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Original Article

Cola acuminata Mitigates Cognitive Deficit and Oxidative Stress in Mercury Chloride-induced Neurotoxicity in Male Wistar Rats

Abraham O. Asuku[1], Maryam T. Ayinla[2], Tobiloba S. Olajide[2], Zaidat Yakub[2], Bamidele V. Owoyele[2]

[1]Department of Medical Biotechnology, Bioresources Development Centre, National Biotechnology Development Agency, Ogbomoso, Nigeria: [2]Department of Physiology, Faculty of Basic Medical Sciences, College of Health Sciences, University of Ilorin, Ilorin, Nigeria

ABSTRACT

Cola acuminata is used in traditional medicine for the management of memory impairment and other neurodegenerative conditions. This study investigated the effects of *Cola acuminata* aqueous leaves extract (ALECA) on mercury chloride-induced neurotoxicity in Wistar rats. Twenty male Wistar rats weighing between 160 and 210 g were randomly assigned to four groups (n = 5). The control group received 0.5 mL of distilled water; the mercury chloride ($HgCl_2$) group received $HgCl_2$ (5 mg/kg b.w.); the ALECA100 and ALECA300 groups received ALECA (100 and 300 mg/kg b.w., respectively), followed by the administration of $HgCl_2$ (5 mg/kg b.w.) for two weeks. The rats were subjected to behavioural tests in the Morris water maze and light and dark field box. The rats were then sacrificed to obtain their brains, which were homogenized for biochemical assays of acetylcholinesterase (AChE), malondialdehyde (MDA), total protein (TP), and glutathione (GSH) using standard methods. The results revealed a significant increase in escape latency, a significant decrease in probing frequency and brain GSH, and a significant ($p<0.05$) increase in brain MDA and TP levels and AChE activity in the rats exposed to $HgCl_2$. However, administration of either 100 or 300 mg/kg ALECA protected against memory impairment with a significantly reduced escape latency, increased probing frequency and brain GSH, and decreased ($p<0.05$) MDA, TP and AChE. This study concludes that ALECA mitigated $HgCl_2$-induced neurotoxicity via reduction of oxidative stress and enhanced cholinergic functions.

Keywords
Cola acuminate, Mercury chloride, Oxidative stress, Glutathione, Malondialdehyde

Correspondence: Abraham O. Asuku, MSc; Bioresources Development Centre, National Biotechnology Development Agency, Ogbomoso, Nigeria. E-mail: asufem2017@gmail.com; Phone number: + 2348077427135; ORCID: 0000-0003-0071-0531

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INTRODUCTION

Neurotoxicity is any adverse effect on the structure or function of the nervous system caused by exposure to biological, chemical, or physical agents (Mohammad et al. 2016). Mercury is utilized in many fields, such as industry, agriculture, and medicine (Jha et al. 2019). Mercury is a significant neurotoxicant that predominantly damages brain tissue, impairs brain function, and affects brain structure (Xu et al. 2012). Elemental, inorganic, and organic mercury are the three types of mercury that can be found in the environment.

Mercury (Hg) is present in the environment due to either natural events or anthropogenic sources (UNEP 2013). Natural sources include volcanic eruptions and rock weathering, while anthropogenic sources include industrial consumption of fossil fuels, incineration of solid wastes, contact with topical medicine, accumulated mercury in seafood, cement production, use of mercury measuring instruments, dental amalgam, cosmetics, and artisanal small-scale gold mining. Accumulated mercury in sea foods is the most common source of human consumption (Jha et al. 2019). Routes of exposure could be oral, inhalational, or dermal (Sadeeq et al. 2013). Mercury is a dangerous environmental and industrial neurotoxicant that,

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upon exposure, causes many neurological problems (Xu et al. 2012). Tremor, emotional tenderness, insomnia, memory loss, neuromuscular changes (weakness, muscle atrophy, and muscle withdrawal), headache, and polyneuropathy are the signs and symptoms of mercury exposure (McNutt 2013). Early-stage exposure to mercury compounds results in the development of chronic and irreversible neurodegenerative conditions like Parkinson's disease and Alzheimer's disease (Yorifuji et al. 2011). Mercury has been reported to have adversely affected the central nervous system (Korogi et al. 2011). The cerebral cortex and the cerebellum are the regions of the brain that are most frequently affected by mercury toxicity, according to Xu et al. (2012). Multiple lines of evidence suggest that elevated levels of reactive oxygen species are linked to mercury neurotoxicity (Farina et al. 2011; Mieiro et al. 2011; Ahmed 2015).

