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Cognitive, Anticholinesterase and Anti-Oxidative Potentials of *Zingiber officinale* Rhizome Extracts against Aluminium Chloride-Induced Neurotoxicity in Swiss Mice

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ABSTRACT

Aluminium neurotoxicity is implicated in Alzheimer's disease, which is marked by progressive memory loss, cognitive impairment and structural degeneration, leading to complete incapacitation. Formation of excess reactive oxygen species causes oxidative stress, which is the hallmark of aluminium toxicity. A quest to counteract these pathologies led to investigating *Zingiber officinale* (ZO) extracts on cognitive and anti-oxidative potentials against aluminium chloride ($AlCl_3$)-induced neurotoxicity in Swiss mice. The oral lethal dose of ZO was estimated as 4,743 mg/kg. Forty-eight adult female Swiss mice of weight 21-27 g were then assigned to eight groups (n=6): Group 1 were the control (40 mL/kg distilled water), while groups 2-8 were respectively, administered $AlCl_3$ (100 mg/kg) alone, and with Donepezil (2.5 mg/kg), ZO ethanol extract (474, 949 and 1,423 mg/kg), ZO dichloromethane (949 mg/kg), and ZO methanol (949 mg/kg) extracts for 21 days. The classic labyrinth test was carried out subsequently, the animals sacrificed, and their brain homogenized for biochemical assay. There was a significantly ($p<0.05$) increased latency to complete the labyrinth test by the $AlCl_3$ group compared with the control. The ZO extracts treated groups had decreased latency to complete the labyrinth test, and these were significant ($p<0.05$) in the 949 and 1,423 mg/kg ethanol extract groups. Biochemically, $AlCl_3$ significantly ($p<0.05$) elevated acetyl cholinesterase and malondialdehyde levels, while reducing superoxide dismutase activity: These adverse effects were reversed significantly ($p<0.05$) following treatment with extracts of ZO. In conclusion, ZO ethanol extract and its dichloromethane and methanol fractions improved cognitive activities, and possessed anticholinesterase, anti-oxidant and neuroprotective potentials.

Key words: *Aluminium, Cholinesterase, Classic labyrinth test, Lipid peroxidation, Neuroprotection, Zingiber officinale*

INTRODUCTION

Alzheimer's disease (AD) is the most common neurodegenerative condition of the elderly characterized by a slow impairment of memory and other cognitive processes, and often leads to incapacitation and death (Zhao et al. 2014; Kumar et al. 2021). AD is idiopathic, however, imbalances in the redox state, involving the formation of excess reactive oxygen species has been suggested (Cheignon et al. 2018; DeTure and Dickson 2019), while decreased brain acetylcholine is implicated in

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cognitive decline (Marucci et al. 2021). The female sex is reported as being more predisposed to AD than the male counterparts, probably due to their hormonal and genetic makeup (Savolainen-Peltonen et al. 2019).

In normal metabolism, oxygen is utilized within cells. However, some of the oxygen may be converted to hydrogen peroxide and superoxide radicals, which are known free radicals (Phaniendra et al. 2015). The malfunction of the antioxidant system and its inability to counteract the free radicals result in oxidative stress (Madireddy and Madireddy 2020). There is excessive synthesis of superoxide and hydrogen peroxide in the presence of aluminium, with resultant tissue damage (Yuan et al. 2012; Mesole et al. 2022). Mold et al. (2021) reported that oxidative stress association with AD is most of the time linked to aluminium exposure, and as such linked to cognitive impairment. Calvin (2014) reported such link in AD, and the up-regulation of acetyl cholinesterase expression. Aluminium is ubiquitous (Lubkowska and Chlubek 2015), and therefore likely to be absorbed by humans. So protection against it is paramount, as there is no effective treatment of aluminium neurotoxicity.

