Antioxidant and Neuroprotective Effects of Resveratrol in aluminium chloride-induced Alzheimer-type neurodegeneration in adult male Wistar rat

ABSTRACT

Aims: Alzheimer's disease is a neurodegenerative disease characterized by deficiency in memory and cognition coupled with neuron loss. Previous studies reported that resveratrol is renowned for its pleiotropic effects and diverse health benefits to mankind especially in reversal of neurodegenerative disorders. The study is tailored towards investigating the ameliorative role of Resveratrol in Alzheimer's disease (AD) pathology.

Methodology: Forty (40) adult male Wistar rats (150±20g) were divided into four groups (n=10) and Drug administration spanned for a 45 days period. Group A served as the placebo to which normal saline only was administered, Group B served as the negative control group and received 200mg/kgbw of $AlCl_3$ only, Group C received a combination of 200mg/kgbw of $AlCl_3$ and 50mg/kgbw of resveratrol and Group D received 50mg/kgbw of resveratrol only. All animals were subjected to Neurobehavioral tests (Morris Water Maze and Y-Maze). At the end of the experiment, all animals were sacrificed and organs were harvested.

Results: Biochemical estimations of antioxidant levels (GSH, CAT and SOD), stress markers (MDA), Monoamine neurotransmitters (dopamine, serotonin and norepinephrine) and histomorphology were done. Results showed that $AlCl_3$ administration brought about a decrease in antioxidant enzyme levels and neurotransmitters (except norepinephrine) while resveratrol countered these effects (*P=.05)*. Oxidative stress marker levels were however elevated by $AlCl_3$ administration while resveratrol initiated a decrease (*P=.05)*. Neuro-behavioural assessments such as Morris water maze and Y maze test indicated a decline in long-term and short-term memory due to $AlCl_3$ administration while resveratrol served to improve these functions (*P=.05)*.

Conclusion: These results confirmed that potent capacity of resveratrol in reversing neurodegeneration in a wistar rat model of Alzheimer disease due to its antioxidant properties. Given its well documented presence in dietary sources such grapes etc, and its recognized antioxidant benefits, these findings suggest its potential as a neuroprotective agent in humans. Further translational research, including clinical trials is necessary to explore its efficacy, optimal dosage and long-term effects in Alzheimer's disease management.

Keywords: *Resveratrol, Aluminium Chloride, Antioxidant, Alzheimer's disease, Neurodegeneration, Cognition*

1. INTRODUCTION

Aluminium (Al) is an abundant agent of neurotoxicity (Brough and Jouhara, 2020), mostly found in combination with other elements, especially oxygen and silicon (Ahmed *et al*., 2023). Al exposure occurs usually through food, water and Al-based products intake (the most common), occupational exposure (Al production and user industries) and chronic use of buffered

aspirins as well as antacids that contain Al (Ogunlade *et al*., 2020). Being a renowned environmental neurotoxicant, Al has been underlined in the cause of neurodegenerative disorders like Alzheimer's disease etc (Benyettou *et al*., 2017), and reported to have a negative effect on embryogenesis and the brain's morphological integrity (Klotz *et al*., 2017), as well as a capability for the induction of severe oxidative damage (Samir and Rashed, 2018). Previous studies on degenerating neurons (Shaw *et al*., 2014) and neurofibrillary degeneration (Liu *et al*., 2024) has indicated a high-level Al exposure. The brain has an increased vulnerability to free radicals as a result of its low glutathione content (Benyettou *et al*., 2017) and Al exposure takes advantage of this vulnerability of the brain in inducing oxidative damage and severe toxic manifestations in the central nervous system by production of excess free radicals in the brain (Yuan *et al*., 2012). It also possesses an elevated affinity level for negatively charged brain phospholipids that are easily attacked by reactive oxygen species (ROS), ultimately resulting in neurodegeneration (Huang *et al*., 2020).

Alzheimer's Disease (AD), depending on the level of progression, usually presents in victims with many different symptoms ranging from severe memory loss, dementia and severe cognitive decline to speech impediments as well as an inability to perform tasks that could previously have been considered by the victim as basic or ordinary (Hajipour *et al*., 2016; Kasper *et al*., 2015). Different hypotheses describing the pathogenesis of the disease are in existence; the amyloid cascade hypothesis (Behl, 2024), the tau hypothesis (Nelson *et al*., 2012) the cholinergic hypothesis (Babri *et al*., 2014), etc. There is also the involvement of heavy metal neurotoxicants such as Lead, Al, Cadmium, Nickel, etc (Bakulski *et al*., 2012). Studies of the brains of AD patients have exhibited similar characteristics over the years; the presence of amyloid plaques and neurofibrillary tangles (NFTs) in the extracellular and intracellular regions of the neurons (Coman and Nemes, 2017) and these findings are consistent with research into the effects of Al exposure on neurons. Some studies have associated the presence of NFTs and amyloid plaques in the brain with an increased concentration of Al (Ahmed *et al*., 2023), thus proving its involvement with Alzheimer-type neurodegeneration either through a direct or indirect mechanism of action (Ogunlade *et al*., 2020).