Mercury exposure is known to harm essential parts of the central nervous system, primarily through oxidative stress (Enogieru and Omoruyi 2022). Mercury exposure has also been linked to the causes of cognitive deficits and behavioural dysfunction (Cardenas et al. 2017). Mercury toxicity is fast becoming a global problem as its concentration is continuously increasing due to increased domestic, industrial, and medicinal uses. The developing and adult central nervous systems are two of the most susceptible organs affected by mercury toxicity. It harms the primary areas of the cerebral cortex, the hippocampus, and the granule layer of the cerebellum, leading to the loss of neurons in these brain parts (Korogi et al. 2011). Despite extensive research into developing novel medications to combat mercurial toxicity, there are still no efficient cures for this toxin. Chelating agents are used to help the body remove mercury from the tissues (Carvalho et al. 2007). However, due to their unfavourable side effects and inability to pass the blood-brain barrier, these medications seem to be of limited benefit (Martins et al. 2009). Therefore, there is a need to explore options in medicinal plants for the treatment of various neurological disorders. Antioxidants are well known for reducing oxidative stress by scavenging the free radicals produced to stop damage (Farombi and Owoeye 2011). Adding nutritional antioxidants to the diet may help with cognitive impairment and brain damage (Bisson et al. 2008; Head 2009). *Cola acuminata* is a species in the genus Cola, of the family Malvaceae, native to tropical Africa. It is famous for its fruit, the kola nut, which was once used to give manufactured beverages like Coca-Cola their cola flavour.

When chewed, it stimulates the nervous system and is also used as an astringent, diuretic, digestive tonic, and antidepressant (Barwick 2004). Caffeine, theobromine, and kolatine are the active ingredients. Cola is used as a non-addictive stimulant against dysentery, vomiting, headaches, and migraines (Hubert et al. 2015). *Cola acuminata* is a plant that contains alkaloids, saponins, flavonoids, steroids, terpenoids, glycosides, and proteins (Dewole et al. 2013). The antioxidant role of *Cola acuminata* seed has been well documented (Oboh et al. 2014; Ishola et al. 2018; Oboh et al. 2018). However, there is no report on the effect of an aqueous leaf extract of *Cola acuminata* (ALECA) on the cognitive deficit and oxidative stress in mercury chloride-induced neurotoxicity in male Wistar rats. Hence, the present study was designed to examine the possible mitigating role of ALECA on the cognitive deficit and oxidative stress in mercury chloride-induced neurotoxicity in male Wistar rats.

MATERIALS AND METHODS

Collection of Plant Material

Fresh leaves of *Cola acuminata* plant were procured from Ilupeju in Oye Local Government Area of Ekiti State, Nigeria. They were identified and authenticated in the Department of Plant Biology, University of Ilorin, Ilorin, Nigeria with the voucher number UILH/001/701/2021.

Preparation of *Cola acuminata* Leaf Extract

Cola acuminata leaves were dried in a well-aerated and shaded environment. Afterward, it was ground into powder to aid in the percolation of the solvent. A known weight of the powder (140 g) was extracted in two litres of distilled water for 24 h and filtered. The filtrate was concentrated by freeze-drying (Freeze dryer Model: HXLG10-50DG, Hunan Kaida Scientific Instruments Co. Ltd.). The concentrate was refrigerated at 4°C for storage.

Drugs and Reagents

The drug solutions were freshly prepared before use, and all chemicals, drugs, and reagents used were of analytical grade. Mercury chloride (Sigma-Aldrich, Germany) and ketamine (Paksons Pharma Pvt Ltd, India) were utilized in this study. Mercury chloride was dissolved in normal saline and administered according to the body weight.

Procurement and Acclimatization of Animals

Twenty male Wistar rats weighing between 160 and 210 g were procured from the breeding colony of the Department of Biochemistry, University of Ilorin, Ilorin. They were kept in cages and fed with a standard diet and water *ad libitum*, in the animal house of the Central Research Laboratory, College of Health Sciences, University of Ilorin, Ilorin. The rats were kept under standard laboratory conditions (12 h light/dark cycle, temperature: 22±3 ℃) and acclimatized for 14 days before the experiment.