Potential protection strategy for aluminium neurotoxicity is the application of natural products (Ekong et al. 2017; Ekong et al. 2021; Mesole et al. 2022). Zingiber officinale Roscoe (*Z. officinale*) commonly called ginger, is another natural product having rich phytochemicals with medicinal values (Zanariah et al. 2015; Mao et al. 2019; Sanusi et al. 2019), and also appropriate against neurotoxicity, as previously reported in memory improvement (Lim et al. 2014; Huh et al. 2018). It is a perennial herb that is globally used as spices, and especially in the South East Asian countries (Mele 2019). It is a member of the Zingiberaceae family and known by different Nigerian languages: Jinga in Ibibio and Igbo, Cithar in Hausa, and Ata-ile in Yoruba (Sutarno et al. 1999). The potentials of Z. offiinale birthed the quest to carry out this study on its cognitive and anti-oxidative effects against aluminium chloride induced-neurotoxicity in Swiss mice.

MATERIALS AND METHODS

Experimental Procedure and Chemicals

The study took place in the Department of Medical Physiology, Faculty of Basic Medical Sciences, University of Uyo, Uyo, Nigeria. It was carried out in accordance with International Guidelines for Care and Use of Laboratory animals (National Research Council 2011), while ethical approval was obtained from the Faculty of Basic Medical Sciences Research and Ethical Committee, University of Uyo. Sixty healthy adult female Swiss mice weighing 21-27 g were obtained from the animal house of the Department of Pharmacology and Toxicology, University of Uyo, Nigeria. They were housed in the same facility in clean polypropylene cages with sterile paddy husk as bedding, and maintained at room temperature (23 ± 2℃), relative humidity of 50 ± 5 % and a 12 h light/dark cycle. The animals were allowed one week acclimatization and access to feed and water *ad libitum*. All the mice were minimally handled, and at the base of their tails at all times, except during force feeding.

The pharmacological solutions were of analytical grade, freshly prepared before use: Donepezil hydro-chloride (Bionique Pharma, India) and aluminium chloride (Sigma-Aldrich Corporation, USA) were dissolved in water and saline respectively, and delivered orally via oral tubes.

Preparation of the Extract of Plant Material

The plant, *Z. officinale* was obtained from a local farm in Anua-Offot in Uyo Local Government area of Akwa Ibom State, Nigeria. It was identified in the Department of Botany and Ecological Studies, and deposited at the herbarium in the department with the voucher number: UUH4099 (Uyo).

The rhizomes of the *Z. officinale* were cleaned, air-dried, sliced into smaller bits, and pulverized into powder (1,500 g). The powdered material was macerated for 72 h in each of these solvents (2.5 L); ethanol, n-hexane, dichloromethane, ethyl-acetate, and methanol. The liquid filtrates were evaporated to dryness at 40℃ in a rotary evaporator, and stored at 4℃ until use (Okokon et al. 2017).

Acute Toxicity Study

The acute toxicity (LD_{50}) study was carried out according to Lorke's method (Lorke 1983). Twelve of the mice were divided into 4 groups of three animals each. The animals were administered orally with single doses of *Z. officinale* ethanol extract (3,000, 4,000, 4,500, and 5,000 mg/kg, respectively). They were observed for 1 h post-administration and then after 24 hours for physical signs of toxicity and mortality. The animals were subsequently humanely sacrificed.

Animal Handling and Grouping

The remaining forty-eight mice were equally divided into eight groups (n = 6), and were orally administered $AlCl_3$ at 100 mg/kg body weight (Ekong et al. 2017; Adighije et al. 2020), and *Z. officinale* ethanol, dichloromethane (DCM), and methanol extracts daily for 21 days: Group 1 were the control administered 40 mL/kg of distilled water daily; group 2 were administered 100 mg/kg $AlCl_3$ only; group 3 were concurrently administered 100 mg/kg $AlCl_3$ and 2.5 mg/kg of donepezil; while groups 4-6 were concurrently administered 100 mg/kg $AlCl_3$ and 474 mg/kg (10% LD_{50} low dose), 949 mg/kg (20% LD_{50} intermediate dose), and 1,423 mg/kg (30% LD_{50} high dose) *Z. officinale* ethanol extract; groups 7 and 8

were concurrently administered 100 mg/kg $AlCl_3$ and 949 mg/kg DCM or 949 mg/kg methanol fractions of *Z. officinale*.