Various researches carried out with the intent of discovering possible ways of alleviating the symptoms that present with AD have discovered the therapeutic role of resveratrol. Resveratrol (3, 5, 4'-trihydroxy-trans-stilbene) is a plant-based polyphenol that occurs naturally in the skin of red grapes, blueberries, peanuts and red wine (Tian and Liu, 2019) and has been shown in rodent models of Alzheimer's disease to possess important neuroprotective properties (Witte *et al*., 2014). Intake of resveratrol has been proven to prevent and protect against cognitive and learning impairment (Ciecero *et al*., 2019), as well as hippocampal neurodegeneration (Surya *et al*., 2023). Resveratrol induces these neuroprotective benefits through a decrease in dysfunction of the mitochondria (Albani *et al*., 2010), and a reduction in chronic inflammation and oxidative damage (Miguel *et al*., 2021). It also assists in the improvement of vascular function and activation of longevity genes (Sun *et al*., 2011). In addition, spatial memory performance in a primate study was found to be improved drastically due to supplementary administration of resveratrol over a period of 18 months (Dal-Pan *et al*., 2011). Resveratrol possesses many potential health benefits against neurotoxicity and Alzheimer-type neurodegeneration, and this research paper is aimed at understanding the underlying mechanisms of its therapeutic actions, and the role it could play against $AICL_3$ induced neurotoxicity and neurodegeneration indicated in Alzheimer's disease.

2. MATERIAL AND METHODS

2.1 Chemicals

Aluminium Chloride ($AlCl_3$) and Resveratrol were procured from Sigma Company (St. Louis, MO, USA). All other chemicals used in the study were of analytical grade.

2.2 Animals and experimental design

A total of Forty (40) adult male Wistar rats (*Rattus norvegicus*) weighing between 150g and 190g were purchased from the breeding colony, College of Medicine, University of Lagos, Nigeria. The rats were housed in the Laboratory Animal house, Department of Anatomy, College of Medicine, University of Lagos, Nigeria. The rats were subjected to a suitable temperature of 32 to 37°C, 24 h light supply, full aeration which was enhanced by wire gauzed cage properly partitioned into four chambers and roomy enough to allow for proper ventilation and free movement within it. The floor of the cage was lined with carpet pieces and sprayed with coarse saw dust which served as a cushion. The coarse saw dust was changed every day to dispose waste droppings and maintain proper hygiene. The rats were fed with grower's marsh (pellets), purchased from a feed store- Agro feeds and flour mills, and water during the period of the experiment. The rats went through an acclimatization period of 7 days.

2.3 Experimental Design

The animals were divided into four groups (n= 10). ($AlCl_3$) dosage (Ogunlade *et al*., 2020) and Resveratrol (RSVT) dosage (Zhou *et al.,* 2022) were dissolved in distilled water and prepared freshly each day for administration. The groups were as follows.

- Group A (control) received normal saline solution (NaCl) orally as *placebo*
- Group B received 200 mg/kgbw of $AlCl_3$ only orally
- Group C received 50 mg/kgbw of RSVT simultaneously with 200 mg/kgbw of $AlCl_3$ orally
- Group D received 50 mg/kgbw of RSVT only orally

All the groups were treated under the same housing conditions for a period of 45 days. The animals were weighed and behavioural observations were recorded. The animals underwent behavioural studies after the last administration. At the end of the experiment, animals were sacrificed through cervical dislocation. The organs were excised, cleaned and washed with saline (0.9 % sodium chloride).

2.4 Behavioural Assessment

Prior to the termination of the experiment, the rats underwent neurobehavioral testing using Morris water maze and Y maze tests for spatial memory and working memory (Vorhees and Williams, 2006; Kraeuter *et al*., 2019).

2.5 Tissue collection and processing

After the behavioural tests were concluded, the rats were subjected to cervical dislocation, and the brain tissues were immediately excised and dissected into two hemispheres. All the right hemispheres were fixed in 4% paraformaldehyde for histological processing, while the left hemispheres were rinsed three times in 0.25 M sucrose for five minutes and stored in 30% sucrose at 4°C.Paraffin wax sections were obtained for histological analysis. The hippocampus was excised from the fixed brain and dehydrated in ascending grades of alcohol (50%, 70%, 90%, and 100%). The tissues were then cleared in xylene twice for 15 min each. Infiltration and embedding were done with paraffin wax in Leica hot air oven at 56°C with tissues eventually embedded in paraffin wax at similar orientations. Tissue sections were obtained serially using a rotary microtome (Leica RM2245) and then mounted on glass slides. Sections were taken at 30 µm for Hematoxylin and Eosin staining process using the method modified by (Fischer *et al*., 2008). The slides were analysed using Leica®DM5000B microscope and photographed with Leica EC3 digital camera.

2.6 Antioxidants markers

The determination CAT and SOD activity was conducted using method by (Clairborne, 1995) and (Sun and Zigma, 1978) respectively. A method by (Jollow et al., 1974) and (Farombi *et al*., 2000) used adopted for determining GSH and MDA activity.