Animal Grouping and Administration

The rats were assigned to four groups, of five animals each, and kept in separate cages during the experiment as follows: Control, mercury chloride only, and *Cola acuminata* leaves extract (ALECA) at 100 and 300 mg/kg body weight (b.w.).

Rats in the control group received 0.5 mL of distilled water orally, rats in the mercury chloride group received 5 mg/kg body weight of mercury chloride orally (Agbon et al. 2016). Those in the ALECA100 received 100 mg/kg body weight of ALECA orally (Ishola et al. 2018) and 5 mg/kg body weight of mercury chloride orally, while the ALECA300 group received 300 mg/kg body weight of ALECA orally (Shama et al. 2011) and 5 mg/kg body weight of mercury

chloride orally. The administrations were conducted in the morning (between 08:00 and 10:00 A.M.), orally and carried out daily for 15 days. The experiment was approved by the Faculty of Basic Medical Sciences, College of Health Sciences' Ethics and Research Committee of the University of Ilorin, and it was carried out in accordance with the guidelines of the National Institutes of Health's Guide for the Care and Use of Laboratory Animals (NIH 2011). On the last day of administration, the Morris water maze (MWM) and modified light and dark box were used to assess spatial memory function.

Behavioural Tests

Morris Water-Maze Test

Spatial memory was assessed using the Morris water maze (Morris 2008) as described by Agbon et al. (2017); Ayinla et al. (2019). The maze consisted of a circular open pool with a depth of 70 cm and a diameter of about 200 cm, which was filled with water up to the 60 cm level. A hidden platform with a top surface of approximately 15 cm was submerged at a depth of 1.5 cm below the water surface during the experiment. By adding milk to the water to make it opaque, the platform was able to blend almost completely into the background. Animals were initially trained to find the platform. The maximum cut-off time limit for swimming was set at 60 s. The timer was stopped when the rat found the invisible platform, and it was then removed but if the rat did not find the platform within the allotted time, the rat was guided onto the platform. After the experiment, the rats were taken out of the water, towel-dried, and returned to their original cages to keep them warm. The escape latency (EL): The time it took to find the hidden platform during the acquisition trial was noted as an index of learning and recorded using a video system. Each rat was subjected to four acquisition trials per day for five consecutive days before the commencement of drug administration. Only the rats that learned were used for the study after the probe test. The animals were tested for spatial and long-term memory abilities after fifteen days of treatment, and a video camera positioned above the centre of the pool recorded the swimming rats. The escape latency was noted as an index of memory.

Light and Dark Box

The light and dark box, a tool often used to assess mood, was altered to test spatial memory (Ayinla et al. 2019). The tool had two compartments: the bright and dark sections. The apparatus measured 50 × 30 × 100 cm, and the two sections were connected by an 8 cm^2 aperture. Before the administrations, rats had three days of training, consisting of three trials per day, and lasting five minutes each. Only the animals that had memorized the opening path between the light and dark compartments at the end of training were utilized in the experiment. The opening path from the dark box was closed with a black plank to establish the formation of memory in rats. Following the reintroduction of animals and their freedom of movement, increased probing of the blocked-exit revealed memory formation. On day 15 (after the last administrations), the rats were reintroduced to the modified light and dark box and allowed to explore the maze for five minutes. An overhead camera (Logitech Webcam, 5MP) recorded the activities. The recorded activities were later analysed by an investigator blinded to the groupings. Each rat's frequency of probing the blocked aperture was recorded as an index of intact/enhanced spatial memory.

Sample Collection

On the last day of administration, and after behavioural assessments, the rats were anaesthetized with an intraperitoneal injection of ketamine (100 mg/kg). Their brains were isolated weighed and homogenized in 0.1 M phosphate buffer solution (pH 7.4). Before biochemical analysis, the homogenate was centrifuged at 3000 rpm for 10 min, and the supernatant separated and kept at -20℃.

Biochemical Analyses

Estimation of Acetylcholine Esterase (AChE) Level

The cholinergic marker, AChE, was estimated using an AChE activity assay kit. The test kit is an improved version of Ellman's procedure (Ellman 1961), in which 5,5-dithiobis (2-nitrobenzoic acid) interacts with thiocholine generated by AChE. This homogenate was incubated for 5 min with 0.1 mL of Ellman's reagent (5, 5-dithiobis 2-nitrobenzoate, DTNB) and 2.7 mL of phosphate buffer. Following the addition of 0.1 mL of freshly made acetylthiocholine iodide (pH 8), the absorbance was measured at 412 nm.