The Classic Labyrinth Test (CLT)

Twenty four hours after the last administrations, the classic labyrinth test (CLT) was carried out. The labyrinth was square-shaped with start and end points, and housed in a behavioural test room with a low-intensity white light source. The animals were trained by allowing free exploration of the labyrinth for 10 min. Five trials were performed for each animal: The first four trials represented the training, during which mice were motivated by a reward (biscuit) to reach the end point (the target). On the test day, however, no such reward was allowed (Gasmi 2018). The time (latency) the animal travelled from the start location to the end point (arrival time) was recorded.

Termination of the Experiment and Tissue Analysis

The animals were sacrificed by cervical dislocation immediately after the neurobehavioural test. Whole brains were carefully removed from the skull, and the hippocampal and prefrontal regions of the mice were gently excised, weighed and homogenized. A 10% (w/v) tissue homogenate was made in 0.1 M phosphate buffer (pH 7.4, at 4℃). The homogenates were centrifuged for 10 min at 3,000 rpm, and aliquots of the supernatants were used for biochemical analyses of acetyl cholinesterase (AChE), superoxide dismutase (SOD) and malondialdehyde (MDA) activities following the manufacturers' instructions.

Statistical Analysis

Statistical analysis was done with GraphPad prism (version 8.0) software. One-way analysis of variance and Tukey's multiple comparisons post hoc test were carried out. Only five animals per groups (except for the LD_{50}) were analysed, and probability level of $p < 0.05$ was regarded as statistically significant, and results are presented as mean ± standard error of mean (SEM).

RESULTS

Lethal Dose of *Z. officinale*

The lethal dose (LD_{50} of *Z. officinale* ethanol extract as determined by Lorke's method was 4,743 mg/kg, and presented in Table 1. Groups 1-3 animals survived, while group 4 animals died.

Assessment of the Classic Labyrinth Test

The latency of the mice to complete CLT is presented in Figure 1. The results showed that the $AlCl_3$ treated group spent significantly ($p<0.05$) more time to complete the CLT compared with the control group. The donepezil group, although spent less time compared with the $AlCl_3$ group, spent significantly ($p<0.05$) more time to complete the CLT compared with the control group. The groups treated with *Z. officinale* extracts, except for methanol, spent less time to complete CLT, where the group administered *Z. officinale* ethanol extract (949 and 1,423 mg/kg) spent significantly ($p<0.05$) less time compared with the $AlCl_3$ group. There was also a significant ($p<0.05$) less latency in the 949 mg/kg *Z. officinale* ethanol extract group compared with the donepezil group.

Table 1: Acute toxicity screening of *Z. officinale*

Group (n=3)	Dosage of *Z. officinale* (mg/kg)	Mice mortality
Group 1	3000	0/3
Group 2	4000	0/3
Group 3	4500	0/3
Group 4	5000	3/3

0 = number of death, 3 = number of mice used for test

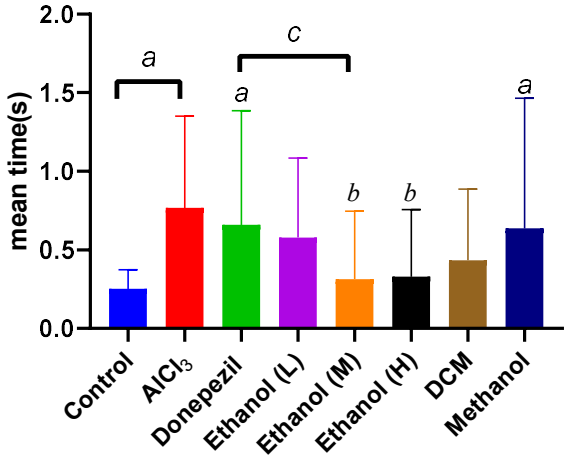

Fig. 1: The latency to complete the classic labyrinth test. a - significant ($p<0.05$) compared with the control group; b - significant ($p<0.05$) compared with the $AlCl_3$ group; c - significant ($p<0.05$) compared with donepezil group; ANOVA followed by Tukey post-test. Data presented as Mean±SEM; (n=5).

