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(RESEARCH ARTICLE)

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Anxiogenic, impaired memory and motor functions due to lead-induced cerebral cortex and hippocampal injury in Wistar rat is attenuated by lauric acid

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Abstract

Background: The present study used lauric acid to attenuate anxiety, impaired memory and motor functions due to lead-induced cerebral cortex and hippocampal injury in wistar rat.

Methodology: Thirty-five adult male wistar rats (150 – 200g) were divided into seven groups of experimental protocols: Food only, Pb^{2+} only, Noral saline + 1000mg/kg LA, (500mg/kg LA + Pb^{2+}), (1000mg/kg LA + Pb^{2+}), (2000mg/kg LA + Pb^{2+}), and (0.2mg/kg Donepezil + Pb^{2+}). Anxiety, impaired cognitive and motor functions were induced by oral administration of 120mg/kg of Pb^{2+} daily, for 7 days and treated with lauric acid for 14 days. Elevated plus maze, Y maze and walking beam test were performed on the animals. After the experimental period, the animals were sacrificed via cervical dislocation. Perfusion was made, and the brains were harvested, rinsed in normal saline, fixed in 10% formal saline, and subjected to histological studies.

Results: There is a statistically significant ($p < 0.05$) increase in the percentage alternation and novel arm entry in the lauric acid post-treated groups after Pb^{2+} induced anxiogenic activity, impaired cognitive and motor functions when compared with the rats treated with Pb^{2+} without lauric acid intervention. In walking beam test, there is a statistically significant ($p < 0.05$) decrease in exploratory and locomotive activities of rats treated with Pb^{2+} when compared with the normal control and lauric acid treated. Also, there is a statistically significant ($p < 0.05$) decrease in open arm entry and open arm time for rats treated with lead (Pb^{2+}) without lauric acid intervention when compared with the normal control and lauric acid intervention. The histology presents normal appearance of the neuroglial cells, with conspicuous apical and basal dendrites, and no signs of degeneration in the donepezil and lauric acid post-treated rats.

Conclusion: There were comparable degrees of abatement as evidenced by the neurobehavioural results, normal histological appearance of the cerebral cortex and hippocampal architecture, with conspicuous apical and basal dendrites, and no signs of degeneration in the lauric acid treated rats. This indicates that lauric acid has the potential that may have restored the anxiogenic activity, cognitive and motor deficits caused by the Pb^{2+}. Therefore, lauric acid has justified in this study that reduced anxiety, restored cognitive and motor functions may be the indication of its anxiolytic and anti-neurodegenerative properties. Meanwhile, it is worthwhile to consider this aspect at a deeper level of investigation using different animal models and methods.

Keywords: Anxiogenic; Memory and Motor impairement; Cerebral cortex; Hippocampus; Lauric acid

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1. Introduction

Lead (Pb^{2+}) toxicity is a prominent risk factor for impaired memory and motor functions, Ezugwu et al., 2022; Zhang et al., 2017. In rats, lead toxicity causes anxiogenic activities, impaired memory and motor functions Ashayeri et al., 2020; 2021; Panahi et al., 2019; Liu et al., 2021; Khan et al., 2020; Iqubal et al., 2020; Issa et al., 2020; Ahmed et al., 2013; Bhattacharyya and Bhunia, 2021. Through inflammation, this eventually disrupt or even kill pyramidal cells, which are cells that process and transmit signals in the brain and other parts of the nervous system, Gorji, 2022; Ben-Azu et al., 2020. Consequently, cognitive and motor deficits occur, Habas, 2013; Amanzadeh et al., 2019; Taejib et al., 2022; Balogun et al., 2021. Lead, as a neurotoxicant, crosses the blood-brain barrier to cause oxidative stress, Barkur and Bairy, 2015, morphologic damage, neurodegeneration, cognitive and motor impairment in the brain, particularly that of the developing brain, Zhang et al., 2017. Lauric acid is a medium-chain fatty acids (MCFA). MCFAs act as a non-carbohydrate fuel source by enhancing the formation of ketones or ketone bodies, (Leppano et al., 2017). Ketone bodies are important alternative energy source in the brain, and is beneficial to people developing or already with memory impairment, as in Alzheimer's disease (AD), (Fernando, 2015). Lauric acid is a MCFA which constitutes the majority of coconut oil nutritional content, (Leppano et al., 2017). Lauric acid attenuates the inflammatory response induced in microglial cell, (Nishimura et al., 2018; Sona et al., 2018). Lauric acid promotes neuronal maturation mediated by astrocytes in primary cortical cultures, (Shingo and Hiroshi, 2020). Astrocyte-conditioned medium after lauric acid treatment also enhanced the presynaptic protein levels in the cortical neuron cultures, (Shingo and Hiroshi, 2020). Also, lauric acid directly activates the neuronal ERK and Akt signaling to prevent amyloid β toxicity (Nafar et al., 2017).

Lead remains a considerable occupational and public health problem (Ezugwu et al., 2021), which is known to cause a number of adverse effects like impaired cognitive functions, severe behavioural anomalies, neuromuscular weakness, and decreased hearing, (Adekomi et al., 2017; Highab et al 2018). There is reported cases of lead poisoning in Zamfara and Ebonyi state of Nigeria, Zhang et al., 2017. Most current drugs for lead-induced neurotoxicity are not effective, have side effects, and are quite expensive, (Thangarajan et al., 2018). There are scanty discoveries on safe medicinal plant or natural remedy as treatment options for lead induced brain damage in our environment, (Varma et al 2017).