Estimation of Malondialdehyde (MDA) Level

Malondialdehyde (MDA), a marker of oxidative stress was indirectly estimated by determining the 2-thiobarbituric acid reactive substances (TBARS) based on the method of Mihara and Uchiyama (1978). Three millilitre of 1% H_3PO_4 and 1 mL of 0.6% TBA aqueous solution were added to 0.5 mL of 10% homogenate of the tissue sample. The mixture was stirred and heated on a boiling water bath for 45 min, and allowed to cool. Then, 4 mL of nbutanol was added, shaken, and the butanol layer was centrifuged. The optical density was read at 535 and 520 nm accumulation of thiobarbituric acid reactive substances.

Estimation of Reduced Glutathione (GSH) Level

Reduced glutathione was assayed using the method Ellman (1959). Using glutathione reductase and Ellman's reagent, 5-5-dithiobis (2-nitrobenzoic acid (DTNB), a carefully optimized enzymatic recycling method was used in the colorimetric assay. Glutathione reductase reduced glutathione disulphide (GSSG) to reduced glutathione (GSH). DTNB reacts with GSH to produce a yellow colour chromophore, 5 – thionitrobenzoic acid (TNB), and GS-TNB. The glutathione reductase reduced the GS-TNB to GSH and TNB. The absorbance was measured at 415 nm and compared with the standard curve for GSSG.

Estimation of total protein

The Biuret method according to Plummer (1988) was used to estimate the total protein. The 0.0, 0.2, 0.4, 0.6, 0.8, and 1 mL of working standards were pipetted into series of labelled test tubes. A millilitre of the sample was pipetted into another test tube. The volume was made up to 1 mL in

all the test tubes. A tube with 1 mL of distilled water served as the blank. Biuret reagent (3 mL) was added to all the test tubes including the 'blank'. The contents of the tubes were mixed by vortexing and subsequently maintained at 37℃ for 10 min. The contents were allowed to cool to room temperature and their absorbance read at 540 nm against the blank. The standard curve was plotted by taking the concentration of protein along the X-axis and absorbance at 540 nm along the Y-axis. The concentration of protein in the given sample was then determined using this standard curve.

Statistical analysis

Data were expressed as mean ± standard error of the mean (SEM). Statistical analysis was performed with Graph-Pad (Prism 5) statistical software (Lab Archives Computer software, Carlsbad, USA). Test of variance was done using one-way analysis of variance, followed by Newman-Keuls post-hoc test to compare the significant difference among the groups. Statistically significant differences were accepted at $p < 0.05$

RESULTS

In Figure 1, the mercury chloride-treated group showed increase in escape latency (EL) compared with the control, which is an indicator of cognitive impairment (as this group of rats took a longer time to identify the escape platform).

The administration of ALECA (100 and 300 mg/kg b.w.) enhanced memory function as depicted by a significant ($p<0.05$) decrease in EL when compared with the group that received mercury-chloride only.

Also, there was no significant difference between the intervention groups as they show similar pattern (100 mg/kg and 300 mg/kg b.w)

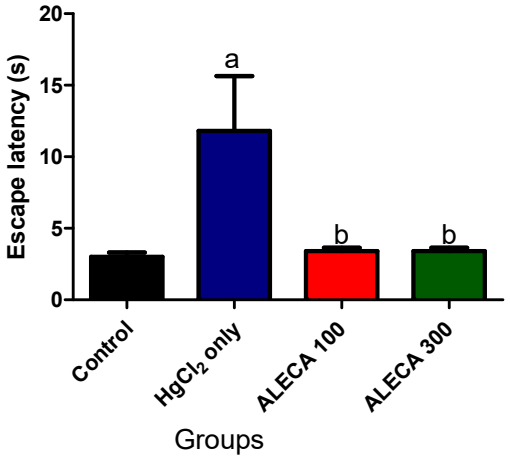

Fig. 1: Effects of *Cola acuminata* aqueous leaves extract (ALECA) on the escape latency in Morris water maze test. Results are expressed as Mean ± SEM of 5 rats per group, $^{a}p < 0.05$ vs. control; $^{b}p < 0.05$ vs. $HgCl_2$. $HgCl_2$ = mercury chloride.

