrocytes in the hippocampus of rats treated with HgCl₂ only when compared to control. However, normal pyramidal cells of the hippocampus (CA1) were observed in HgCl₂-exposed rats pretreated with AESA comparable to the rats treated with HgCl₂ only. Conclusively, *S. aromaticum* possesses significant neuroprotective effects, suggesting its potential as a therapeutic agent in the prevention and management of neurodegenerative disorders.

Keywords: *Syzygium aromaticum*, mercury, neurotoxicity, hippocampus

Introduction

Mercury, a toxic heavy metal, has been utilized for medicinal and poisonous purposes for centuries and continues to be employed in various commercial applications (Broussard *et al.*, 2002). However, growing concerns about environmental exposure have renewed public interest. Notable sources of mercury exposure that have gained public attention include contaminated seafood consumption, infant vaccinations, dental fillings, and traditional remedies (Broussard *et al.*, 2002). Mercury has multiple toxic effects, which is influenced by the type of compound and the route of exposure. Nevertheless, its neurotoxic effects, which have severe health implications, are the primary concern for toxicology experts (Branco *et al.*, 2021).

Over 80% of the global population relies on medicinal plants to treat health issues, as these plants contain essential bioactive compounds that are vital for drug development (Khare *et al.*, 2019). A substantial number of medicinal plants have demonstrated significant therapeutic benefits, including, antioxidant, anti-inflammatory, anticancer, antiseptic, anti-depressant, antiviral, antifungal, and antibacterial activity properties and *Syzygium aromaticum* is one of such plants (Batiha *et al.*, 2020). *Syzygium aromaticum*, commonly referred to as clove, is the dried, unopened flower bud of a tree native to Indonesia's Maluku islands, now cultivated in various regions globally (Cortés-Rojas *et al.*, 2014). It is regarded as a promising natural preservative for various food products, particularly in meat processing, owing to its antioxidant and antimicrobial properties, which could potentially replace synthetic preservatives (Cortés-Rojas *et al.*, 2014). Clove essential oil (CEO) has been traditionally utilized for its medicinal properties, including treating burns, wounds, tooth infections, and toothaches, as well as providing pain relief in dental care (Batiha *et al.*, 2020). Additionally, CEO has industrial applications and is widely used in the production of perfumes, soaps, and as a cleaning agent in histological preparations (Sarrami *et al.*, 2002). Reports also suggest *S. aromaticum* has neuroprotective activity, its efficacy in inhibiting degenerative diseases is largely due to its high concentration of chemical constituents, which possess high antioxidant activity (Astuti *et al.*, 2019).

Materials and Methods

Plant Material

Syzygium aromaticum was obtained from Lagos Street market, 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, and assigned an herbarium number UBH-S385. Ten grams of the sample were weighed and transferred into an electric blender. One hundred milliliters (100 ml) of cool boiled-out distilled water was added and then blended for 30 minutes. The mixture was transferred into a clean, dry sample bottle and allowed to stand for 72 hours. After 72 hours, the mixture was then filtered into another clean, dry sample bottle which was adequately labeled and corked.