2.7 Brain Monoamine Neurotransmitters Analysis

Monoamine neurotransmitter (DA, 5-HT and NE) level was estimated using HPLC technique and the brain content of these neurotransmitters was made using the equation of (Pagel *et al*., 2000).

2.8 Statistical analysis

The data were normal distributed and Statistical analysis was performed by one-way analysis of variance (ANOVA) with Tukey's multiple comparisons test using Graph Prism® software. The sample was calculated using an effect size of 0.5 based on the prior studies of resveratrol neuroprotective effects and a power of 80% together with 0.05 significance level were employed. The data were reported as means ± SEM, while differences between means at P=.05 were considered significant.

3. RESULTS:

3.1 Effect of Resveratrol on MWM Test in Aluminum chloride induced neurotoxicity in normal and treated rats.

The results of the MWM test showed the highest escape latency period in the group of rats treated with $AlCl_3$ only. On the other hand, the group treated with resveratrol only exhibited the least period of escape latency. The rat group treated with a combination of resveratrol and $AlCl_3$ however showed a slightly lower period of escape latency than the rat group treated with $AlCl_3$ only.

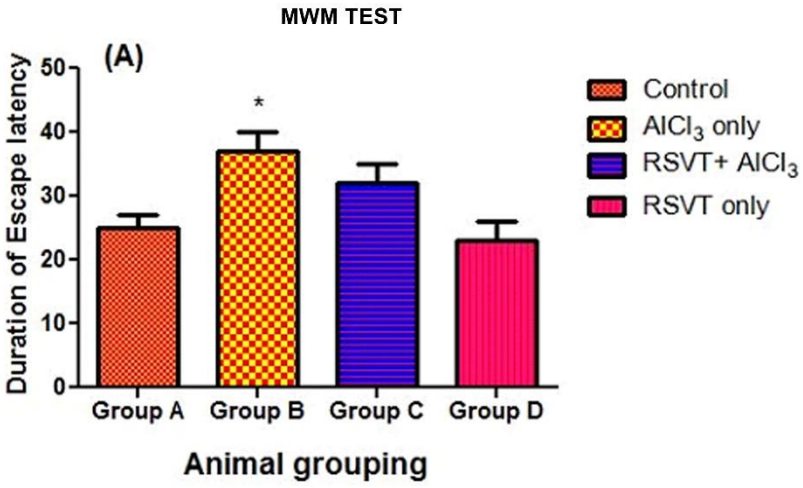

Figure 1A: Effects of $AlCl_3$ and RSVT on MWM Test. Values are Mean ± SEM.

($\eta^2 = 0.5$, *P=.05 **vs** RSVT + $AlCl_3$, RSVT only). $AlCl_3$—Aluminum Chloride, RSVT--Resveratrol, MWM—Morris Water Maze)

3.2 Effect of Resveratrol on Y-Maze Test in Aluminum chloride induced neurotoxicity in normal and treated rats.

Results from the Y-maze test showed the least percentage correct alternation in the group of rats treated with $AlCl_3$ only. The highest percentage correct alternation was seen in the control group and the rat group to which only resveratrol was administered. The group of rats that received a combination of resveratrol and $AlCl_3$ however showed slightly higher percentage of correct alternation when compared to the group to which only aluminium chloride was administered.

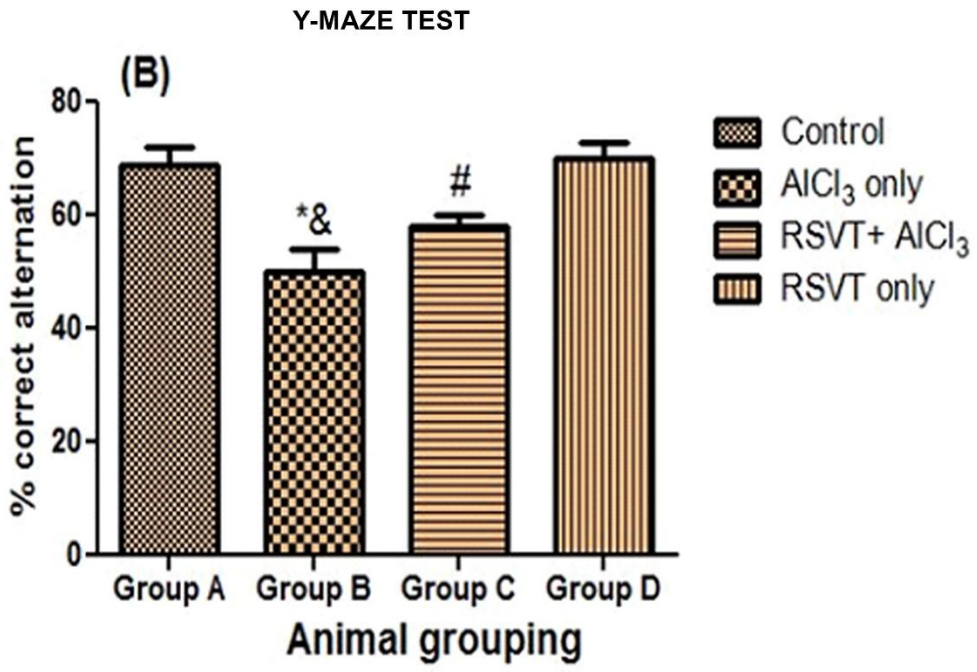

Figure 1B: Effects of $AlCl_3$ and RSVT on Y-Maze Test. Values are Mean ± SEM.