2. Materials and method

2.1 Materials

2.1.1 Experimental animals

Thirty-five (35) adult male wistar rats (150 – 205g) were procured and caged in a well ventilated animal house. They were divided into seven groups of experimental protocols (Table 2.2.1). Each group had five (5) rats. The experimental period lasted for 21 days, after which the animals were sacrificed via cervical dislocation. Perfusion was made, and the brains were harvested, rinsed in normal saline, weighed, fixed in 10% formal saline, and subjected to histological studies.

Extracts, Drugs and Chemicals

All the extracts, drugs and chemicals used in this study were purchased from Nigerian markets, Nigerian chemical stores and Pharmacy, and they are of analytical standard.

2.1.1.1 Extract and Chemical

Extracts and chemicals were purchased from Okey Scientific Store, Enugu main market, Enugu, Enugu State, Nigeria. They were authenticated at the department of Applied Biochemistry, University of Nigeria, Nsukka.

2.1.1.2 Donepezil

Donepezil was purchased from Care-Root Pharmacy and Stores, Trans-Ekulu, Enugu, Enugu State of Nigeria.

Experimental Protocol

Table 1 Experimental Protocol

Treatment	Administration
Food only	Received food and normal saline only
Control: Lead (Pb^{2+})	Received 120 mg/kg Pb^{2+} daily for 7 days
1000mg/kg Lauric acid (LA)	Received normal saline daily for 7 days. Then, 1000mg/kg lauric acid for 14 days
120mg/kg Pb^{2+} + 500mg/kg LA	Received 120 mg/kg Pb^{2+} daily for 7 days. Then, 500mg/kg lauric acid for 14 days
120mg/kg Pb^{2+} + 1000mg/kg LA	Received 120 mg/kg Pb^{2+} daily for 7 days. Then, 1000mg/kg lauric acid for 14 days
120mg/kg Pb^{2+} + 2000mg/kg LA	Received 120 mg/kg Pb^{2+} daily for 7 days. Then, 2000mg/kg lauric acid for 14 days
120mg/kg Pb^{2+} + 0.2mg/kg Donepezil	Received 120 mg/kg Pb^{2+} daily for 7 days. Then, 0.2mg/kg donepezil daily for 14 days

2.2 Neurobehavioural Studies

2.2.1 Elevated Plus Maze

The elevated plus maze relies upon rodents' proclivity to closed arm of the elevated plus maze (approach) and an unconditioned fear of heights/open arm (avoidance). This test is used to to determine anxiogenic behaviours in rats, Olakunle et al., 2012.

2.2.2 Y Maze Spontaneous Alternation Test

Y Maze Spontaneous Alternation is a behavioral test for for measuring memory and learning via the willingness of rodents to explore new environments (Olakunle et al., 2012).

Number of triads = (Total entries – 2) Triad (set of three letters) containing all three letters is scored as alternation.
Percent alternation = $\frac{\text{No of alternation x 100}}{\text{No of tiad}}$

2.2.3 Beam Balance (Beam walking) test

The beam walking test is used to assess fine motor coordination and balance in rodents, especially in experimental models associated with an alteration of motor skills, Southwell et al., 2009.

2.3 Wistar Rats Sacrifice

After 24 hours following the last administration, the animals were sacrificed by cervical dislocation, and the blood samples were collected via orbital puncture from each rat and put in a plain blood specimen bottle for biochemical assay. The brain tissues were removed and fixed in buffered formalin solution. The specimens were taken to the histology laboratory for tissue processing (Highab et al., 2018).

2.4 Haematoxylin and Eosin (H and E) Staining Method

The methods of H and E and CFV staining were carried out according (Highab et al., 2018). Sections of the tissues were viewed under a light microscope, and photomicrographs were made using a digital am scope (MD 900) microscope. Pyramidal cells of the cerebrum and hippocampus were counted using Digimizer image analysis software. Pyramidal cells, neuroinflammatory and oxidative stress assays were done.

2.5 Data Analysis

Data obtained were expressed as mean ± SEM (standard error of mean). One-way analysis of variance (ANOVA) was used to compare the mean differences. Tukey's post hoc test was done where the result was significant. P-value less

than to 0.05 was considered statistically significant. All results were analysed using the Statistical Package for Social Sciences (SPSS version 22).