Phytochemical Screening

The qualitative screening of the chemical composition of *S. aromaticum* was done using standard methods. Alkaloids, glycosides, tannins, phenols, saponins, flavonoids, eugenols, steroids, and terpenoids were assayed for. Briefly, for alkaloids, 2 ml of the plant extract was evaporated to dryness. Then the resultant residues were dissolved in 5 ml of HCl (2 mol/dm³) and filtered. The filtrate was divided into two test tubes. To the first test tube, a few drops of Mayer's reagent were added, and the formation of a yellow-coloured precipitate indicates the presence of alkaloids. The second test tube was treated with a few drops of Wagner's reagent, and the brownish-red precipitate formation indicates alkaloids. For glycosides, 0.5 mg of the extract was dissolved in about 1 ml of water and then aqueous NaOH solution was added. The formation of a yellow color indicates the presence of glycosides. For tannins, to 1 ml of the extract, 1 ml of 1% gelatin solution containing sodium chloride was added. The formation of a white precipitate indicates the presence of tannins. For phenols, 1 ml of the plant extract was treated with 4 drops of ferric chloride solution. The formation of a bluish-black colour indicates the presence of phenols. For saponins, 0.5 g of the plant extract was shaken with 2 ml of distilled water. The formation of foam which persists for 10 minutes indicates the presence of saponin. For flavonoids, the plant extract was treated with a few drops of lead acetate solution. The formation of a yellow color precipitate indicates the presence of flavonoids. For eugenols, about 2 ml of the extract was mixed with 5 ml of 5% KOH solution. The aqueous layer was separated and filtered. A few drops of HCl were added to the filtrate. A pale-yellow precipitate was indicative of a positive test. For steroids, 2 ml of acetic anhydride was added to 0.5 g of the extract of each with 2 ml of H₂SO₄. The colour change from violet to blue or green in some samples indicates the presence of steroids. For terpenoids, 0.2 g of the extract of the plant sample was mixed with 2 ml of chloroform (CHCl₃) and concentrated H₂SO₄ (3ml) was carefully added to form a layer. A reddish-brown colouration in the interface indicates positive results for the presence of terpenoids.

Animals

Thirty-six (36) adult Wistar rats weighing between 180 to 190 g were purchased and housed in the Animal House of the Department of Anatomy, University of Benin, Benin City. They were kept in clean cages and allowed access to feed (Grower's mash, a product of Premier Feed Mills Co Ltd) and water ad libitum throughout the experimental period.

Experimental Design

The thirty-six (36) Wistar rats were randomized into six (6) groups of six (6) rats each and were allowed to acclimatize for two weeks. Group A served as control, group B rats were administered 4 mg/kg mercury chloride (HgCl₂), group C rats were administered 250 mg/kg of aqueous extract of *Szygium aromaticum* (AESA) only, group D rats were administered 500 mg/kg AESA only, group E rats were administered 4 mg/kg HgCl₂ and 250 mg/kg AESA and group F rats were administered 4 mg/kg HgCl₂ and 500 mg/kg AESA. Administration was done via the oral route and lasted for 28 days.

Determination of Body Weight

After the last day of administration, the rats were euthanized with low level anesthesia, followed by cervical dislocation. The rats' brains were excised from their skulls, blotted clean of blood and weighed and recorded in the nearest decimal.

Assessment of Biochemical Parameters

The brains were homogenized in ice-cold 20 mM

Tris-HCl buffer (pH 7.4), and the homogenates were then centrifuged at 10,000 g for 10 minutes at 4 °C (Montilla et al., 2005). The supernatants were collected and evaluated for superoxide dismutase (Misra and Fridovich, 1972), catalase (Cohen, 1983), glutathione peroxidase (Nyman, 1959) and malondialdehyde (Buege and Aust, 1978).

Histological Evaluation

The hippocampi were fixed in 10% buffered formal saline for 72 hours. Thereafter, samples were processed through the paraffin wax embedding method as previously reported. The haematoxylin and eosin staining (Drury and Wallington, 1980) was also performed.

Statistical Analysis

The data were analyzed using the IBM statistical package for social science (SPSS) version 20. Values were presented as mean ± standard error of mean (SEM), and one-way analysis of variance (ANOVA) followed by Tukey's multiple comparisons post hoc test was used to determine statistical significance (p<0.05).

Results

Phytochemical Screening

The qualitative phytochemical screening showed that *S. aromaticum* contains a diverse range of bioactive compounds like alkaloids, glycosides, tannins, phenols, saponins, flavonoids, eugenols, and terpenoids. This suggests that *S. aromaticum* is rich in phytochemical constituents.

Table 1: Qualitative phytochemical screening of aqueous extract of *S. aromaticum*

Phytochemicals	Result
Alkaloids	+
Glycosides	++
Tannins	+
Phenols	+
Saponins	+
Flavonoids	+
Eugenols	+
Steroids	-
Terpenoids	+

Key: Present (+), highly present (++), absent (-)

Effect of Treatment on Body and Brain Weights

Figure 1 shows the change in body weights of rats across the experimental groups. There was a significant decrease ($p < 0.05$) in the body weight change of rats treated with HgCl₂ only when compared to control, however, there was a significant increase ($p < 0.05$) in body weights change of rats treated with AESA only and in HgCl₂-exposed rats pretreated with AESA when compared to HgCl₂ only.