($\eta^2 = 0.5$, *, & P=.05 vs Control, RSVT + $AlCl_3$, RSVT only; # P=.05 vs $AlCl_3$ only). $AlCl_3$—Aluminum Chloride, RSVT--Resveratrol, MWM—Morris Water Maze).

3.3 Effect of Resveratrol on Antioxidant parameters (CAT, SOD and GSH) in Aluminum chloride induced neurotoxicity in normal and treated rats.

Tests carried out to assess the levels of antioxidant enzymes showed a decrease in the levels of GSH, SOD and CAT in the group of rats to which only $AlCl_3$ was administered, in comparison with the other rat groups. There was however a very significant elevation in the antioxidant enzyme levels in the group treated with only resveratrol. The control group and the group treated with resveratrol only showed very little difference in CAT and SOD levels although the GSH level was slightly higher in the control group. The group treated with a combination of $AlCl_3$ and resveratrol showed higher antioxidant enzyme level than the $AlCl_3$ only-treated group, but lower enzyme levels in comparison with the resveratrol only-treated group.

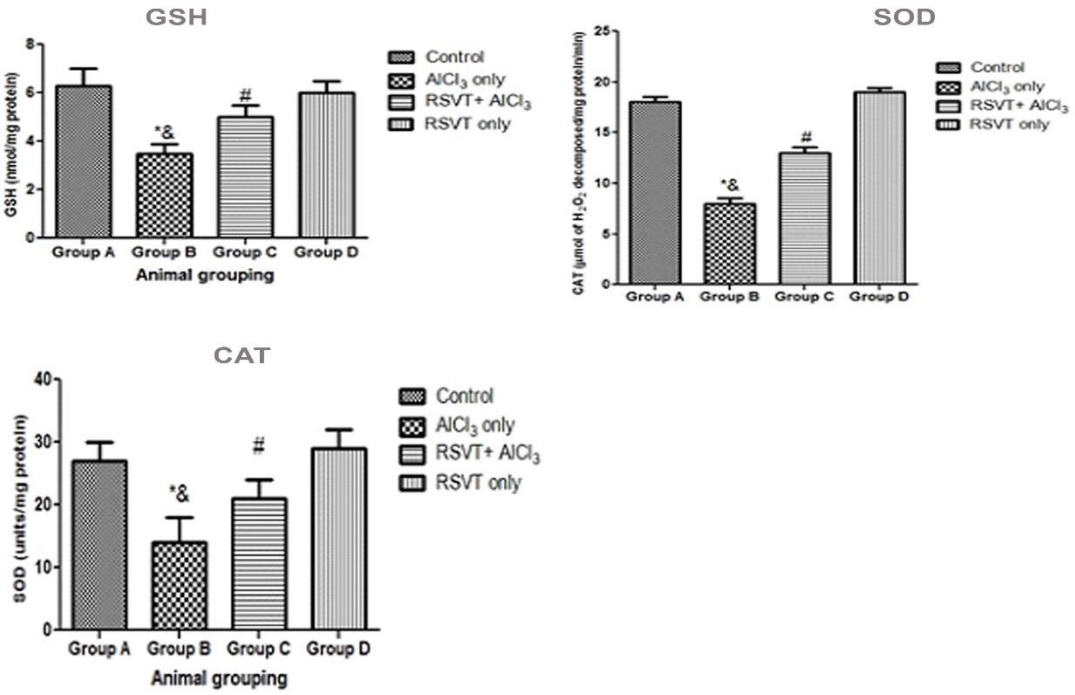

Figure 2: Effects of $AlCl_3$ and RSVT on Antioxidant Parameters. Values are Mean ± SEM.

($\eta^2 = 0.5$, *, & P=.05 vs Control, RSVT + $AlCl_3$, RSVT only; # P=.05 vs $AlCl_3$ only). $AlCl_3$—Aluminum Chloride, RSVT--Resveratrol.

3.4 Effect of Resveratrol on brain neurotransmitters (Dopamine, Serotonin and Norepinephrine) in Aluminum chloride induced neurotoxicity in normal and treated rats.

Tests carried out to measure neurotransmitter activities revealed a very significant decrease in dopamine and serotonin levels in the group of rats treated with $AlCl_3$ only in comparison with the other groups. On the contrary, norepinephrine levels in the $AlCl_3$-treated group were greatly elevated when compared with the other groups. The control group showed slightly lower dopamine and serotonin levels in comparison with the resveratrol only-treated group. Norepinephrine level was lowest in the resveratrol only-treated group and the group treated with a combination of $AlCl_3$ and resveratrol showed a higher norepinephrine level in comparison with the resveratrol only group, and a lower norepinephrine level compared to the group treated with $AlCl_3$ only.