Assessment of the Acetyl Cholinesterase Activity

The effect of *Z. officinale* extracts on AChE activity is presented in Figure 2. The result showed that $AlCl_3$ treated group had significantly ($p<0.05$) raised AChE level compared with the control group. The donepezil group, although had less AChE level compared with the $AlCl_3$ group, had significantly ($p<0.05$) raised AChE level compared with the control group. The groups treated with 474 and 949 mg/kg *Z. officinale* ethanol extract had significantly ($p<0.05$) raised AChE level compared with the control group, and

invariably significantly ($p<0.05$) less AChE level compared with the $AlCl_3$ group. The group administered *Z. officinale* ethanol (1,423 mg/kg), DCM (949 mg/kg) and methanol (949 mg/kg) extracts, were not different from the control, but had significantly ($p<0.05$) less AChE level compared with the $AlCl_3$ and donepezil groups.

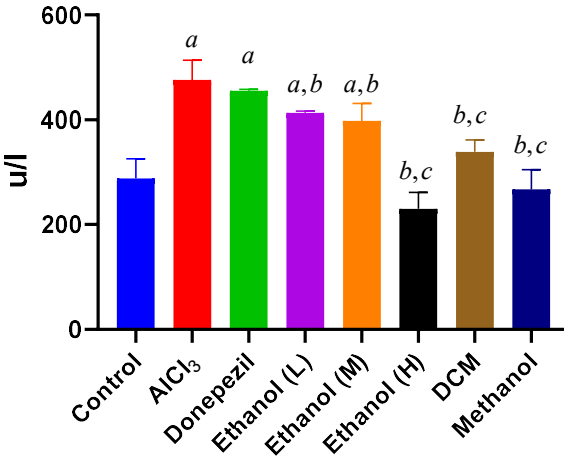

Fig. 2: The brain AChE activity; a - significant ($p<0.05$) compared with the control group; b - significant ($p<0.05$) compared with the $AlCl_3$ treated group; c - significant ($p<0.05$) compared donepezil group; ANOVA followed by Tukey post-test. Data presented as Mean±SEM; (n=5).

Assessment of the Superoxide Dismutase Activity

The effect of *Z. officinale* extracts on SOD activity is presented in Figure 3. The results showed that $AlCl_3$ treated group had significantly ($p<0.05$) less SOD level compared with the control group. The donepezil group, although had an insignificantly ($p>0.05$) raised SOD level compared with the $AlCl_3$ group not different compared with the control group. The group treated with 1,423 mg/kg *Z. officinale* ethanol extract had significantly ($p<0.05$) raised SOD level compared with the control, $AlCl_3$ and donepezil groups. The groups treated with *Z. officinale* (474 and 949 mg/kg) ethanol, DCM and methanol extracts were not different from the control, but the *Z. officinale* (949 mg/kg) ethanol, DCM and methanol extracts groups had significantly ($p<0.05$) raised SOD level compared with the $AlCl_3$ group. The *Z. officinale* methanol extract group also had significantly ($p<0.05$) raised SOD level compared with the donepezil group.

Assessment of the Malondialdehyde Activity

The effect of *Z. officinale* extracts on MDA activity is presented in Figure 4. The results showed that $AlCl_3$ treated group had significantly ($p<0.05$) raised MDA level compared with the control group. The donepezil group, although had less MDA level compared with the $AlCl_3$ group, and was not different from the control group. AChE level compared with the control group Except for the 1,423 mg/kg *Z. officinale* ethanol extract, which was significantly ($p<0.05$) less, there was no difference between the rest of the treatment groups and the control. All the groups administered *Z. officinale* extracts had significantly ($p<0.05$) less MDA level compared with the $AlCl_3$ group. The 1,423 mg/kg *Z. officinale* ethanol and methanol extracts groups also had significantly ($p<0.05$) less MDA level compared with the donepezil group.