In Figure 2, there was a significant ($p<0.05$) reduction in the probing frequency (number of times the rat visited the escape route/aperture) in the mercury chloride-treated rats when compared with control. Intervention with ALECA (100 and 300 mg/kg) significantly increased the probing frequency compared with mercury chloride group. However, there was no significant difference in the probing frequency between the intervention groups

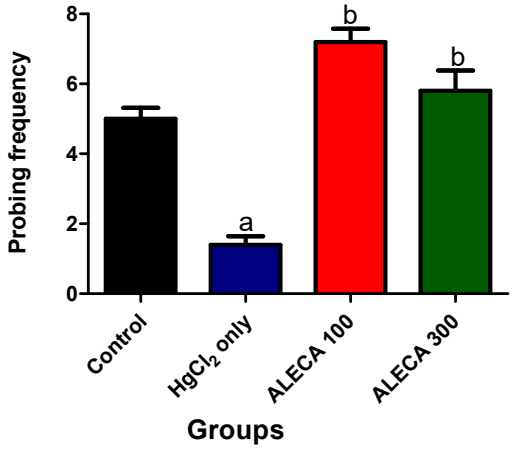

Fig. 2: Effects of *Cola acuminata* aqueous leaves extract (ALECA) on probing frequency in light and dark box test. Results are expressed as Mean ± SEM of 5 rats per group, $^{a}p < 0.05$ vs. control; $^{b}p < 0.05$ vs. $HgCl_2$. $HgCl_2$ = mercury chloride

In Figure 3, the activity of AChE was significantly increased ($p< 0.05$) in the mercury chloride group when compared with control. Conversely, the administration of ALECA (100 and 300 mg/kg) reduced its activity when compared with the merccury chloride group. However, there was no significant difference in between the intervention groups.

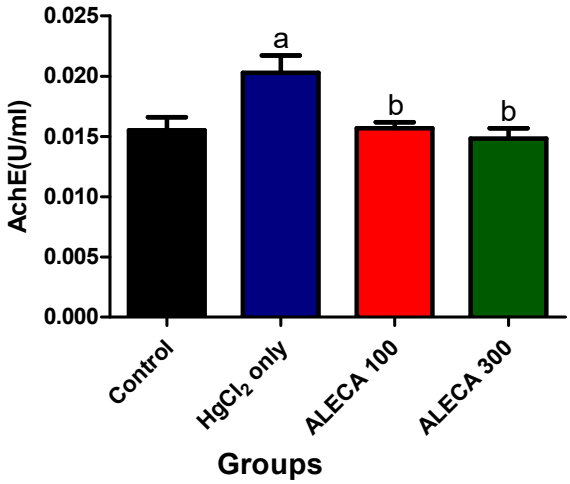

Fig. 3: Effects of *Cola acuminata* aqueous leaves extract (ALECA) on acetylcholinesterase (AChE) activities. Results are expressed as Mean ± SEM of 5 rats per group, $^{a}p < 0.05$ vs. control, $^{b}p < 0.05$ vs. $HgCl_2$. $HgCl_2$ = mercury chloride.

The level of malondialdehyde (MDA) was significantly increased (p<0.05) in the mercury chloride group when compared with the control. Conversely, the administration of ALECA (100 and 300 mg/kg) significantly (p<0.05) reduced MDA level when compared with the mercury chloride group (Fig. 4).

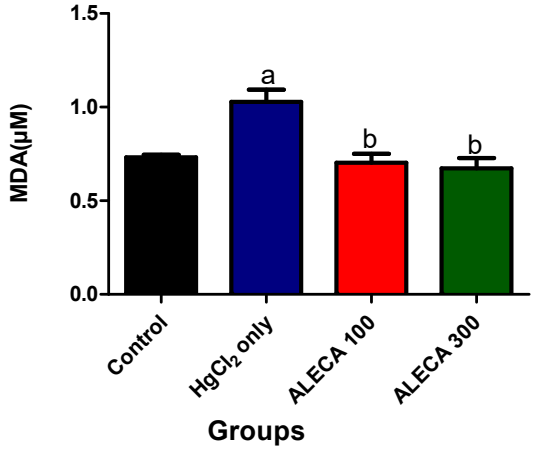

Fig. 4: Effects of *Cola acuminata* aqueous leaves extract (ALECA) on malondialdehyde (MDA) levels. Results are expressed as Mean ± SEM of 5 rats per group, $^{a}p < 0.05$ vs. control, $^{b}p < 0.05$ vs. $HgCl_2$. $HgCl_2$ = mercury chloride

The level of reduced glutathione (GSH) was significantly decreased (p< 0.05) in the mercury chloride group when compared with the control. However, the administration of ALECA (100 and 300 mg/kg b.w) significantly (p<0.05) increased GSH level when compared with the mercury chloride group (Fig. 5).