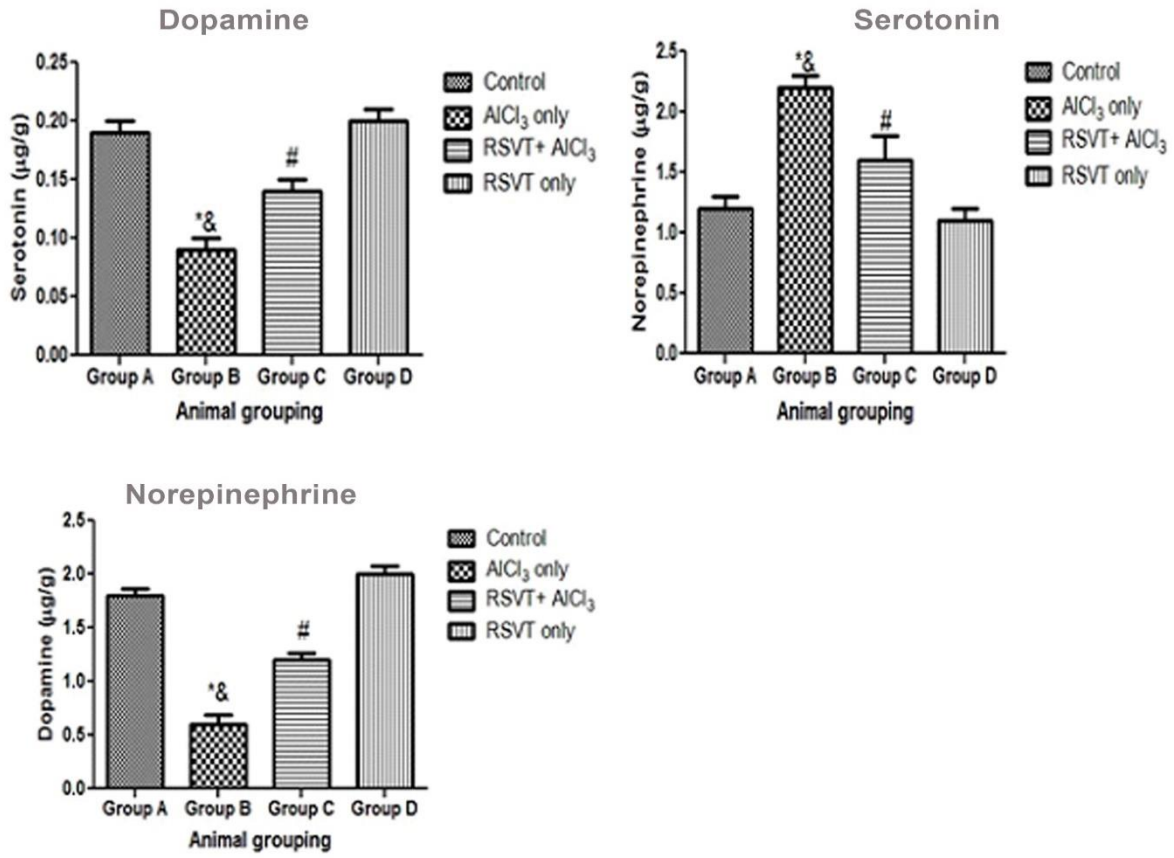

Figure 3: Effects of $AlCl_3$ and RSVT on Monoamines Neurotransmitters Levels. Values are Mean ± SEM.

($\eta^2 = 0.5$, *, & P=.05 vs Control, RSVT + $AlCl_3$, RSVT only; # P=.05 vs $AlCl_3$ only). $AlCl_3$—Aluminum Chloride, RSVT—Resveratrol.

3.5 Effects of resveratrol on oxidative stress markers (MDA) in Aluminum chloride induced neurotoxicity in normal and treated rats.

Oxidative stress marker levels were assessed and the result showed an elevation in MDA levels in the $AlCl_3$ only-treated group in comparison with the other groups of rats. The control group and resveratrol only-treated groups exhibited similarly low levels of MDA with almost no difference between them. The group to which a combination of $AlCl_3$ and resveratrol was administered showed higher MDA level when compared with the control group and resveratrol only group, but lower MDA level when compared with the $AlCl_3$ only-treated group.

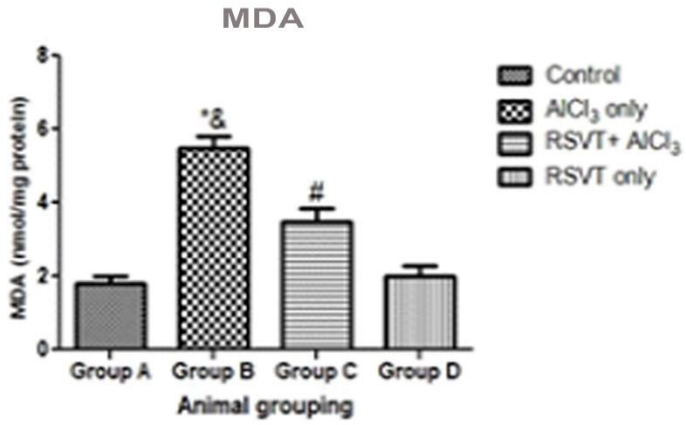

Figure 4: Effects of $AlCl_3$ and RSVT on MDA levels. Values are Mean ± SEM.

