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Protective Effect of *Buchholzia coriacea* (Wonderful Kola) on Aluminium Chloride Induced Neurotoxicity on the Prefrontal Cortex of Adult Male Wistar Rat

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ABSTRACT

Aluminium is highly prevalent in the environment, and due to its possible neurotoxicity, this study assessed the neuroprotective effect of *Buchholzia coriacea* seed extract (B.C.) on the prefrontal cortex of aluminium chloride ($AlCl_3$)-induced neurotoxicity in adult Wistar rats. Twenty-five male rats weighing 119 to 286 g were divided into five groups of five rats each. 1 mL of distilled water was administered to the control group, while other groups received 250 mg/kg B.C. only, 200 mg/kg $AlCl_3$ only, 200 mg/kg $AlCl_3$ + 50 mg/kg B.C., and 200 mg/kg $AlCl_3$ + 250 mg/kg B.C. The study employed the Y-maze test to assess for spatial memory, biochemical analyses of malondialdehyde (MDA), glutathione (GSH), superoxide dismutase (SOD), and catalase (CAT) levels to determine possible oxidative stress and cellular damage, as well as histological techniques using haematoxylin and eosin (H&E) staining to determine morphological changes in the cells. Results showed a significant decrease ($p<0.05$) in the total arm entries, percentage alternation, SOD, CAT, and GSH. However, the MDA level was significantly ($p<0.05$) increased in the $AlCl_3$ group when compared to the control. Prefrontal cortex histology revealed several fragmentations, vacuolated cells, dark pyknotic neurons, and neuropil in $AlCl_3$-treated groups, which suggest neurodegeneration. B.C., on the other hand, caused a significant decrease in MDA levels and a significant increase in CAT and SOD levels and attenuated the prefrontal cortex neuronal cells following $AlCl_3$ exposure. This study therefore concludes that $AlCl_3$-induced oxidative stress and neurotoxic effects, which the B.C. protected from.

Keywords

Buchholzia Coriacea, Aluminium Chloride, Neurotoxicity, Prefrontal Cortex

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INTRODUCTION

Aluminium (Al) is the most abundant metal on earth, and it may get into living systems, including the human body, through food, food additives, drinking water, cooking utensils, and the use of cosmetics (Stahl *et al*., 2017). There is strong evidence that Al can pass through the blood-brain barrier and deposit in different parts of the brain, such as the hippocampus and cerebral cortex, which are involved in memory formation and learning (Sadek *et al*., 2019; Baranauskaite *et al*., 2020). Moreover, infiltration of inflammatory cells and neuronal loss appear in the brains of aluminium chloride ($AlCl_3$)-treated rats (Sadek *et al*., 2019). $AlCl_3$ accumulation in the brain has been linked to neurological diseases like Parkinson's and Alzheimer's, according to a study by Amber *et al*. (2018).

In previous studies on adult animals, Al induced the production of reactive oxygen species (ROS) and caused oxidative damage in the brain (Kowalczyk *et al*., 2004). Excessive dietary $AlCl_3$ exposure during pregnancy and lacta-

tion did not have any harmful consequences for the dam, but it left the pups with long-lasting neurobehavioural impairments, including impairments in sensory motor reflexes, locomotor activity, learning capacity, and cognitive behaviour (Gonda *et al*., 1996; Abu-Taweel *et al*., 2011). Al may exert its toxic effects on the nervous system, especially at high concentrations, causing loss of memory, speech disturbances, dysparaxia, tremour, jerking movements, impaired muscular coordination, and paralysis (Drago *et al*., 2008). $AlCl_3$ can induce neurotoxicity via free radical production (Moumen *et al*., 2001; Sethi *et al*., 2008), although Al itself is not a transition metal and cannot catalyse redox reactions (Exley, 2004). Al ions have a strong affinity for biomembranes. It is capable of increasing the cellular oxidative milieu by potentiating the pro-oxidant properties of transition metals (Bondy *et al*., 1998; Becaria *et al*., 2003). Its exposure also associates with impairment of mitochondrial functions *in vitro* (Niu *et al*., 2005) and *in vivo* (Kumar *et al*., 2008) and also impairs the antioxidant defence system, which may lead to the generation of oxidative stress (Kumar *et al*., 2009).

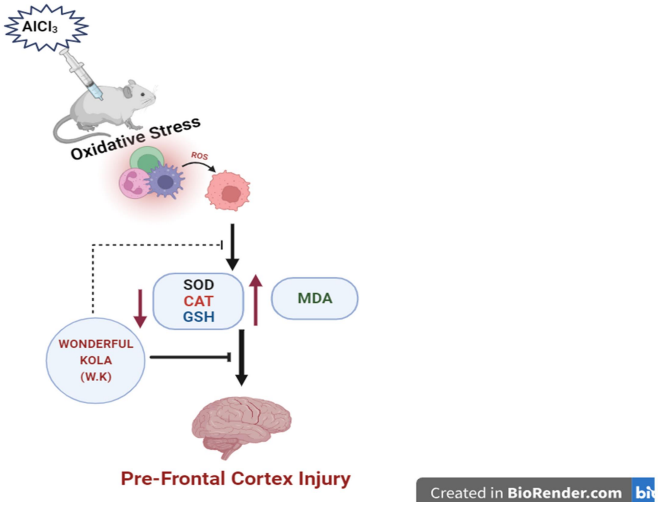

Fig. 1: Schematic representation of the mitigating effects of *Buchholzia coriacea* extract (B.C.) on aluminium chloride ($AlCl_3$)-induced neurotoxicity.