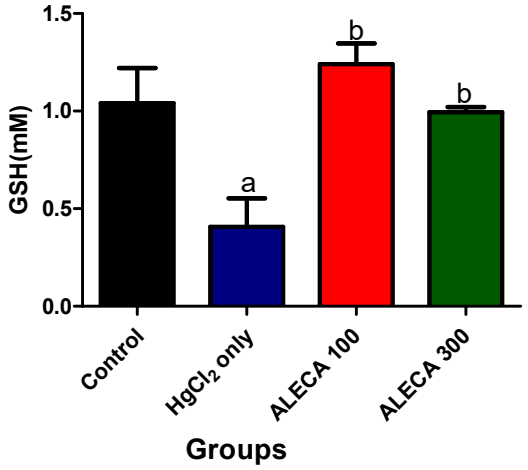

Fig. 5: Effects of *Cola acuminata* aqueous leaves extract (ALECA) on reduced glutathione (GSH) levels. Results are expressed as Mean ± SEM of 5 rats per group, $^{a}p < 0.05$ vs. control, $^{b}p < 0.05$ vs. $HgCl_2$. $HgCl_2$ = mercury chloride

Moreover, the level of total protein (TP) was significantly increased (p<0.05) in the mercury chloride group when compared with the control. However, the administration of ALECA (100 and 300 mg/kg) significantly (p<0.05) decreased its level when compared with the mercury chloride group (Fig. 6).

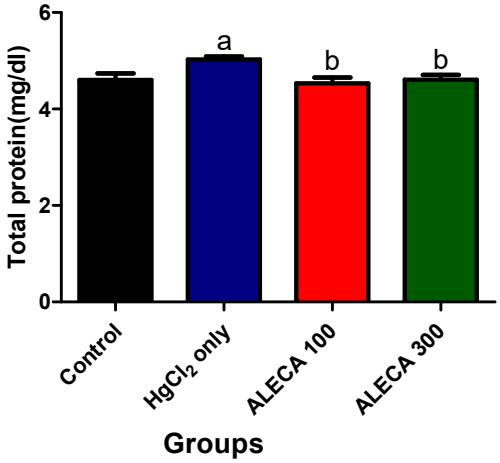

Fig. 6: Effects of *Cola acuminata* aqueous leaves extract (ALECA) on total protein (TP) levels. Results are expressed as Mean ± SEM of 5 rats per group, $^{a}p < 0.05$ vs. control, $^{b}p < 0.05$ vs. $HgCl_2$. $HgCl_2$ = mercury chloride

DISCUSSION

The Morris water maze is one of the most widely used tasks in behavioural neuroscience for studying the psychological processes and neural mechanisms of spatial learning and memory (He et al. 2011). Learning and memory of Wistar rats is reflected by the escape latency. In this study, increased escape latency as observed in mercury chloride-only group indicates learning and memory impairment. Teixeira et al. (2014) reported that, exposure of rats to mercury chloride induced short- and long-term memory impairments, and correlated cognitive dysfunction to accumulation of mercury chloride in the hippocampus. Results are in accordance with Yasutake et al. (2010) which infer that acute doses of inorganic mercury induced cognitive damage in mice. Recent study has shown that memory functions of hippocampus was damaged when mercury caused damage to the hippocampus (Wu et al. 2016). However, the significant reduction in the escape latency recorded in the groups treated with ALECA (100 mg/kg and 300 mg/kg) showed the plant's ability to improve memory. This confirms the reports of Ishola et al. (2018), which stated that *Cola acuminata* seed extract had significant protective effect against memory deficit.

Similarly, the increase in the frequency of visiting the blocked escape route (modified light and dark box test) by rats treated with ALECA (100 and 300 mg/kg) indicates an improvement in cognitive impairment and memory restorative effect of ALECA which might be as a result of its

phytochemical constituents, as it has been reported to contain alkaloids, saponins, flavonoids, steroids, terpenoids, glycosides, and proteins (Dewole et al. 2013).