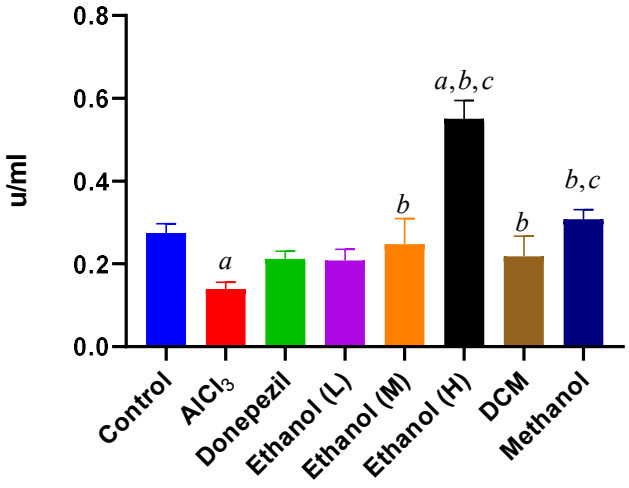

Fig. 3: The brain tissue SOD activity; a - significant ($p<0.05$) compared with the control group; b - significant ($p<0.05$) compared with the $AlCl_3$ treated group; c - significant ($p<0.05$) compared donepezil group; ANOVA followed by Tukey post-test. Data presented as Mean±SEM; (n=5).

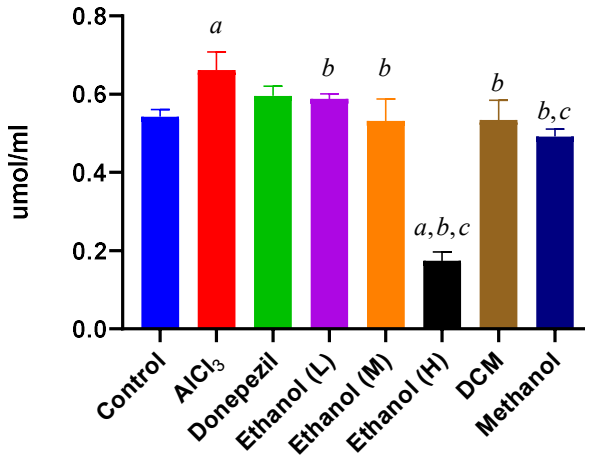

Fig. 4: The brain tissue MDA activity; a - significant ($p<0.05$) compared with the control group; b - significant ($p<0.05$) compared with the $AlCl_3$ treated group; c - significant ($p<0.05$) compared donepezil group; ANOVA followed by Tukey post-test. Data presented as Mean±SEM; (n=5).

DISCUSSION

This study was to investigate *Z. officinale* antioxidant potentials against $AlCl_3$-induced neurotoxicity in Swiss mice. To determine the appropriate dosages the LD_{50} of *Z. officinale* was estimated as 4,743 mg/kg, indicating that te plant is relatively safe for oral use. The present result corroborates that of Abdulrazaq et al. (2012) who reported *Z. officinale* oral LD_{50} of 4,525.5 mg/kg in rats.

The assessment of spatial learning and memory was evaluated using the CLT. There were significantly ($p<0.05$) increased latency in the labyrinth by the $AlCl_3$ group compared with the control. $AlCl_3$ is reported in cognitive, memory and structural impairment (Ekong et al. 2017; Adelodun et al. 2021), and may have resulted in the poor outcome in the present study. The donepezil group spent less time to complete the test, although not significantly ($p>0.05$) compared to the $AlCl_3$ group. Donepezil, an acetyl cholinesterase inhibitor is used in the management of cognitive disability, especially in AD (Nozawa et al. 2009). However, it is known to induce psychotic and extrapyramidal symptoms (Li et al. 2020), which may have affected cognitive ability in the present study.