3. Results

3.1 Body and Brain Weight Results

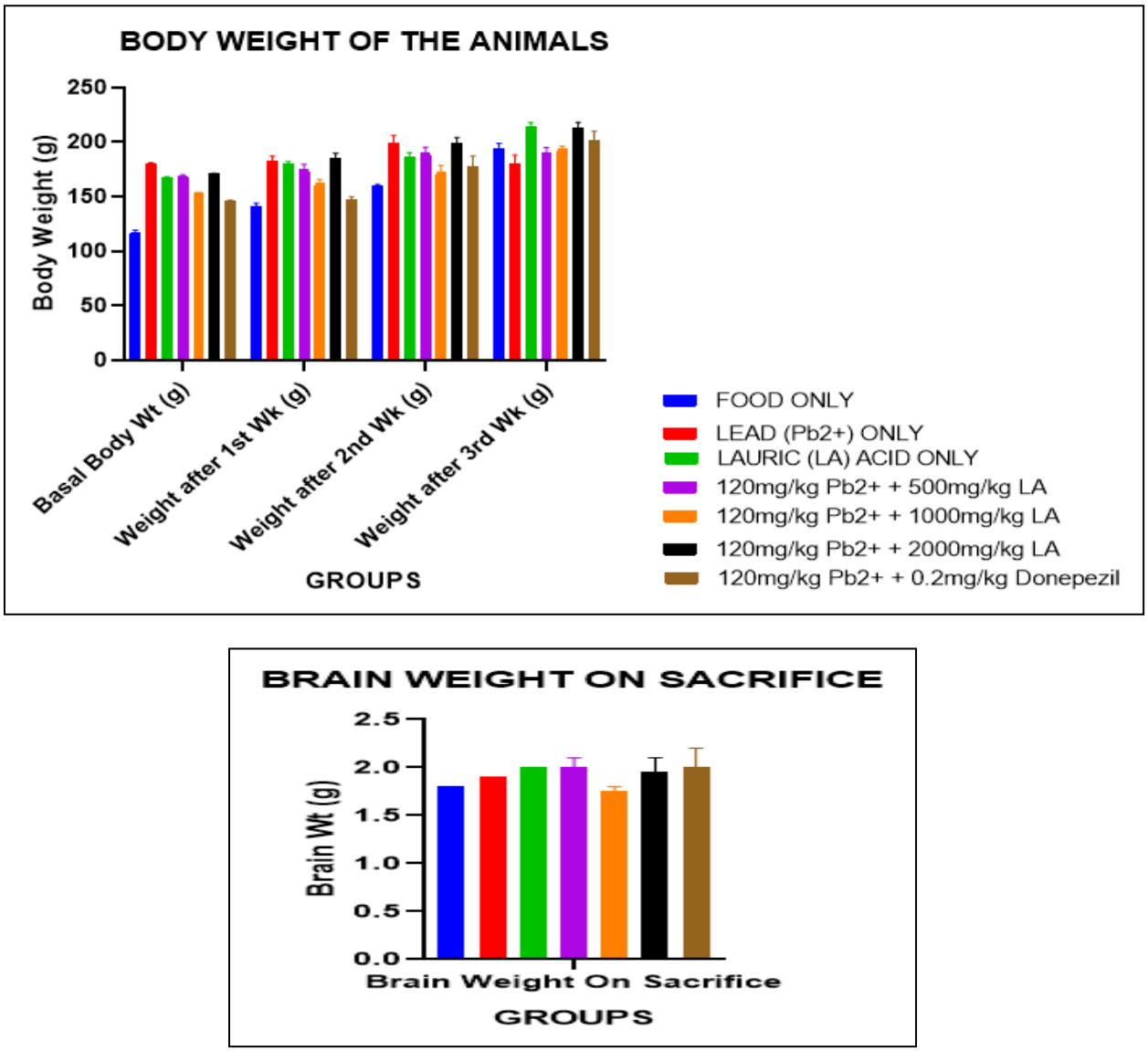
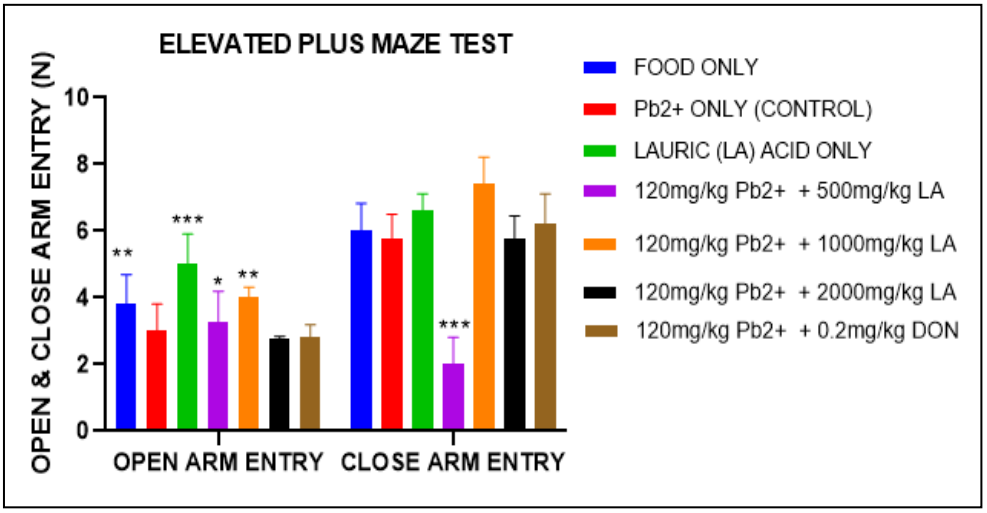


Figure 1 Body and brain weight of the animals

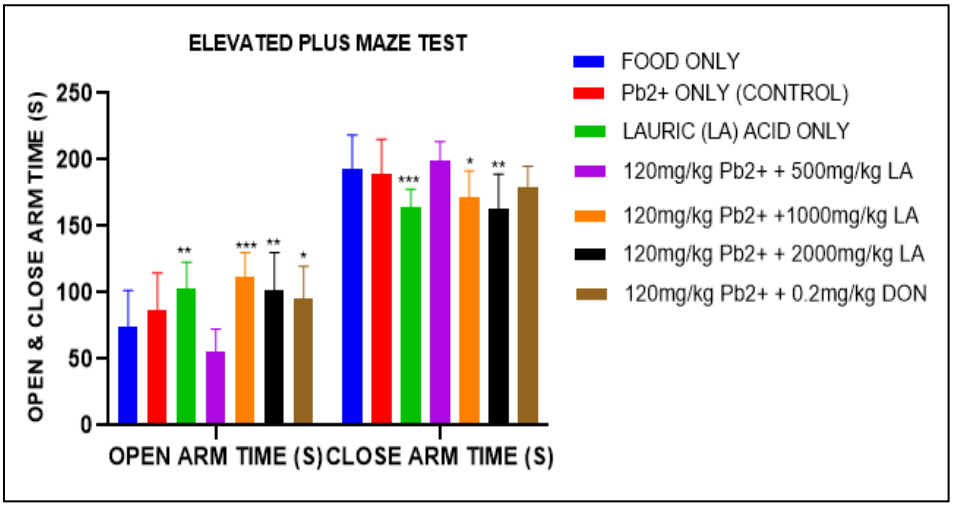
3.2 Neurobehavioural results

3.2.1 Elevated Plus Maze (EPM)



Values are mean ± SEM; n = 5 in each group, (P < 0.05) = Statistically significant. ; * Significant when compared to the control at P < 0.05; ** Significant when compared to the control at P < 0.01; *** Significant when compared to the control at P < 0.001