Figure 2 shows the whole brain weight (A) and relative brain weights (B) of rats across the experimental groups. There was no significant difference ($p > 0.05$) in both the whole brain and relative brain weights of rats across the groups.

Effect of Treatment on Antioxidant Enzymes Activity and Lipid Peroxidation

Figure 3 shows the effect of treatment on antioxidant enzymes (SOD, CAT and GPx) activity and lipid peroxidation (MDA) concentration across experimental groups. There was a significant decrease ($p < 0.05$) in SOD activity of rats treated with HgCl₂ only when compared to control, however, there was a significant increase ($p < 0.05$) in SOD activity of rats treated with AESA only and in HgCl₂-exposed rats pretreated with AESA when compared to HgCl₂ only. There was a significant

decrease ($p < 0.05$) in CAT activity of rats treated with HgCl₂ only when compared to control, however, there was a significant increase ($p < 0.05$) in CAT activity of rats treated with AESA only and in HgCl₂-exposed rats pretreated with AESA when compared to HgCl₂ only. There was a significant decrease ($p < 0.05$) in GPx activity of rats treated with HgCl₂ only when compared to control, however, there was a significant increase ($p < 0.05$) in GPx activity of rats treated with AESA only and in HgCl₂-exposed rats pretreated with 500 mg/kg AESA when compared to HgCl₂ only. There was a significant increase ($p < 0.05$) in MDA concentration of rats treated with HgCl₂ only when compared to control, however, there was a significant decrease ($p < 0.05$) in MDA concentrations of rats treated with AESA only and in HgCl₂-exposed rats pretreated with AESA when compared to HgCl₂ only.

Effects of Treatment on Histology of the Hippocampus

Figure 4 shows the histological sections of the hippocampus (CA1) stained with H&E, revealing normal morphology in both the control and *S. aromaticum*-treated groups, with normal pyramidal cells. However, HgCl₂-treated rats showed atrophy and vacuolation of both the pyramidal cells and astrocytes.