According to Devin et al. 2020, the aggregation of specific proteins, such as amyloid beta, phosphorylated tau, and α-synuclein, is typically linked to neurodegenerative disorders. In this study, the mercury chloride group had significantly higher brain protein than the control. The total protein were significantly reduced upon ALECA (100 or 300 mg/kg) treatment, showing its neuroprotective abilities.

Mercuric ion is one of the strongest thiol-binding agents: Binding of mercuric ions to thiol groups may cause decrease in glutathione (GSH) levels, leading to increased levels of reactive oxygen species (ROS), such as superoxide anion radicals, hydrogen peroxide, and hydroxyl radicals, which provoke lipid, protein, deoxyribonucleic acid (DNA), and ribonucleic acid (RNA) oxidation (Li *et al.* 2006). In the present study, it was observed that mercury chloride lowered the level of GSH in the rat brains. As a result, lipid peroxidation was activated, as seen by the noticeably elevated brain MDA level. Studies have showed that mercury causes oxidative stress in rat brains by lowering GSH levels and consequently raising MDA (Ansar 2015; Moneim 2015; Salman et al. 2016), and the present findings is consistent in this regard. The capacity of mercury to interact with and deplete sulfhydryl (-SH) groups found in GSH is the known mechanism by which mercury inhibits antioxidant enzymes and molecules (Moneim 2015; Mesquita et al. 2016; Adedara et al. 2019). Enzymes with sulfhydryl groups as well as GSH are rendered inactive by the Hg-SH complex that is produced: This reduction may greatly increase redox imbalance (Aoyama and Nakaki 2013). And as such simultaneously sets off oxidative stress in brain cells that result in oxidative neurotoxicity, which underlies the biochemical findings of the present study.

Interestingly, treatment with ALECA attenuated the oxidative stress indices. This was demonstrated by increased GSH levels, and a considerable drop in MDA levels in the brain. The antioxidant activity of *Cola acuminata* has been reported (Oboh et al. 2014; Ishola et al. 2018; Oboh et al. 2018). Its reported phytochemicals may act against ROS directly or by enhancing and maintaining the activity of antioxidant enzymes comparable to the control group in this study (Obho 2006). The reduction of MDA level and increase in GSH level by ALECA suggest an antioxidant ability contributed by its phytochemicals.

The cholinergic system is important for neurotransmission, learning, and memory. Through interactions with AChE and neurotransmitters, toxic metals are known to interfere with the cholinergic system (Akinyemi et al. 2015). Our findings showed that mercury chloride increased AChE activity in the brain. Our findings are in line with earlier research showing that cadmium and lead exposure increases AChE activity in the brain (Akinyemi et al. 2015). The activation of AChE implies that exposure to mercury may result in cholinergic or cognitive deficits (Ishola et al. 2017). Alkaloids and flavonoids exhibit various bioactive abilities including neuroprotective potentials (Nwanna et al. 2016; Mohammad et al. 2019).The mechanisms of action of anticholinesterase drugs involve enhancement of cholinergic neurotransmission by inhibiting intracellular degradation of acetylcholine (Kozurkova et al. 2011). Our findings demonstrated that ALECA (100 and 300 mg/kg) are effective inhibitors of AChE. This ALECA action may be due to it phytochemicals as reported by Oboh (2006). The inhibitory effects of these phytochemicals on AChE activity suggest their ability to increase acetylcholine levels in the brain, which in turn could improve transmission of nerve impulses and cognitive functions in cognitive impaired patients (Nwanna et al. 2016).

Findings from this study showed increased AChE activity in mercury chloride-only group which was ameliorated upon intervention by ALECA (100 and 300 mg/kg). This effect suggests that the extracts act by inhibiting the production and action of acetylcholine esterase activity, thereby enhancing cholinergic transmission that restores memory deficit.

Conclusion

This study revealed that ALECA mitigated mercury chloride-induced neurotoxicity via reduction of oxidative stress and enhanced cholinergic functions.

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No funding was received.

Conflict of Interest

None declared.

Acknowledgement

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Authors' Contribution

MTA and BVO - Conception and design of the research; AOA, TSO and SY - Experimentation and data collection; AOA - Data analysis and interpretation; MTA and AOA - Drafting of the manuscript; MTA - Critical revision of the manuscript.

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