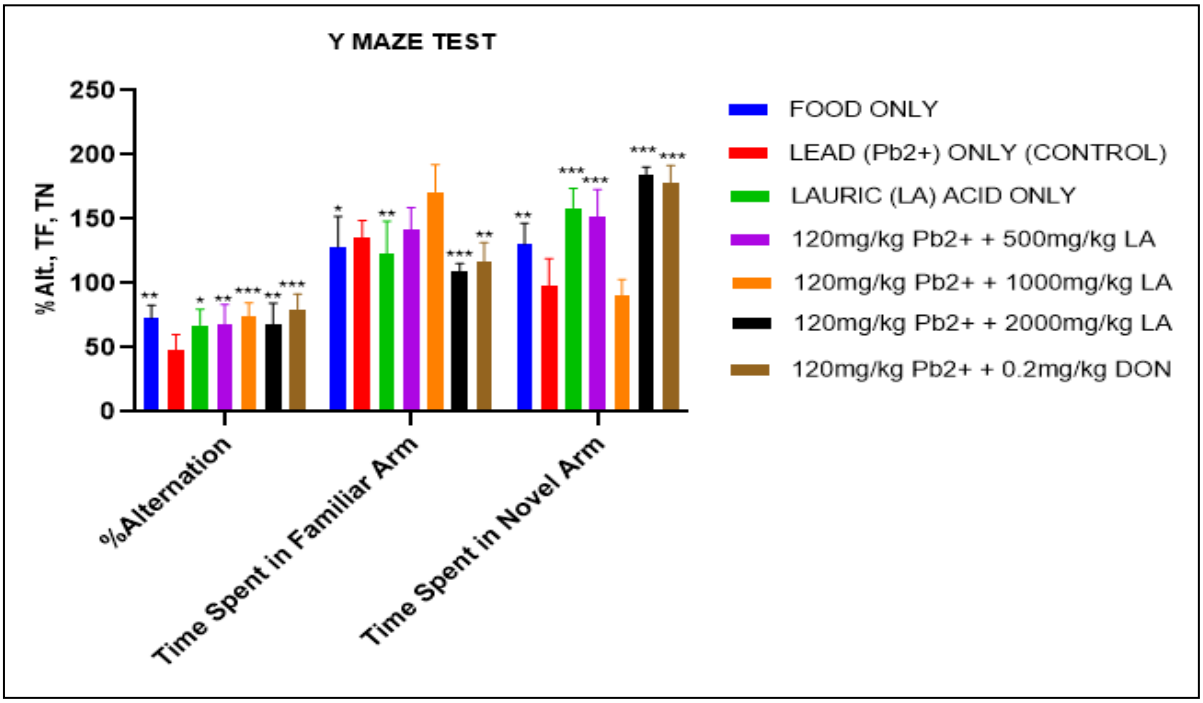
Figure 2 Open and Close arm entry of the elevated plus maze test



Values are mean ± SEM; n = 5 in each group, (P < 0.05) = Statistically significant. ; * Significant when compared to the control at P < 0.05; ** Significant when compared to the control at P < 0.01; *** Significant when compared to the control at P < 0.001

Figure 3 Open and Close arm time of the elevated plus maze test

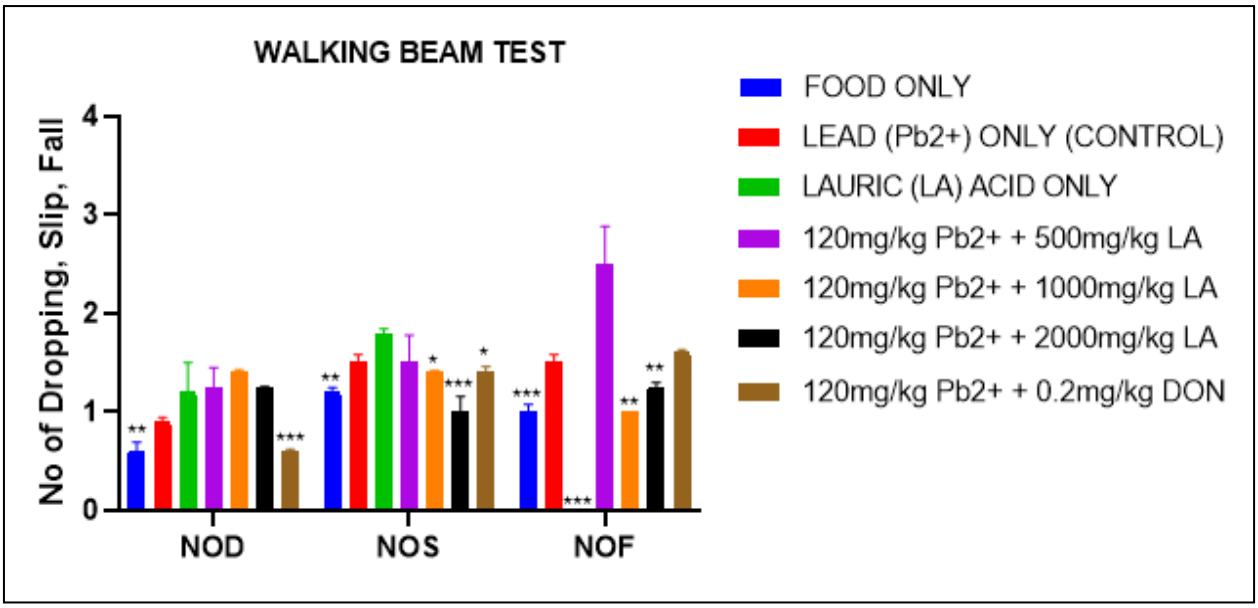
3.2.2 *Y Maze Test*



Values are mean ± SEM; n = 5 in each group, (P < 0.05) = Statistically significant. ; * Significant when compared to the control at P < 0.05; ** Significant when compared to the control at P < 0.01; *** Significant when compared to the control at P < 0.001