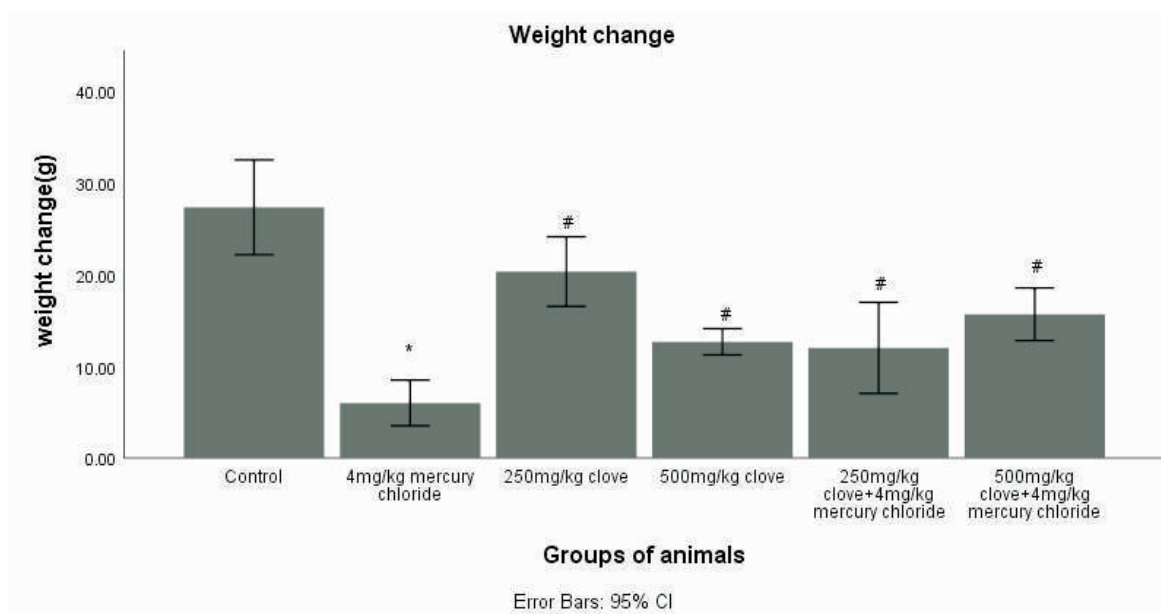
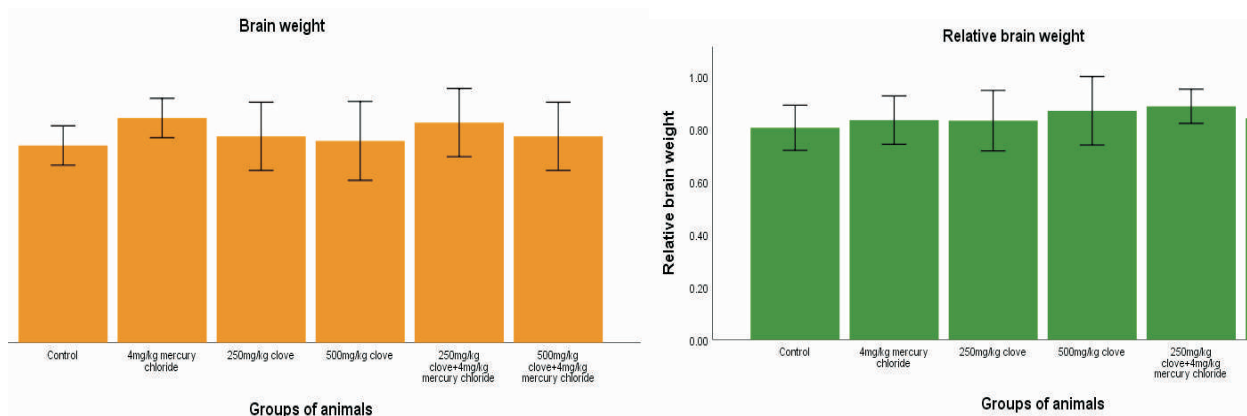


Figure 1: Body weight change of rats across experimental groups. * $p < 0.05$ decrease compared to control. # $p < 0.05$ increase compared to HgCl₂ only group.



Figures 2: Whole brain weight and relative brain weights of rats across the experimental groups.