The *Z. officinale* extracts treated groups decreased the latency in the labyrinth, although only significantly ($p<0.05$) in the 949 and 1,423 mg/kg ethanol extract groups. These results indicate a neuroprotective potential of *Z. officinale*, resulting in the memory enhancing efficacy of its naturally occurring phytochemicals, and is consistent with previous findings (Lim et al. 2014; Huh et al. 2018). In the present study, *Z. officinale* ethanol extract appeared to have been more efficacious compared to the DCM and methanol extracts.

Aluminium easily gains access to the brain where it forms a complex with L-glutamic acid. This complex accumulates in different brain regions including the striatum, hippocampus and cortex, and leads to neuronal and glial disorders (Deloncle et al. 1995). In the present study, brain AChE was significantly elevated in the $AlCl_3$ group indicating its action on acetylcholine metabolism. AChE hydrolyses the neurotransmitter acetylcholine, essential for cognitive functions (Baxter and Crimins 2018). The cholinergic depletion is essentially linked to memory impairment, which supports the declining cognitive ability in the present study. Moreover, exposure to aluminium is also associated with changes in the levels of the monoamines, gamma aminobutyric acid and glutamate (Beal et al. 1989), which are also vital for normal brain functions. The present result collaborates a previous study by Kafeel et al. (2013), who reported significant brain AChE level increase in $AlCl_3$ administration. The donepezil group had decreased AChE, although not significantly ($p>0.05$) compared to the $AlCl_3$ group. Donepezil inhibits AChE, which may be a reason for such in the present study.

The *Z. officinale* ethanol (1,423 mg/kg), DCM (949 mg/kg) and methanol (949 mg/kg) extracts showed significantly decreased AChE activity compared to the $AlCl_3$-treated group, indicating AChE inhibitory activity. Our present results corroborate previous studies on *Z. officinale* AChE inhibitory activity (Oboh et al. 2012; Tung et al. 2017).

Aluminium elicits neurotoxicity through oxidative stress which is marked by SOD and MDA levels among others (Mold et al. 2021). In the present study, $AlCl_3$ significantly ($p<0.05$) reduced superoxide dismutase, while elevating malondialdehyde, collaborating its lipid peroxidation and oxidative stress potential (Nehru and Anand 2005; Naidu et al. 2013). The donepezil group showed raised SOD, with reduced MDA levels, although not significantly ($p>0.05$) compared to the $AlCl_3$ group indicating its role in cognitive improvement. Donepezil is reported in MDA level control (Saxena et al. 2008), which invariably translates to SOD level improvement, even though not as much in the present study.

The *Z. officinale* ethanol, DCM and methanol extracts showed significantly decreased AChE activity, indicating its anti-oxidative role. Our present results corroborate a previous study on *Z. officinale* (Yusof and Abdul-Aziz 2005) who reported its anti-oxidant effects. *Z. officinale* was able to protect the brain by elevating SOD activity, while reducing lipid peroxidation, and thereby preventing oxidative stress. It also regulated AChE level limiting its hydrolytic effect on acetylcholine and leading to cognitive improvement.

Conclusion

$AlCl_3$ caused cognitive impairment, raised AChE and oxidative stress. These adverse effects were not altered following treatment with extracts of Z *officinale*. Thus, *Z. officinale* improved cognition and showed anti-AChE, anti-oxidant and neuroprotective activities, and may be exploited AD management.

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Conflict of Interest
None declared.

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Authors Contribution
UAI - Conception, Writing of initial draft manuscript; KD - Supervised project and read draft manuscript;

SOI – Supervised project; MBE - Advised and Wrote the final draft; ARN - Literature search and data collection; AEA & IUU - statistical analysis.

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