Buchholzia coriacea (B.C.), popularly known as wonderful kola, belongs to the family Capparaceae and is widely distributed in several tropical countries. Its leaf and seed are reputed scientifically to have good antihelmintic (Ajaiyeoba *et a*l., 2001), antibacterial (Mbata *et al*., 2009), antimicrobial (Ezekiel and Onyeoziri, 2009), hypoglycaemic (Adisa *et al*., 2011), antimalarial (Okoli and Okere, 2010), abortifacient, and cytotoxicity effects (Adjanohoun *et al*., 1996). Research indicates that $AlCl_3$ can cause hippocampal damage and memory impairment (Adelodun *et al*., 2021), while B.C. seed extract, on the other hand, has demonstrated neuroprotective effects against neurotoxicity induced by substances like mercury and sodium azide (Abayomi *et al*., 2019). Thus, using B.C. seed extract could be beneficial in protecting memory and cognitive impairment caused by $AlCl_3$-induced neurotoxicity due to its proven neuroprotective properties and therapeutic potential demonstrated in various studies. We therefore evaluated the neuroprotective potentials of B.C. on $AlCl_3$-induced neurotoxicity in memory and cognitive impairment using biomarkers of oxidative stress by assaying for superoxide dismutase (SOD), malondialdehyde (MDA), catalase (CAT), and glutathione (GSH) enzymes, as well as the histology of the prefrontal cortex.

MATERIALS AND METHODS

Ethical Clearance

All protocols and treatment procedures were done according to the Animal Care and Use Committee guidelines (National Institutes of Health, 2011) and as approved by the Faculty of Basic Medical Sciences Ethics Review Committee, Bingham University, Karu, Nigeria, with approval number BHUCAUC/2022/014.

Experimental Design

Twenty-five adult male Wistar rats with an average weight of 160 ± 10 g were randomly assigned into five groups, and each group had five animals (n = 5). LD50 for B.C. was carried out, and it was safe up to 5,000 mg/kg b.w. Two doses, 1/100th = 50 mg/kg b.w. (low dose, LD) and 1/20th = 250 mg/kg b.w. (high dose, HD), were selected for this study. The B.C. group was administered B.C. only (250 mg/kg), while rats in the $AlCl_3$-only group received $AlCl_3$ (200 mg/kg), serving as a negative control. Rats in the $AlCl_3$ + B.C. LD Group received $AlCl_3$ (200 mg/kg) and 50 mg/kg of B.C. The rats in the $AlCl_3$ + B.C. HD group received $AlCl_3$ (200 mg/kg) and 250 mg/kg B.C. The control group rats serving as the control received only 1 mL of distilled water. $AlCl_3$ and B.C. were simultaneously administered orally for 30 days using an oral cannula. All treatment was done daily by 9 a.m. Before administration, a neurobehavioral test (Y-maze) was conducted on each rat. During administration, Y-maze was conducted on days 7 and 14, before the animals were humanely sacrificed.

Neurobehavioural Study

Spontaneous alternation using a Y-maze with three equal arms and a differing arm separated at 120-degree angles. Each arm was labelled A, B, and C. The rats were placed at the centre of the "Y" and given a set time of 5 min to explore all three arms of the maze. The choices are recorded, and at the end of the set time, the maze was cleaned with diluted methylated spirit to eliminate odour traces. The spontaneous alternation behaviour (SAB) score was calculated by dividing the number of three successive choices by the total number of opportunities for alternation. Percentage spontaneous alternation was calculated as [number of alternations/(total arm entries-2)] x 100 (Kim *et al*., 2023).

Biochemical Analyses

On completion of treatments, rats for histological analysis were euthanized using 20 mg/kg of ketamine (intraperitoneal). Transcardial perfusion was done by exposing the left

ventricle and perfusing 50 mL of 0.1 M PBS (pH 7.4) followed by 400 mL of 4% paraformaldehyde (PFA) while the rat was suspended in an inverted position (gravity). Some excised brains containing prefrontal cortex were collected and homogenised in phosphate buffer solution (PBS) for biochemical studies. The tissue homogenates were centrifuged at an appropriate centrifugal force for 10 min, and the supernatant was used for different estimations according to the method of Bradford (1976). The supernatant was used to assay MDA, SOD, CAT, and GSH using spectrophotometric methods.

Histological Study

Excised brain tissues collected for histological studies were fixed in a 10% formalin solution. Staining was carried out in paraffin wax embedded sections (4 µm) that were stained with haematoxylin and eosin using the methods described by Fischer *et al*. (2008). Prefrontal cortex H&E-stained sections were captured using an Olympus binocular research microscope (Olympus, New Jersey, USA), which was connected to a 5.0 MP Amscope camera (Amscope Inc., USA).