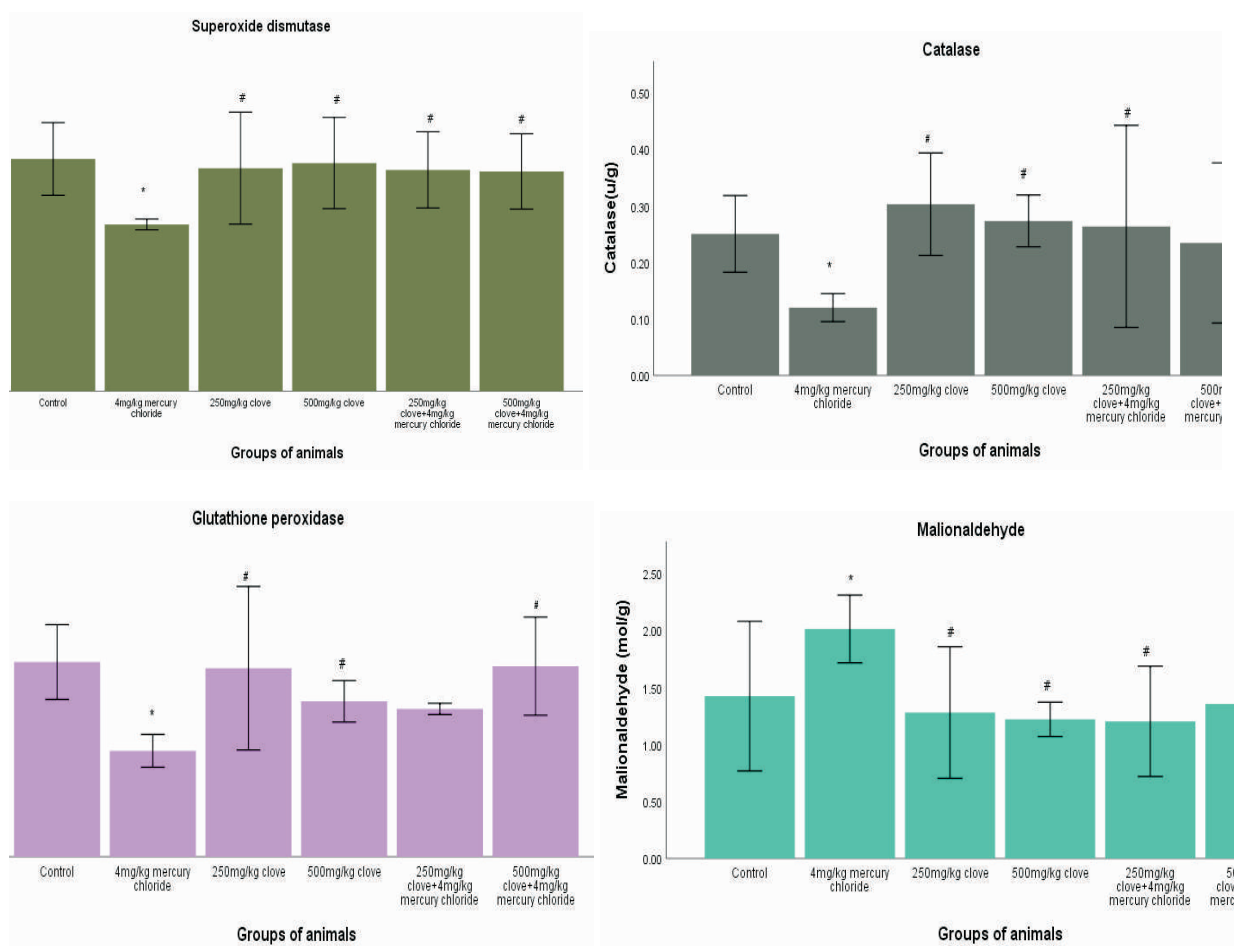


Figure 3: Effect of treatment on antioxidant enzymes (SOD, CAT and GPx) activity and lipid peroxidation (MDA) concentration across experimental groups

Key: * $p < 0.05$ decrease compared to control. # $p < 0.05$ increase compared to HgCl₂ only group.