($\eta^2 = 0.5$, *, & P=.05 vs Control, RSVT + $AlCl_3$, RSVT only; # P=.05 vs $AlCl_3$ only). $AlCl_3$—Aluminum Chloride, RSVT--Resveratrol, MWM—Morris Water Maze.

3.6 Histological observation

The representative photomicrograph of the Lead acetate only group (Group B) showed darkened loosely arranged granular cells decrease number of pyramidal cells in the pyramidal layer with shrunken glial cell layers with decreased cell number, dilated blood vessels and vacuolated neuropils (Fig. 5B) when compared with the control (Group A) (Fig. 5A). However, combine administration of SFN and Lead acetate (Group C) revealed decreased pathological features in the hippocampus thereby resulting in almost normal brain morphology (Fig. C) similar to control and SFN only groups (Groups A and D) (Fig. 5A & 5D respectively). Additionally, the SFN only group (Group D) showed closely packed cells within the granular layer with visible pyramidal cells both in the external granular layer and the pyramidal layer (Fig. 5D) similar to the control (Group A) (Fig. 5A).

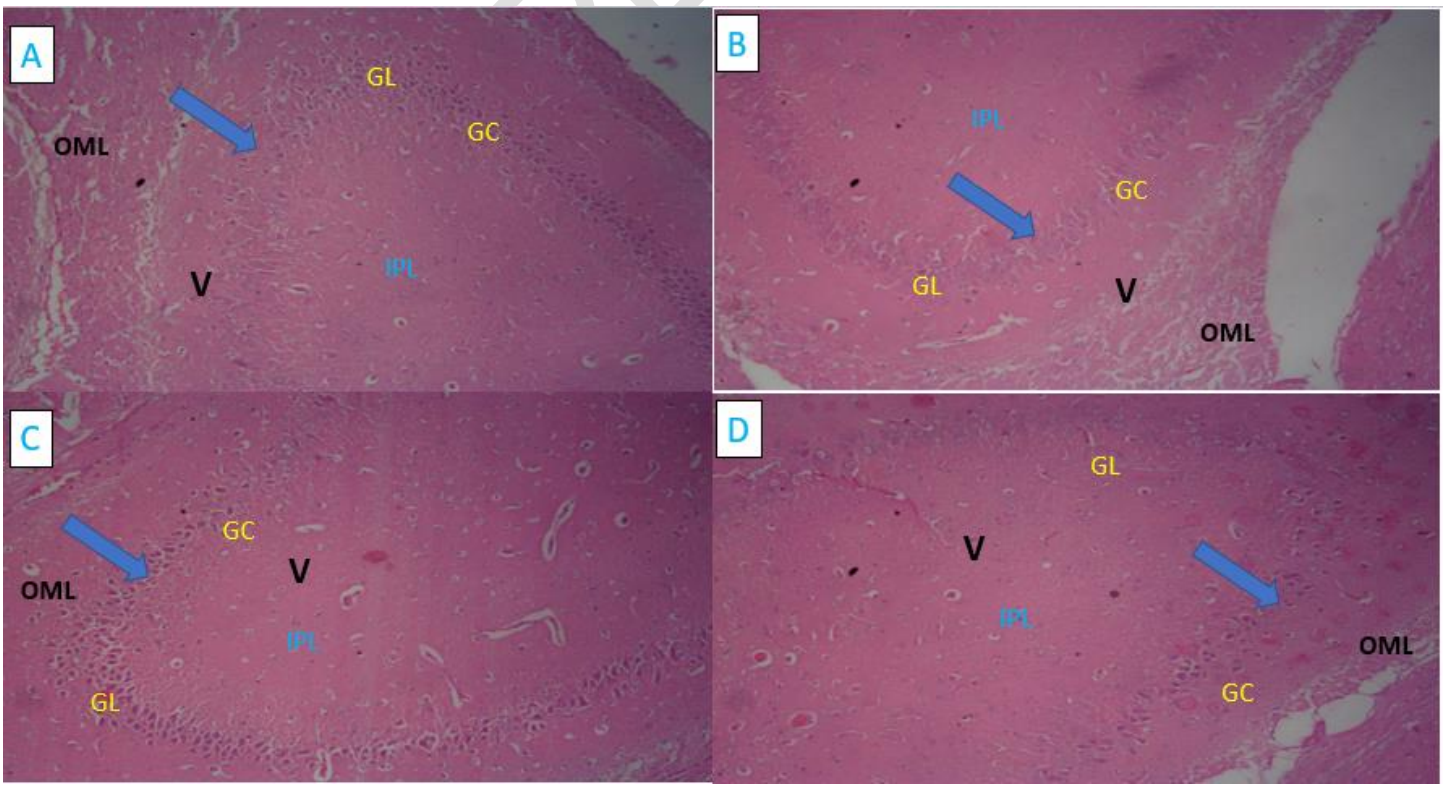

Figure 5: **A**: Normal hippocampus morphology with numerous glial cells (arrow) within the glial layer , **B:** Few pyramidal cells with distorted glial cells (arrow) within the glial layer between the inner pyramidal layer and outer marginal layer and Vacuolated neuropils, **C:** Preserved proliferation of glial cells (arrow) within the glial layer interspersed between the inner pyramidal layer and outer marginal layer similar to control, **D:** Normal orientation of glial cells within the glial layer between the inner pyramidal layer and outer marginal layer similar to the control.