Data Analyses

All quantitative data were analysed using GraphPad Prism® (version 8.0) and SPSS (version 20) softwares. One way analysis of variance analysed neurobehavioural assessments and biochemical study outcomes, followed by Tukey's multiple comparisons test. The significance was set at $p<0.05$, $p<0.01$, and $p<0.001$. The results were represented in bar charts with error bars to show the mean and standard error of the mean (mean±SEM), respectively.

RESULTS

Rats in the B.C. group showed no significant difference when compared to the control group, as it showed almost equal percentage alternation and total arm entry when compared to the control group. There was a significant decrease ($p<0.05$) in the total arm entries, number of alterations, and percentage alternation in the $AlCl_3$-only treated group and the $AlCl_3$ + B.C. (50 mg/kg) (low dose) treated group when compared with the control (Fig. 2). However, B.C. extract at a high dose (250 mg/kg) mitigated the $AlCl_3$-induced decrease in total arm entry and the number of alternations in the $AlCl_3$ + B.C. (250 mg/kg) group.

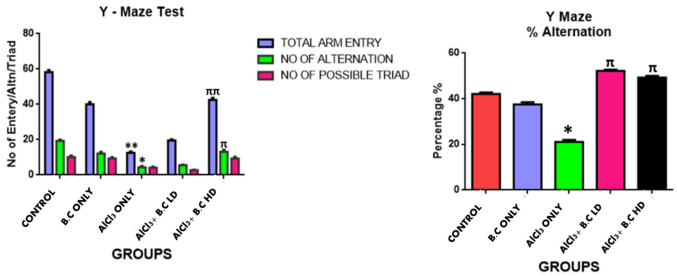

Fig. 2: Total arm entry, number of alternation, number of possible triad and % alternation.

Rats treated with $AlCl_3$-only expressed significantly decreased levels in the activities of the SOD, CAT, and GSH enzymes when compared with the control. The results showed significant increases ($p< 0.05$) in SOD, CAT, and GSH in the B.C. (50 mg/kg and 250 mg/kg)-treated rats when compared to the control group and $AlCl_3$ group. MDA levels significantly increased in the prefrontal cortex of rats treated with $AlCl_3$ only when compared with the control group and other groups treated with B.C. Rats treated with B.C. in the B.C. group (LD and HD) had significantly lower MDA levels when compared with the control and $AlCl_3$ groups. B.C. mitigated the $AlCl_3$-induced increase in MDA levels in the prefrontal cortex of rats (Fig. 3).

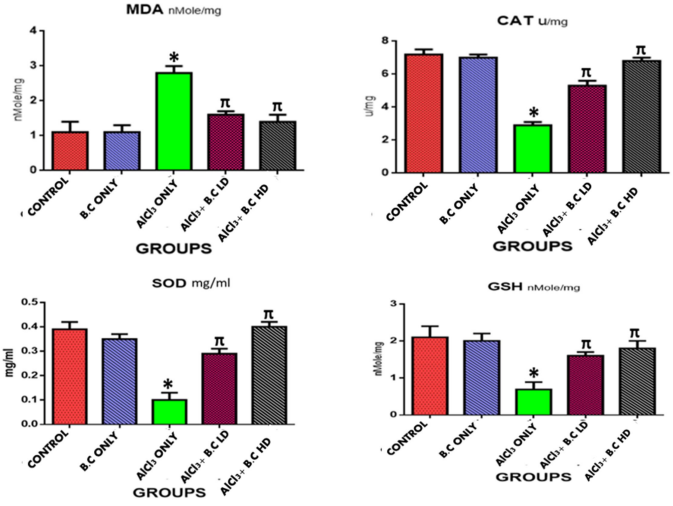

Fig. 3: *Buchholzia coriacea* (B.C.) mitigates aluminium chloride $AlCl_3$-induced prefrontal cortex injury in rats. B.C. reduced tissue MDA and increased CAT, SOD, and GSH in $AlCl_3$-intoxicated rats. The data are presented as the mean ± SEM (n = 5). *P ≤ 0.05 versus control, and π P ≤ 0.001 versus $AlCl_3$-treated groups.

Histology Result

Rats in the control and B.C. groups had a normal panoramic morphological presentation of the prefrontal layer (III) at various exposures and magnifications (Fig. 4A and B). The well-outlined array of cells within the prefrontal were distinctly arranged in layer III. $AlCl_3$ treatment, on the other hand, showed severe degenerative changes in the prefrontal cortex and was characterised by fragmentations and observable pyknotic cells (Fig. 4C). Also, the $AlCl_3$ + B.C. (LD) group showed dark pyknotic neurons, fragmentations, and regeneration (Fig. 4D). $AlCl_3$+ B.C. (LD) group revealed rounded pyramidal neurons, vacuolated cells, dark pyknotic neurons, and regeneration (Fig. 4E).