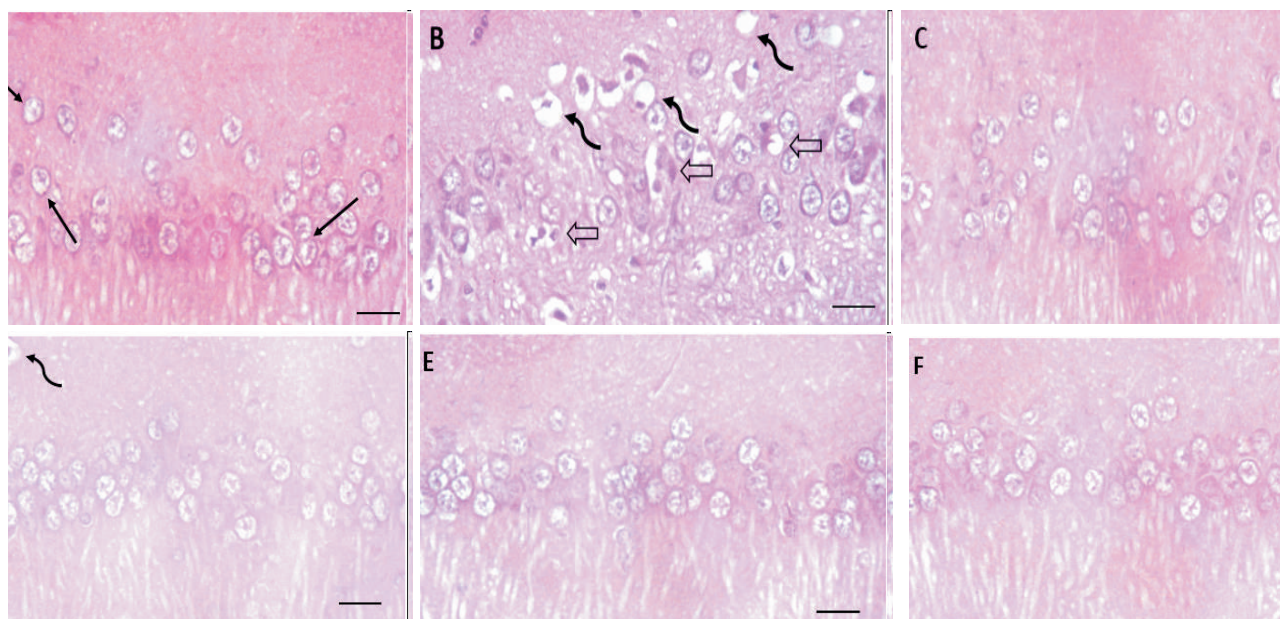


Figure 4: Photomicrograph of the hippocampus across the experimental groups (A-F). A control [showing normal pyramidal cells (black arrows)], B 4 mg/kg HgCl₂ [showing vacuolated pyramidal cells (transparent arrows) and atrophied astrocytes (curved arrows)], C 250 mg/kg AESA only (showing normal pyramidal cells), D 500 mg/kg AESA only (showing relatively normal pyramidal cells with mild vacuolation [curved arrow]), E 250 mg/kg AESA + HgCl₂ (showing normal pyramidal cells) and F 500 mg/kg AESA + HgCl₂ (showing normal pyramidal cells). (H&E 400x; Scale bar: 25µm).

Discussion

As one of the world's most valuable medicinal plants, *S. aromaticum* and its essential oil are widely employed in folk medicine, the food industry, and cosmetic production, leveraging their broad pharmacological potential (Barak *et al.*, 2024). The nutritional profile of *S. aromaticum* is characterized by an abundance of essential compounds, such as amino acids, proteins, fatty acids, and vitamins (Xue *et al.*, 2022). Results from the preliminary phytochemical analysis revealed that the plant contains a diverse range of bioactive compounds, including alkaloids, glycosides, tannins, phenols, saponins, flavonoids, eugenols, and terpenoids. This is consistent with findings from previous studies (Sadiq *et al.*, 2019; Bharadwaj, 2020). Research has identified numerous potential health benefits associated with these compounds, including their capacity to combat oxidative stress, inflammation, cancer, and microbial infections, as well as their potential to support mental health and overall well-being, making them potential therapeutics for the prevention and management of many

health disorders (Batiha *et al.*, 2020). The phenolic compounds and flavonoids present in *S. aromaticum* contribute to its antioxidant and anti-inflammatory activities (El-Maati *et al.*, 2016; Xue *et al.*, 2022). Phenols have been shown to exert anti-inflammatory effects through multiple mechanisms, including the inhibition of pro-inflammatory enzymes like LOX and COX, as well as modulation of cellular signaling pathways such as Nuclear factor-kappa B (NF-κB), Mitogen-activated protein kinase (MAPK), and phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt), ultimately leading to reduced inflammation (Liu *et al.*, 2023). Reports suggest that saponins may contribute to the regulation of excessive immune responses (Lacaille-Dubois, 2005; Tezuka and Imai, 2024). Accumulating evidence have shown that eugenol demonstrate a potent free radical scavenging, antioxidant, and antimicrobial activities (Fu *et al.*, 2007; Kamatou *et al.*, 2012).