GC (Glial Cells), V (Vacuolated Neuropils), GL (Glial Layer), IPL (Inner Pyramidal Layer), OML (Outer Marginal Layer). H and E: x400. Scale bar-50µm

3.7 DISCUSSION

Alzheimer's Diseases (AD) has for a long time posed a mental health threat and has been a tremendous socioeconomic burden in civilized populations (Sanabria-Castro *et al*., 2017). Its prevalence is quite high and it is fast becoming a defining characteristic in most modern industrialized societies (Kumar *et al*., 2016). Due to the severe symptoms it presents with in its victims (cognitive decline, memory impairment, dementia, etc.) (Sanabria-Castro *et al*., 2017), medical researchers have carried out various investigations into its causes and possible methods of treatment.

Aluminium (Al) neurotoxicity is indicated in the pathogenesis of neurodegenerative disorders (Benyettou *et al*., 2017; Ogunlade *et al*., 2020), partly due to its prevalence in the environment (Ahmed *et al*., 2023) and its readiness to cross the blood-brain barrier as well as induce oxidative damage due to production of free radicals in the brain (Ahmed *et al*., 2023). There are several mechanisms by which Al induces cortical and hippocampal neurodegeneration as seen in AD pathology and this research attempts to further illuminate these mechanisms as well as probe into the health benefits and ameliorative potential that resveratrol could possess in reversing the resulting neurodegeneration.

During the course of this research, neurobehavioral assessments were carried out on the rat groups treated with aluminium chloride and resveratrol. The Morris Water Maze (MWM) test was designed specifically to evaluate long term memory, while the Y-maze test is important in the evaluation of short-term memory (Omotoso *et al*., 2018). The MWM measures the duration of the escape latency period so as to assess the long-term memory of the test subjects while the Y-maze test assesses short term memory by measuring the percentage of correct alternation in the different rat groups (Omotoso *et al*., 2018). The results of the neurobehavioral assessment showed the highest escape latency period in the group of rats treated with $AlCl_3$ only, suggesting a decline in long term memory induced by aluminum chloride administration. On the other hand, the group treated with resveratrol only exhibited the least period of escape latency, proving resveratrol's capability to reverse deterioration of long-term memory. Furthermore, it was observed from the Y-maze test results that the least percentage of correct alternation occurred in the group of rats treated with $AlCl_3$ only. The highest percentage correct alternation was seen in the control group and the rat group to which only resveratrol was administered. Collectively, these results indicate a deterioration in long-term and short-term memory made possible by aluminium chloride and the subsequent reversal in deterioration brought about by resveratrol administration.

Cholinergic neurons are linked majorly to the regions of the cortex and hippocampus that are responsible for cognitive functions such as learning and memory (haam and Yakel, 2017) and thus function in the processes of learning and memory. Al presence in the brain decreases the entire cholinergic system function (as determined by the measure of acetylcholinesterase enzyme) (Justin *et al*., 2015). Consequently, long-term and short-term memory functions are affected. Resveratrol is however capable of countering the negative effects of aluminum chloride. Kennedy *et al*., (2010) conducted a study in which a single dose of 250 and 500mg of resveratrol resulted in an immediate increase in cerebral blood flow. It was further suggested that after a much longer duration of resveratrol intake, beneficial improvements on brain perfusion may ultimately translate into improvements in behavior (Witte *et al*., 2014) and this proves resveratrol's positive influence on cognition, learning and memory.

The tests carried out to assess the levels of antioxidant enzymes revealed a decrease in GSH, SOD and CAT levels in the Wistar rat group to which only $AlCl_3$ was administered, suggesting a deleterious effect of Al on antioxidant enzymes in the brain. There was however a very significant elevation in antioxidant enzyme levels in the resveratrol-treated group. Also, the group treated with a combination of $AlCl_3$ and resveratrol showed higher antioxidant enzyme level than the $AlCl_3$ only-treated group, further indicating that while aluminium depletes antioxidant reserves in the brain, resveratrol reverses this effect. It has been established that resveratrol has the capacity to increase levels and activities of SOD and GPx due to its high antioxidant activity. Resveratrol is a stilbene compound that has a phenolic ring and a phytoalexin in its constitution (Catagol *et al*., 2012) and its antioxidant ability is conferred upon it due to the presence of these linked rings in its structure (Navarro-Cruz *et al*., 2017).