DISCUSSION

Assessing behavioural outcomes is a crucial component of determining the well-being of an animal (Jacobson and Truax, 1991). As a correlative test for cellular and neuropathological changes within the prefrontal cortex in this study, we assessed memory in treated rats using the Y-maze test. The Y-maze test is very useful to assess spatial working memory. The Y-maze test is based on the natural ten-

dency of animals to explore new environments and their preference for novelty. A high rate of spontaneous alternation indicates intact spatial working memory (Horst and Laubach 2012).

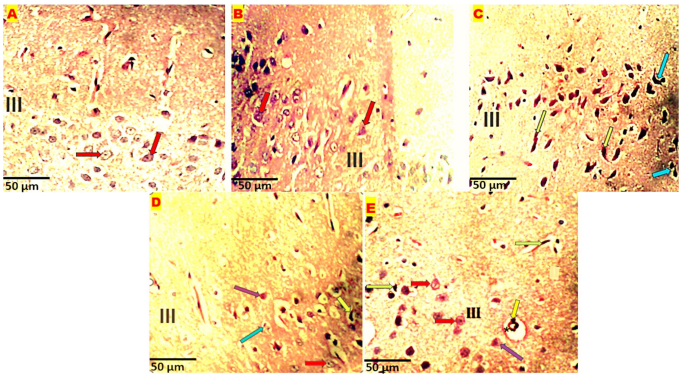

Fig. 4: Photomicrographs of the prefrontal cortex show the external pyramidal layer (III). (A): The control prefrontal cortex contains pyramidal cells (red arrow) and vesicular nuclei. (B): The Buchholzia coriacea (B.C.)-only group prefrontal cortex shows several rounded pyramidal cells (red arrow). (C): The aluminium chloride ($AlCl_3$)-only group is characterised by several fragmentations (blue arrow) and dark pyknotic neurons (green arrow). (D) The $AlCl_3$ and B.C. LD group with rounded pyramidal neurons (red arrow), dark pyknotic neurons (green arrow), fragmentations (blue arrow), and regeneration (purple arrow) H&E (Mag x 400). (E): The $AlCl_3$ and B.C. HD Group is characterised by rounded pyramidal neurons (red arrow), vacuolated cells (yellow arrow and black star), dark pyknotic neurons (green arrow), and regeneration (purple arrow). H&E (Mag x 400).

The result of the study revealed a significant decrease ($p<0.05$) in the total arm entries, number of alterations, and percentage of alternations in the $AlCl_3$-only treated group when compared with the control, indicating that $AlCl_3$-induced neurodegeneration affects regions such as the prefrontal cortex leading to impaired cognitive functions related to spatial memory and navigation. However, B.C. extract (HD) mitigated $AlCl_3$-induced decrease in total arm entry and number of alternations, while B.C. at low dose could not mitigate the $AlCl_3$-induced decrease of total arm entry and number of alternations. The result of the test also revealed a significant increase in the number of alternations in group $AlCl_3$ + B.C. (LD) when compared to the control. This is an indication that the phytochemical constituents of B.C. may interact with neurotransmitter systems, affecting mood and cognitive processes. These interactions could contribute to alterations in maze behaviour, further indicating that B.C. has neuroprotective properties, which may influence behaviour in maze tasks and enhance exploratory behaviour, leading to an increase in total arm entries and alterations. This is in agreement with the work of Adelodun *et al*. (2021), who reported that B.C. exhibited neuroprotective ability on $AlCl_3$-induced CA3 hippocampal field neuronal damage and demonstrated memory impairment reversing ability. $AlCl_3$ could have caused a lesion to the prefrontal cortex and a possible alteration of normal mitochondrial redox and glucose bioenergetics, leading to memory impairment, as confirmed in the study carried out by Jo *et al*. (2007) and Tokunbo *et al*. (2023). However, B.C. extract (HD) mitigated the $AlCl_3$-induced decrease in spontaneous alternation in the rats exploring the Y-maze, suggesting that B.C. extract had a beneficial effect on prefrontal cortex dependent cognition and working memory. Its ameliorative properties may be primarily due to the presence of flavonoids, antioxidant vitamins, and enzymes (Ibrahim and Fagbonun, 2013).

According to Sahu *et al*. (2017), the brain's biochemical indices are helpful "markers" for evaluating the integrity of the tissue. In order to investigate and diagnose diseases, it is important to quantify the activity of different enzymes in bodily fluids and tissues (Dhama *et al*., 2019). According to Shittu *et al*. (2015), tissue enzymes have the ability to detect cellular damage to tissue that is caused by chemical compounds in the extract, even before structural damage that can be detected using traditional histology techniques. MDA is a marker for lipid peroxidation, which is the oxidative degradation of lipids. During this process, free radicals deplete electrons from the lipids in cell membranes, resulting in cell damage (Singh *et al*., 2017). From the result, rats that received $AlCl_3$-only showed a significant increase in MDA level when compared to the control group, signifying that $AlCl_3$ exposure induces oxidative stress, and oxidative stress triggers lipid peroxidation, leading to the formation of MDA as a by-product, thereby contributing to neurotoxic effects. This is in line with the work of Shunan *et al.* (2021), who reported that $AlCl_3$ is a potent neurotoxin for inducing oxidative stress associated with neurodegenerative diseases. However, MDA levels were significantly lower in the other treated groups ($AlCl_3$ + B.C. LD and $AlCl_3$ + B.C. HD) when compared to the $AlCl_3$ group. This decrease in MDA level can be attributed to the antioxidant properties B.C. has been found to possess, such as alkaloids, anthraquinones, saponins, tanins, cardiac glycosides, and flavonoids (Adisa *et al*., 2011; Lapshak *et al*., 2016; Agu and Okolie, 2017), that may act directly against ROS or improve and preserve the antioxidant enzyme activity.