Figure 4 Y maze test

3.2.3 *Walking Beam Test*



Values are mean ± SEM; n = 5 in each group, (P < 0.05) = Statistically significant. ; * Significant when compared to the control at P < 0.05; ** Significant when compared to the control at P < 0.01; *** Significant when compared to the control at P < 0.001

Figure 5 Walking beam test for number of Droppings, Slip, and Fall

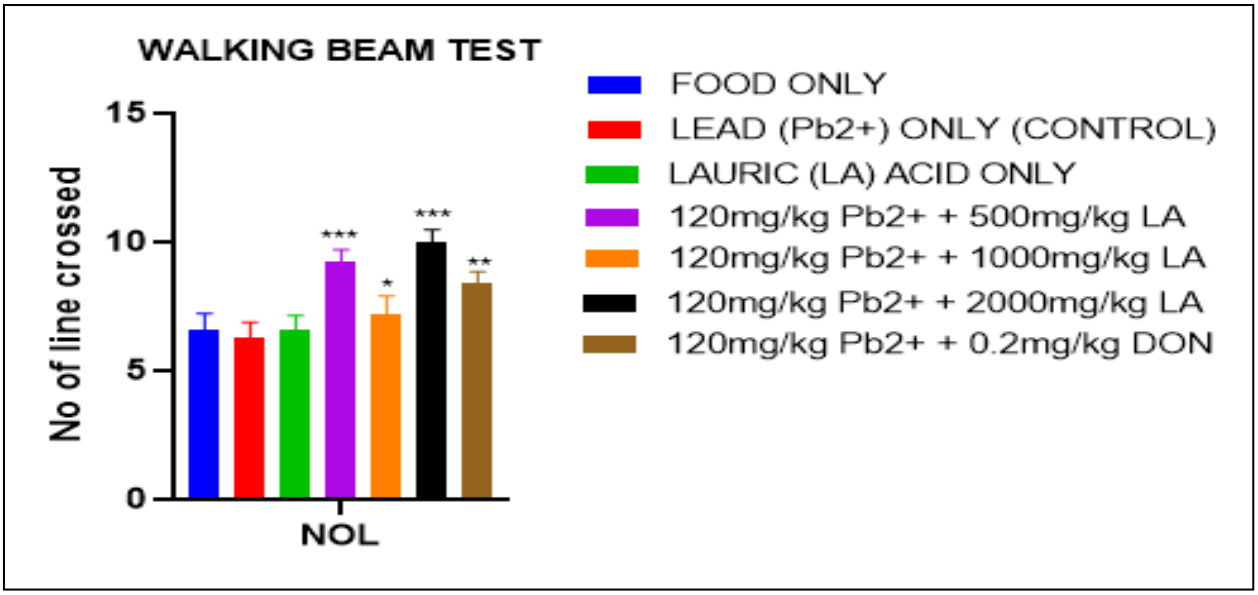


Figure 6 Walking beam test for number of Line crossed

3.2.4 Histology

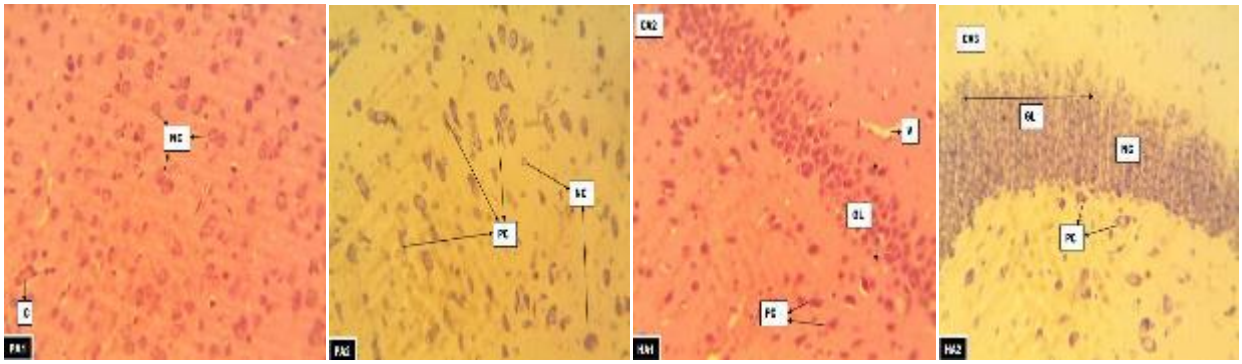


Figure 7: PA1&PA2: The prefrontal cortex normal control presents a normal neurons and shows normal appearance of neuroglial cells (NC); intensively stained normal pyramidal cells (PC) with conspicuous apical and basal dendrites, and no signs of degeneration (H&E stain, X400 and CFV stain, X400).

HA1&HA2: The hippocampus of normal control shows well-defined glandular cell layer (GL) with numerous neroglial cells (NC). Note the well-defined and packed pyramidal cells (PC) in the glandular cell layer (GL) of connus ammonus (CA3) with cytoplasmic Nissl granules. Neurons have features of characteristic large multipolar neurons (H&E stain, X400 and CFV X400).