Monoamine neurotransmitter levels were evaluated during this research and the results revealed a very significant decrease in dopamine and serotonin levels in the group of rats treated with $AlCl_3$ only; this indicates a reduction in monoamine

neurotransmitter levels due to the deleterious effect of aluminium chloride. On the contrary, norepinephrine levels in the $AlCl_3$-treated group were greatly elevated in comparison with the other groups. Norepinephrine level was lowest in the resveratrol only-treated group and the group treated with a combination of $AlCl_3$ and resveratrol showed a higher norepinephrine level in comparison with the resveratrol only group, and a lower norepinephrine level compared to the $AlCl_3$ only group. The occurrence of depression and mood swings in AD patients has in some studies been linked to the depletion of monoamine neurotransmitters (dopamine and serotonin) and consequent reduction of their activities in the brain (Martocchia *et al*., 2014). An increase in dopamine and serotonin levels could therefore be helpful in alleviating depression as seen in AD cases (Gu *et al*., 2019). Resveratrol is capable of significantly increasing the levels and activities of neurotransmitters in the prefrontal cortex, thus increasing neuropeptide expression in the brain, and this can have an antagonistic effect on depression in AD patients (Gu *et al*., 2019).

An evaluation of the level of oxidative stress markers showed an elevation in MDA levels in the $AlCl_3$ only-treated group in comparison with the other groups of rats, suggesting a link between presence of Al and the increase in oxidative stress as indicated by elevated stress marker levels. The control group and resveratrol only-treated groups exhibited similarly low levels of MDA, indicating that resveratrol is capable of combating oxidative stress with evidence in the depleted MDA levels. In addition to its potent antioxidant abilities, the linked structures in resveratrol's constitution also have a proven ability to scavenge hydroxyl radicals that could result in oxidative damage (Navarro-Cruz *et al*., 2017).

Antioxidant enzymes present inherently in the human body are very important in protection from adverse modifications of oxidative stress as well as in the maintenance of redox balance (Pandey and Rizvi, 2010). Many experimental evidences have proven that resveratrol is capable of inducing the activities of these antioxidant enzymes. A study by Cao and li, 2004 demonstrated that endogenous enzymes including superoxide dismutase (SOD), glutathione reductase (GR), glutathione-S-transferase (GST) and NAD(P)H can be induced by resveratrol in low micromolar concentrations (Cao and li, 2004). At concentrations of 10-100mM, resveratrol has also been proven to exert great protection against H_2O_2 induced oxidative injury through an elevation in the levels and activities of GSH (Yen *et al*., 2003). This elevation in GSH levels is brought about by the property of resveratrol to scavenge free radicals (Ates *et al*., 2007).

Resveratrol has had a prolonged history of serving mankind as a part of several different medicinal herbs and preparation, all around the world (Pandey and Rizvi, 2010). Several studies in the past few years have shown that resveratrol is capable of slowing down or altogether preventing the progression of a wide range of diseases in humans. These diseases include cancer, cardiovascular problems, ischemic injuries, etc. It also enhances resistance to stress as well as lengthens the life-spans of various organisms ranging from simple yeasts to complex vertebrates (Markus and Morris, 2008). In addition to the reported plethora of health benefits possessed by resveratrol (cardio-protective, anti-cancer, neuro-protective, anti-diabetic, etc.), it has also been established in this research that resveratrol can positively reverse Alzheimer-type hippocampal and cortical neurodegeneration and its symptoms brought about by exposure to heavy metal neurotoxicants and this healing capacity of resveratrol is mostly attributed to its incredibly potent antioxidant property.

Our findings demonstrate that resveratrol significantly improved cognitive function in an $AICL_3$- induced rat model of Alzheimer disease. This aligns with human studies showing resveratrol's neuroprotective effects. Kennedy et al., (2010) observed that a single dose of resveratrol (250mg and 500mg) improved cerebral blood flow in human subjects, suggesting its potential role in enhancing brain function. Additionally, Writte *et al*., (2014) reported that long term resveratrol supplementation (200mg daily for 26 weeks) resulted in improved memory performance and functional connectivity in the hippocampus of adults. These human studies support our animal findings and highlight the potential of resveratrol as a therapeutic intervention for Alzheimer disease.

4. CONCLUSION

It can thus be concluded that Chronic Aluminium exposure is a major environmental neurotoxicant to the general well-being of the populace due to its involvement in the pathogenesis of Alzheimer's disease and Resveratrol can play a major role in preventing or ameliorating the deleterious neurotoxicity and neurodegeneration as a result to exposure to Aluminium, thereby allowing the proper cognitive function and normal homeostasis of the brain. However, further clinical trials are necessary to determine the optimal long-term effects on human populations.

Ethical Approval:

This study was conducted in accordance to ARRIVE guidelines and the processes of protocols using the experimental animals were in accordance to the Guide for the Care and Use of Laboratory Animals and approved by the Health Research Ethics Committee of the College of Medicine, University of Lagos (HREC/CMUL/023).

Disclaimer (Artificial intelligence)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

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