SOD serves a key antioxidant role. It decreases ROS generation and oxidative stress, inhibits endothelial activation, and indicates modulation of factors that govern adhesion molecule expression and leukocyte-endothelial interactions (Shuvaev *et al*., 2011). The results of this study revealed that animals that received $AlCl_3$ showed a significant ($p < 0.05$) decrease in the activity of SOD, suggesting that $AlCl_3$ exposure can cause oxidative stress in the form of increased production of ROS in the brain, leading to oxidative damage to neuronal cells. Oxidative stress is known to impair cognitive function and memory. B.C. (LD) and B.C. (HD), on the other hand, being potent antioxidants, caused a significant increase in the SOD level, thereby attenuating $AlCl_3$-induced oxidative stress in the prefrontal cortex of adult Wistar rats. Thus, the increase in the SOD level in the treated groups is an indication that B.C. at LD and HD doses is protective against oxidative damage effect in the brain. The result from this study is in line with Auza *et al*. (2023) and Olufunmilayo *et al*. (2023), who reported that B.C. scavenges ROS, reduce oxidative damage, and protect hippocampal cells against Al-induced oxidative stress.

The result also agrees with Moghadamtousi *et al*. (2015), who stated that elevated activity of SOD protects tissue against oxidative damage and accelerates the wound healing process.

CAT and GSH activity decreased significantly ($p < 0.05$) in the $AlCl_3$ group when compared with control. CAT is an enzyme and an important antioxidant that plays significant roles in disease investigation by combating oxidative stress and maintaining redox homeostasis in the body (Ighodaro and Akinloye, 2018). CAT is primarily located in peroxisomes and plays a crucial role in catalysing the breakdown of hydrogen peroxide (H_2O_2) into water and oxygen, thus protecting cells from the harmful effects of this reactive molecule. Altered CAT activity or expression has been observed in conditions associated with oxidative stress, such as neurodegenerative diseases, cardiovascular disorders, and cancer (Nandi *et al*., 2019; Miao *et al*., 2021). The results of this study revealed that animals that received $AlCl_3$ showed a significant ($p < 0.05$) decrease in the activity of CAT, suggesting that $AlCl_3$ exposure can induce oxidative stress in the form of increased production of ROS in the brain, resulting in a reduction in the activity of CAT and compromised antioxidant defence mechanisms. B.C. exhibits antioxidant properties, as seen in the elevation of CAT activity. B.C. at LD and HD enhanced the activity of antioxidant enzymes, which contributes to the scavenging of ROS and reduction of oxidative stress.

GSH is a tripeptide composed of three amino acids: cysteine, glutamate, and glycine. It acts as a major intracellular antioxidant and is involved in several cellular processes, including detoxification, free radical scavenging, and regulation of cellular signalling pathways (Lushchak, 2012). GSH plays a crucial role in protecting cells from oxidative damage (Pizzorno, 2014). It helps protect cells from oxidative damage by directly neutralising ROS and participating in enzymatic antioxidant defence systems (Forman *et al*., 2009). In the context of disease investigation, GSH depletion and impaired GSH-related antioxidant mechanisms have been implicated in various disorders. For example, GSH depletion is observed in neurodegenerative diseases like Parkinson's and Alzheimer's diseases, as well as in liver diseases and respiratory disorders (Sian *et al*., 1994; Auza *et al*., 2023). In this study, there was a significant decrease in GSH activity in the prefrontal cortex of rats in the $AlCl_3$-only group when compared to the control. A significant decrease in GSH may suggest an imbalance between the generation of ROS and the antioxidant defence mechanism, which may contribute to oxidative stress. It could also imply compromised cellular defence mechanisms, potentially leading to damage, dysfunction, and pathological conditions. This is in line with the work of Egba *et al*. (2022), who reported that $AlCl_3$ concomitantly triggers oxidative stress in brain cells, leading to oxidative neurotoxicity underlying biochemical and histopathological observations. However, B.C. exhibits antioxidant properties, elevating GSH activity. B.C. at LD and HD enhanced the activity of antioxidant enzymes, which contributes to the scavenging of ROS and reduction of oxidative stress.