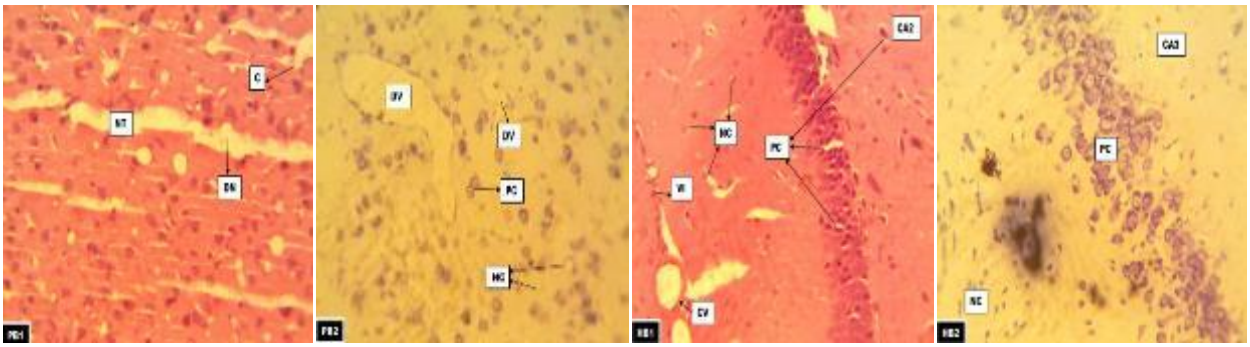


Figure 8: PB1&PB2: The prefrontal cortex (PFC) of Group B induced with lead without treatment (positive control) shows cells with condensed irregular nuclei and large degeneration and vacuolation (DV), and necrosis of neuroglial

cells (NC), abnormal appearance of pyknotic pyramidal cells (PC) with chromatolysis as well as reduced apical and basal dendrites. There is a general sign of histopathological changes. (H&E X400 and CFV stain, X400).

HB1&HB2: The hippocampus of Group B induced with lead without treatment (positive control) shows shrunken neuroglial cells (NC) and necrosis of all layers with a zone of vacuolation deep to the pyramidal layer. The pyramidal cells (PC) present chromatolysis and pyknosis with very reduced apical and basal dendrites. The pyramidal cells in the CA3 region of the hippocampus show pycnotic pyramidal cells organized in a cluster and apoptotic CA3 cells appear to be poorly stained as a sign of degenerative changes. The cellular assortment of the CA3 region of the hippocampus alongside the polymorphic layer adjoining it on either side appears distorted. (H&E X400 and CFV X400).

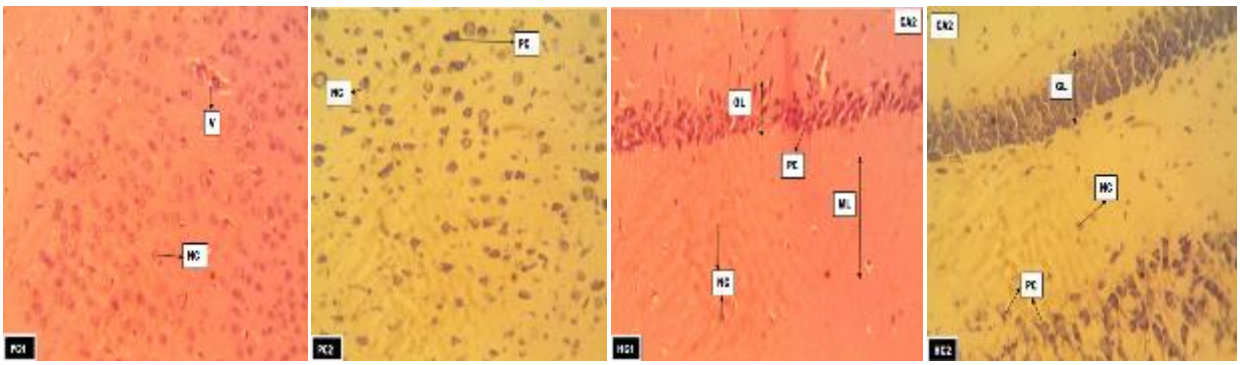


Figure 9: PC1&PC2: The prefrontal cortex (PFC) of Group H treated with normal saline and 1000mg/kg lauric acid (negative control for curative) showed increased cellular density and intensively stained pyramidal cells (PC), with no signs of chromatolysis and pyknosis or degeneration. (H&E X400 and CFV stain, X400).

HC1&HC2: The hippocampus of Group H treated with normal saline and 1000mg/kg lauric acid (negative control for curative) showed normal neuroglial cells (NC) and pyramidal cells (PC). The pyramidal cells (PC) present conspicuous apical and basal dendrites with no obvious chromatolysis and pykinosis (H&E X400 and CFV X400).

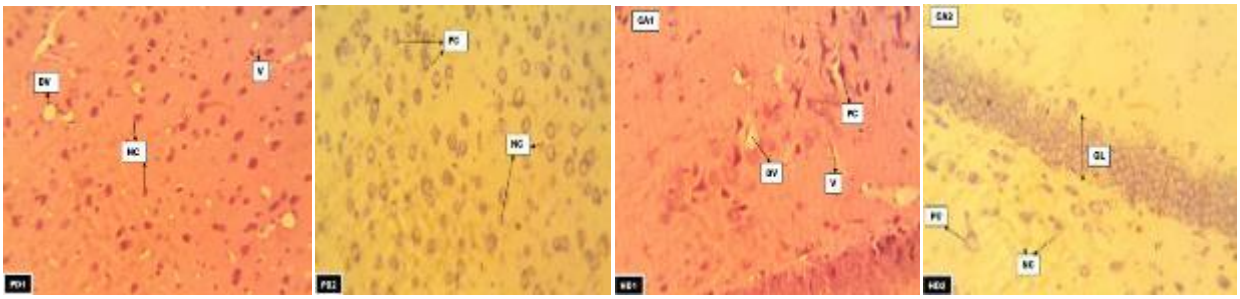


Figure 10: PD1&PD2: The prefrontal cortex (PFC) of Group I induced with lead and treated with 500mg/kg (low dose) lauric acid (curative test) shows cells with regular nuclei and no peripheral vacuolation, and necrosis of the neuroglial cells (NC), but abnormal appearance of pyknotic pyramidal cells (PC) with chromatolysis as well as reduced apical dendrites. There is a mild sign of histopathological changes (H&E X400 and CFV stain, X400).