Studies have shown that changes in body weight can be a crucial indicator of overall health and well-being in animal models, offering a valuable

tool for assessing their general health condition and detecting potential health issues (Ullman-Culleré and Foltz, 1999; Al-Shabanah *et al.*, 2002). Findings from this study showed a significant decrease in body weights of rats treated with HgCl₂ only compared to control. This corroborates previous study by Enogieru and Colleague (2022) who also reported a significant reduction in the body weight of rats treated with HgCl₂. Studies have shown that metal toxicity can lead to considerable weight loss in rats if not treated (Nwokocha *et al.*, 2012; Fiati Kenston *et al.*, 2018). The weight loss associated with metal toxicity may be attributed to depletion of nutrients, impaired protein production, and disrupted metabolic processes (Oyewole and Oladele, 2017). Findings from this study revealed no significant difference in whole brain and relative brain weights of rats treated with HgCl₂ only when compared to control. This is similar to previous studies by Owwoye and colleagues who reported no significant change in brain weights of rats exposed to HgCl₂ despite its toxicity (Owwoye *et al.*, 2018).

Recent studies have indicated that antioxidants play a crucial role in mitigating oxidative stress by neutralizing free radicals, thereby enhancing immune function and promoting overall health and longevity (Tan *et al.*, 2018). Findings from the study showed a significant decrease in SOD activity in rats treated with HgCl₂ only when compared to control. Our findings corroborate the previous study by Ercal and Colleagues (2001) who reported that exposure to HgCl₂ induces oxidative stress which in turn results in depletion of SOD activity. However, a significant increase in SOD activity was observed in HgCl₂-exposed rats pretreated with AESA, as well as AESA only treated groups when compared to HgCl₂ group. This is consistent with previous reports by Zhang and Colleagues (2021) who stated that treatment with *S. aromaticum* extract may have triggered an antioxidant response, leading to increased SOD production. A significant decrease in CAT activity was observed in HgCl₂ group when compared to control. Mercury chloride may have directly inhibited CAT enzyme activity, HgCl₂ can damage cells, leading to reduced CAT production (Shalan, 2022). A significant

increase in CAT activity was observed in HgCl₂-exposed rats pretreated with AESA, as well as AESA only treated groups when compared to HgCl₂ group. Our findings also revealed a significant decrease in GPx activity in HgCl₂ group when compared to control, however, pretreatment with AESA attenuated the toxic effects of HgCl₂ and caused a significant increase in GPx activity when compared to HgCl₂ group. Results from the study showed a significant increase in MDA concentration of rats treated with HgCl₂ only when compared to control. This is consistent with previous studies that reported increase in MDA concentration after exposure to mercury (Baş *et al.*, 2015; Vassallo *et al.*, 2019). However, pretreatment with AESA mitigated the effect of mercury thereby resulting in a significant decrease in MDA concentrations in the AESA groups. The reduction in MDA concentration could be attributed to reduced oxidative stress, leading to decreased MDA levels (Alizadeh and Kheirouri, 2019). This improvement in the brain antioxidant defense system could be attributed to the potent antioxidant property of *S. aromaticum*.

Histological findings play a pivotal role in advancing biomedical and clinical research by providing essential insights into the microscopic structure and organization of tissues (Gurcan *et al.*, 2009). These findings enable researchers to study cellular morphology, tissue architecture, and pathological alterations, which are critical for understanding disease mechanisms, evaluating therapeutic interventions, and developing novel treatments (Gurcan *et al.*, 2009). Histological findings from this study demonstrated that the hippocampus of HgCl₂-exposed rats showed distinct changes specifically in the CA1, ranging from atrophy of astrocytes and vacuolation of the pyramidal cells. These alterations suggest cellular damage and disruption of normal cellular function, potentially leading to cognitive impairment. These findings agree with previous studies (Wu *et al.*, 2016; Aragão *et al.*, 2018). Conversely, HgCl₂-exposed rats pretreated with AESA exhibited substantial protection against hippocampal histological alterations, implying a potential reduction in mercury-induced neurodegenerative effects.

Conclusively, *S. aromaticum* exhibits neuroprotective effects against HgCl₂-induced hippocampal damage, and this is attributed to its antioxidant properties, which help attenuate oxidative stress, minimize neuronal damage, and maintain cognitive functions.

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Conflict of Interest: None declared

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