On histologic examination with H&E staining, rats in the control and B.C. groups had a normal, well-outlined array of cells within the prefrontal cortex that were distinctly arranged in layer III. $AlCl_3$ treatment, on the other hand, showed severe degenerative changes in the prefrontal cortex and was characterised by fragmentations and observable pyknotic cells. The result revealed darkly stained pyknotic neurons, vacuolated cells, and several fragmentations in the nuclei of the $AlCl_3$-treated groups compared to the normal rounded pyramidal neurons in the control group, indicating cell necrosis or apoptosis in the neurons of Wistar rats. The cryptic changes seen in the pyramidal neurons of the $AlCl_3$-treated group suggest an apoptotic mode of neuronal cell death in which cell shrinkage made the cells smaller in size, with dense cytoplasm and the organelles more tightly packed. Similarly, neuronal apoptotic bodies have been described to consist of cytoplasm with tightly packed organelles, with or without a nuclear fragment (Stefanis *et al*., 1997; Abayomi *et al*., 2019). However, treatment with B.C. at LD and HD showed protection of the histological structures almost similar to those in the control group. These results are in accordance with the findings of Buraimoh *et al*. (2012), who reported histological observations such as necrosis, dark pyknotic neurons, and vacuolations due to $AlCl_3$ exposure.

Conclusion

In conclusion, $AlCl_3$ had insulting effects on the prefrontal cortex microarchitecture of adult Wistar rats as well as the expression and activities of certain enzymes, most probably due to oxidative stress and the generation of free radicals. The treatment with B.C. resulted in the protection of the damaging effects of $AlCl_3$.

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Conflict of Interest

None declared.

Authors' Contribution

AA conception, design, and supervision. EAM experimentation and biochemical analyses. MIA - analysed the data and the initial manuscript draft. All the authors reviewed and approved the final manuscript.

REFERENCES

Abayomi, T.A., Tokunbo, O.S., David, O., Obembe, O.O. and Dare, B.J. (2019) Neuroprotective effects of *Buchholzia coriacea* seed extract on sodium azide-induced neurotoxicity of the prefrontal cortex of Wistar rats. Anat J Afr. 8(2):1635-1646.

Abu-Taweel, G.M., Ajarem, J.S. and Ahmad, M. (2011) Neurobehavioral toxic effects of perinatal oral exposure to Aluminium on the developmental motor reflexes, learning,