HD1&HD2: The hippocampus of Group I induced with lead and treated with 500mg/kg (low dose) lauric acid (curative test) shows packed cells in the granular layer (GL) with regular nuclei but mild vacuolation, chromatolysis, and necrosis of the neuroglial cells (NC), abnormal appearance of pyknotic pyramidal cells (PC) with reduced apical and basal dendrites. There is a mild sign of histopathological changes (H&E X400 and CFV stain, X400).

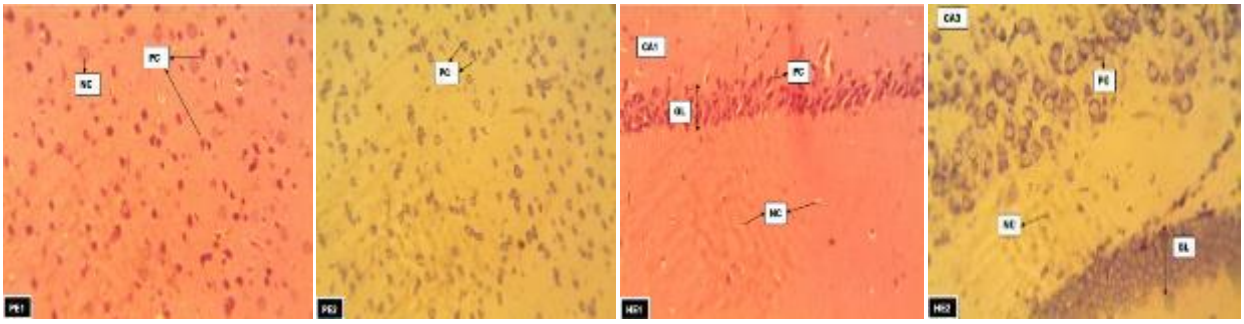


Figure 11: PE1&PE2: The prefrontal cortex (PFC) of Group J induced with lead and treated with 1000mg/kg (medium dose) lauric acid (curative test) presents normal neurons generally; intensively stained normal moderate density pyramidal cells (PC) with conspicuous apical and basal dendrites, and no sign of conspicuous degeneration (H&E X400 and CFV stain, X400).

HE1&HE2: The prefrontal cortex (PFC) of Group J induced with lead and treated with 1000mg/kg (medium dose) lauric acid (curative test) presents packed cells in the granular layer (GL) with regular nuclei. Pyramidal cells (PC) with conspicuous apical and basal dendrites. Neuroglial cells (NC) appear normal. There is no obvious sign of histopathological changes (H&E X400 and CFV stain, X400)

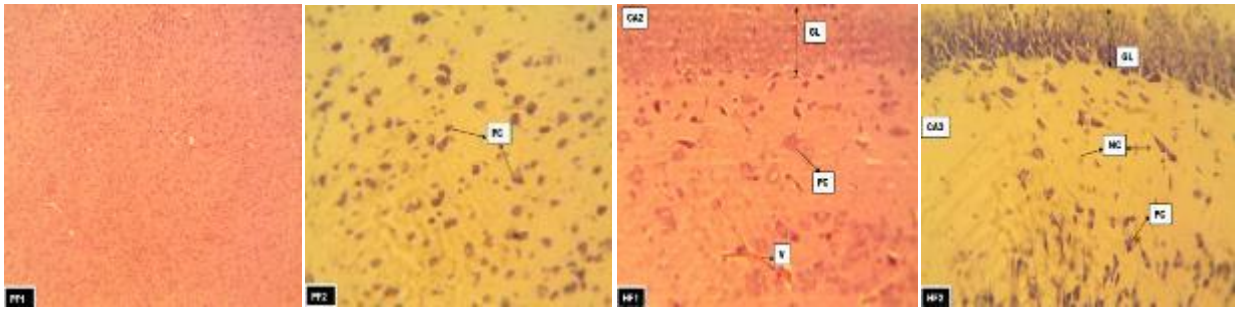


Figure 12: PF1&PF2: The prefrontal cortex (PFC) of Group J induced with lead and treated with 2000mg/kg (high dose) lauric acid (curative test) presents normal neurons generally; intensively stained normal high density pyramidal cells (PC) with conspicuous apical and basal dendrites, and no sign of conspicuous regeneration (H&E X400 and CFV stain, X400).

HF1&HF2: The hippocampus of Group K induced with lead and treated with 2000mg/kg (high dose) lauric acid (curative test) presents generally normal histoarchitecture; intensively stained high density pyramidal cells (PC in the granular cell layer (GL) and conspicuous apical and basal dendrites, and no sign of conspicuous regeneration even in the neuroglial cells (NC) (H&E X400 and CFV stain, X400).

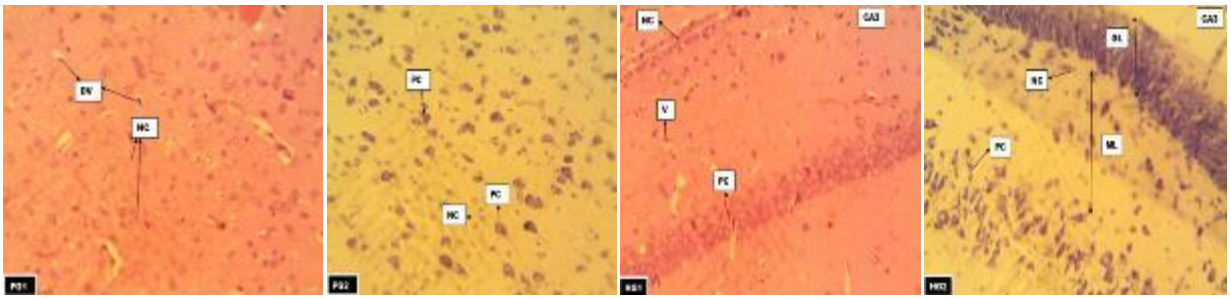


Figure 13: PG1&PG2: The prefrontal cortex (PFC) of Group L induced with lead and treated with 0.2mg/kg Donepezil (curative test) showed increased cellular density and normal appearance of neuroglial cells (NC). Moreover intensively stained high density pyramidal cells (PC) with conspicuous apical (AD) and basal dendrites, and no signs of chromatolysis, pyknosis, or degeneration. (H&E X400 and CFV stain, X400).

HG1&HG2: The hippocampus of Group L induced with lead and treated with 0.2mg/kg Donepezil (curative test) showed increased cellular density in the granular layer (GL) and normal appearance of neuroglial cells (NC). Moreover

intensively stained high density pyramidal cells (PC) with conspicuous apical and basal dendrites, and no sign of chromatolysis, pyknosis, or degeneration even on the cells of the molecular layer (ML). (H&E X400 and CFV stain, X400).

4. Discussion

The body weights (Figure 1) of rats treated with (Pb^{2+}) reduced when compared to the normal control, donepezil, and lauric acid groups. Our results are in agreement with Ahmed et al., 2013; Kumawat et al., 2014, who reported that mice ingested 1/20 LD50 of (Pb^{2+}) showed significant reduction in body weight. In the same trend, Flora et al. (2012) ; Kasten-Jolly et al., (2012) reported a reduction ($p<0.01$) of mean body weight of mice exposed to lead acetate. There is a significant ($p < 0.05$) decrease in open arm entry and open arm time for rats treated with lead (Pb^{2+}) without intervention and (Pb^{2+}) and with 500mg/kg lauric intervention when compared with the normal control (Figure 2 to 3). This shows that the lauric acid has the potential that may have protected the hippocampus (the anxiety centre) from neurodegeneration. This is in accordance with Taejib et al., 2022 report that prefrontal cortex and hippocampus respectively have different components of working memory and anxiety centre in rats. Moreover, in the walking beam test (Figure 4), there were a significant ($p < 0.05$) decrease in exploratory and locomotive activities of rats treated with Pb^{2+} when compared with the normal control, suggesting that Pb^{2+} induced anxiety and poor motor function in the rats. Analysis of the percentage alternation and novel arm entry of the Wistar rats in the Y-maze test indicates that there is a significant ($p < 0.05$) increase in the percentage alternation and novel arm entry in the lauric acid treated groups when compared with the rat treated with Pb^{2+} (Figure 4). It is also in agreement with the Abd Rashed et al., 2021 report on the use of essential oil like lauric acid as an anti-neudegenerative remedies, and Issa et al., 2020 report on impaired memory function due to Pb^{2+} induced toxicity. The histological reports of normal control present normal appearance of neuroglial cells (NC); intensively stained normal pyramidal cells (PC) with conspicuous apical and basal dendrites and no signs of degeneration when compared to the Pb^{2+} treated rats without lauric acid intervention (See Figure 7 to 13: PA to PG and HA to HG). These indicate that lauric acid has potential that may have protected the hippocampal and cerebral cortex pyramidal cells from degeneration. This is in agreement with the earlier report by Abd Rashed et al., 2021, that essential oils like lauric acid have an anti-inflammatory remedy for neurodegenerative diseases. These overall results are in agreement with Ezigbo and Mbaegbu, 2016, report on the medicinal benefits of lauric acid, and also in agreement with Abuhamdah et al., 2015, report on the pharmacological and neuroprotective benefit of essential oil like lauric acid.

5. Conclusion

The results of this study suggest that lauric acid may have therapeutic potential against degenerative changes associated with demyelination and neurotoxicity of hippocampal and cerebral cortex due to lead toxicity. The mechanism underlying this protection seems to involve, in addition to improved permeability across lipid bilayers and blood-brain barrier as a ketogenic molecule. Several lines of data support this hypothesis, for example, cognitive disruption, such as that seen in humans including schizophrenic patients is known to involve alterations in the structure and function of the prefrontal cortex and hippocampal pyramidal cells.

Findings

- There are balance in the neurobehavioural and histological parameters with lauric acid post-treatment.
- Lauric acid restored neurobehavioural, and histological alterations in the hippocampal and cerebral cortex.

Recommendation

We, hereby recommend that the intake of lauric acid should be encouraged to people having neurological disorders. Further studies on the exact molecular mechanisms responsible for the therapeutic role of lauric acid in the nervous system should be carried out. Meanwhile, it is worthwhile to consider this aspect at a deeper level of investigation using different animal models and methods.

Contribution to Knowledge

- Molecular mechanism associated with neurodegeneration and neuroregeneration has been elucidated in this research.
- Lauric acid has been proven in this study as promising anxiolytic and memory improving agent.
- Administration of medium dose lauric acid (1000mg/kg) produced the best abatement than the low dose (500mg/kg) and high dose (2000mg/kg). \

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare that there are no conflicts of interest regarding the publication of this article.

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Dada availability

All data are available at Department of Anatomy, University of Nigeria.

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