memory and brain neurotransmitters of mice offspring. Pharmacol Biochem Behav. 101(1):49–56.
Adelodun, S.T., Ishola, O.A., Abijo, A.Z., Olatunji, S.Y., Owolabi, J.O., Olanrewaju, J.A., et al. (2021) Aluminium chloride-induced hippocampal damage: CA3 hippocampal subfield involvement and the neuroprotective role of *Buchholzia coriacea* ethanolic seed extract. Phytomedicine Plus. 1(4):100104.
Adisa, R.A., Choudhary, M.I. and Olorunsogo, O.O. (2011) Hypoglycemic activity of *Buchholzia coriacea* (Capparaceae) seeds in streptozotocin-induced diabetic rats and mice. Exp Toxicol Pathol. 63(7-8):619-625.
Adjanohoun, J.E., Aboubakar, N., Dramane, K., Ebot, M.E., Ekpere, J.A., Enow-Orock, E.G., et al. (1996) Traditional medicine and pharmacopoeia. Contribution to Ethnobotanical and Floristic Studies in Cameroon. Centre de Production de Manuels Scolaires, Porto-Novo (Rep. Du Benin). P.133.
Agu, K.C. and Okolie, P.N. (2017) Proximate composition, phytochemical analysis, and in vitro antioxidant potentials of extracts of *Annona muricata* (Soursop). Food Sci Nutr. 5(5):1029-1036.
Ajaiyeoba, E.O., Onocha, P.A. and Olarenwaju, O.T. (2001) *In vitro* anthelmintic properties of *Buchholzia coriaceae* and *Gynandropsis gynandra* extracts. Pharmaceutic Biol. 39(3):217-220.
Amber, S., Shah, S.A.A., Ahmed, T. and Zahid, S. (2018) *Syzygium aromaticum* ethanol extract reduces AlCl3-induced neurotoxicity in mice brain through regulation of amyloid precursor protein and oxidative stress gene expression. Asian Pacific J Trop Med. 11(2):123-130.
Auza, M.I., Elijah, S.O., Oguntoyinbo, F.C., Musa, S.A., Danborno, A.M. and Oguche, E.E. (2023) The effect of *Gingko biloba* extract and ascorbic acid on mercury-induced changes on the hippocampus of adult wistar rat. J Anat Sci. 14(2):84-90.
Baranauskaite, J., Sadauskiene, I., Liekis, A., Kasauskas, A., Lazauskas, R., Zlabiene, U., et al. (2020) Natural compounds rosmarinic acid and carvacrol counteract aluminium-induced oxidative stress. Molecules. 25(8):1807.
Becaria, A., Bondy, S.C. and Campbell, A. (2003) Aluminium and copper interact in the promotion of oxidative but not inflammatory events: implications for Alzheimer's disease. J Alzheimer's Dis. 5(1):31-38.
Bondy, S.C., Guo-Ross, S.X. and Truong, A.T. (1998) Promotion of transition metal-induced reactive oxygen species formation by β-amyloid. Brain Res. 799(1):91-96.
Bradford, M.M. (1976) A rapid and sensitive method for the quantitation of microgram quantities of protein utilizing the principle of protein-dye binding. Anal Biochem. 72(1-2):248-254.
Buraimoh, A.A., Ojo, S.A., Hambolu, J.O. and Adebisi, S.S. (2012) Effects of aluminium chloride exposure on the histology of the cerebral cortex of adult Wistar rats. J Biol Life Sci. 3(1).
Dhama, K., Latheef, S.K., Dadar, M., Samad, H.A., Munjal, A., Khandia, R., et al. (2019) Biomarkers in stress related diseases/disorders: diagnostic, prognostic, and therapeutic values. Front Mol Biosci. 6:465402.
Drago, D., Bettella, M., Bolognin, S., Cendron, L., Scancar, J., Milacic, R. et al. (2008) Potential pathogenic role of β-amyloid1–42–Aluminium complex in Alzheimer's disease. Int J Biochem Cell Biol. 40(4):731-746.
Egba, S.I., Famurewa, A.C. and Omoruyi, L.E. (2022) *Buchholzia coriacea* seed extract attenuates mercury-induced cerebral and cerebellar oxidative neurotoxicity via NO signaling and suppression of oxidative stress, adenosine deaminase and acetylcholinesterase activities in rats. Avicenna J Phytomed. 12(1):42.
Exley, C. (2004) The pro-oxidant activity of aluminium. Free Rad Biol Med. 36(3):380-387.
Ezekiel, O.O. and Onyeoziri, N.F. (2009) Preliminary studies on the antimicrobial properties of *Buchholzia coriacea* (wonderful kola). Afr J Biotech. 8(3):472-474.
Fischer, A.H., Jacobson, K.A., Rose, J. and Zeller, R. (2008) Hematoxylin and eosin staining of tissue and cell sections. Cold Spring Harbor Protocols. 2008(5):pdb-prot4986.
Forman, H.J., Zhang, H. and Rinna, A. (2009) Glutathione: overview of its protective roles, measurement, and biosynthesis. Mol Aspects Med. 30(1-2):1-12.
Gonda, Z., Lehotzky, K. and Miklosi, A. (1996) Neurotoxicity induced by prenatal aluminium exposure in rats. Neurotoxicology.17(2):459–470.
Horst, N. K. and Laubach, M. (2012) Working with memory: evidence for a role for the medial prefrontal cortex in performance monitoring during spatial delayed alternation. J Neurophysiol. 108(12):3276-3288.
Ibrahim, T.A. and Fagbonun, E.D. (2013) Antibacterial and antifungal activity of ethanolic and methanolic extract of dried seeds of Buchhlozia coriacea. Greener J Agric Sci. 3(6):458-463.
Ighodaro, O.M. and Akinloye, O.A. (2018) First line defence antioxidants-superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPX): Their fundamental role in the entire antioxidant defence grid. Alexandria J Med. 54(4):287-293.
Jacobson, N.S. and Truax, P. (1991) Clinical significance: A statistical approach to defining meaningful change in psychotherapy research. J Consulting Clin Psychol. 59:12–19.
Jo, Y.S., Park, E.H., Kim, I.H., Park, S.K., Kim, H., Kim, H., et al. (2007) The medial prefrontal cortex is involved in spatial memory retrieval under partial-cue conditions. J Neurosci. 27(49):13567-13578.
Kim, S.B., Ryu, H.Y., Nam, W., Lee, S.M., Jang, M.R., Kwak, Y.G., et al. (2023) The neuroprotective effects of dendropanax morbifera water extract on scopolamine-induced memory impairment in mice. Int J Mol Sci, 24(22):16444.
Kowalczyk, E, Kopff, A., Kędziora, J., Błaszczyk, J., Kopff, M., Niedworok, J., et al. (2004) Effect of long-term aluminium chloride intoxication on selected biochemical parameters and oxidative-antioxidative balance in experimental animals. Polish J Environ Studies. 13(1):41–43.
Kumar, A., Dogra, S. and Prakash, A. (2009) Protective effect of curcumin (*Curcuma longa*), against aluminium toxicity: Possible behavioral and biochemical alterations in rats. Behav Brain Res. 205(2):384-390.

Kumar, V., Bal, A. and Gill, K.D. (2008) Impairment of mitochondrial energy metabolism in different regions of rat brain following chronic exposure to aluminium. Brain Res. 1232:94-103.
Lapshak, L.J., Domkat, L.C. and Nansah, L.S. (2016) The effect of aqueous extract of *Buchholzia coriacea* seeds on some biochemical parameters in normal and alloxan-induced diabetic rats. Int J Biochemy Res Rev. 11(1):1-10
Lushchak, V.I. (2012) Glutathione homeostasis and functions: potential targets for medical interventions. J Amino Acids. 2012:736837. https://doi.org/10.1155/2012/736837
Mbata, T.I., Duru, C.M. and Onwumelu, H.A. (2009) Antibacterial activity of crude seed extracts of Buchholzia coriacea E. on some pathogenic bacteria. J Dev Biol Tissue Eng. 1(1):001-005.
Miao, L., St Clair, D.K. and Regner, K.R. (2021) Systemic catalase protects mouse lung endothelial cells from oxidative stress-induced barrier dysfunction. Free Rad Biol Med. 165:105-115.
Moghadamtousi, S.Z., Rouhollahi, E., Hajrezaie, M., Karimian, H., Abdulla, M.A. and Kadir, H.A. (2015) *Annona muricata* leaves accelerate wound healing in rats via involvement of Hsp70 and antioxidant defence. Int J Surg. 18:110-117.
Moghadamtousi, S.Z., Rouhollahi, E., Hajrezaie, M., Karimian, H., Abdulla, M.A. and Kadir, H.A. (2015*) Annona muricata* leaves accelerate wound healing in rats via involvement of Hsp70 and antioxidant defence. Int J Surg. 18:110-117.
Moumen, R., Ait-Oukhatar, N., Bureau, F., Fleury, C., Bouglé, D., Arhan, P., et al. (2001) Aluminium increases xanthine oxidase activity and disturbs antioxidant status in the rat. J Trace Elements Med Biol. 15(2-3):89-93.
Nandi, A., Yan, L.J., Jana, C.K. and Das, N. (2019) Role of catalase in oxidative stress- and age-associated degenerative diseases. Oxid Med Cell Longev. 2019:9613090.
National Research Council (2011) Guide for the Care and Use of Laboratory Animals: 8th edn. Washington, DC: The National Academies Press. https://doi.org/10.17226/12910
Niu, P.Y., Niu, Q., Zhang, Q.L., Wang, L.P., He, S.C., Wu, T.C., et al. (2005) Aluminium impairs rat neural cell mitochondria in vitro. Int J Immunopathol Pharmacol. 18(4):683-689.
Okoli, B. and Okere, O. (2010) Antiplasmodial activity of *Buccholzia coriancea.* J Med Appl Biosci. 2(1):21-29.
Olufunmilayo, E.O., Gerke-Duncan, M.B. and Holsinger, R.D. (2023) Oxidative stress and antioxidants in neurodegenerative disorders. Antioxidants. 12(2):517.
Pizzorno, J. (2014). Glutathione!. Integr Med (Encinitas). 13(1):8.
Sadek, K.M., Lebda, M.A. and Abouzed, T.K. (2019) The possible neuroprotective effects of melatonin in aluminum chloride-induced neurotoxicity via antioxidant pathway and Nrf2 signaling apart from metal chelation. Environ Sci Pollut Res. 26(9):9174-9183.
Sahu, S., Nag, D.S., Swain, A. and Samaddar, D.P. (2017) Biochemical changes in the injured brain. World J Biol Chem. 8(1):21.
Sethi, P., Jyoti, A., Singh, R., Hussain, E. and Sharma, D. (2008) Aluminium-induced electrophysiological, biochemical and cognitive modifications in the hippocampus of aging rats. Neurotoxicology. 29(6):1069-1079.
Shittu, O.K., Lawal, B., Abubakar, N.A., Berinyuy, B.E., Busari, M.B. and Ibrahim, A.O. (2015) Toxicological implications of methanol extract from nigerian bee propolis on some selected rat tissues. J Pharm Biomed Sci. 05(07):524-531.
Shunan, D., Yu, M., Guan, H. and Zhou, Y. (2021) Neuroprotective effect of Betalain against AlCl3-induced Alzheimer's disease in Sprague Dawley rats via putative modulation of oxidative stress and nuclear factor kappa B (NF-κB) signaling pathway. Biomed Pharmacother. 137:111369.
Shuvaev, V.V., Han, J., Kevin, J.Y., Huang, S., Hawkins, B.J., Madesh, M., et al. (2011) PECAM-targeted delivery of SOD inhibits endothelial inflammatory response. FASEB J. 25(1): 348.
Sian, J., Dexter, D.T., Lees, A.J., Daniel, S., Jenner, P. and Marsden, C.D. (1994) Glutathione-related enzymes in brain in Parkinson's disease. Ann Neurol. 36(3):356-361.
Singh, U. N., Kumar, S. and Dhakal, S. (2017). Study of oxidative stress in hypercholesterolemia. Int J Contemp Med Res. 4(5):1204-1207.
Stahl, T., Falk, S., Taschan, H., Boschek, B. and Brunn, H. (2018) Evaluation of human exposure to aluminum from food and food contact materials. Eur Food Res Tech. 244(12):2077-2084.
Stefanis, L., Burke, R.E. and Greene, L.A. (1997) Apoptosis in neurodegenerative disorders. Curr Opin Neurol. 10(4):299-305.
Tokunbo, O., Abayomi, T., Solomon, B., Abayomi, O. and Obembe, O. (2023) Methanolic fraction of *Buchholzia coriacea* seed extract up-regulates hippocampal bdnf expression and ameliorate cognitive deficits in manganese-induced parkinson-like neuropathology. West Niger J Med Sci. 6(1):74-85.
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