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Neuroprotective Effect of Monodora Myristica on the Lead and Aluminium-Induced Injury of the Cerebral Cortex, Cerebellum, and Hippocampus of Male Wistar Rats

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Keywords: Neurotoxicity; *Mondora myristica*; Antioxidant; lead; Aluminium; Brain

Abstract

Humans are constantly exposed to heavy metals due to their ubiquity in the environment. Plant-derived products with antioxidant activity are useful in reducing heavy metal-induced neurotoxicity. This study investigated the neuroprotective and antioxidant properties of the aqueous *Mondora myristica* against heavy metal-induced neurotoxicity in male Wistar rats.

Methods: Six groups of six weight-matched animals each, were used for the study. Group1 (normal control) was treated with deionized water and group 2 (toxic control) with lead acetate and aluminium at the doses of 20 mg/kg b.wt, and 35mg/kgb.wt respectively whereas group 3 received *M. myristica* 100 mg/kg only, groups 4,5, and 6 were simultaneously treated with lead acetate and aluminium at the doses of 20 mg/kg b.wt, and 35mg/kgb.wt, and 100mg/kg, 200mg/kg, and 400mg/kg of *M myristica* respectively. The treatment was administered orally for 42 days. Biochemical and histopathological investigations were carried out following animal sacrifice at the end of the study period. The neuroprotective effect of *M. myristica* was assessed by measuring redox status (malondialdehyde), enzymatic antioxidant activities (Superoxide dismutase, Catalase, Glutathione peroxidase and glutathione reductase) and histopathology of the cerebral cortex.

Results: The increase in the malondialdehyde, the decrease in the activity of antioxidant enzymes (Catalase, Glutathione peroxidase and reductase), and the altered neurons in the hippocampus, cerebral cortex and cerebellum following treatment by lead acetate and aluminium were mitigated by *M. myristica*

Conclusion: The *Mondora myristica* induced a significant protective effect on lead and aluminium-mediated neurotoxicity in a dose-dependent manner which may be a result of its antioxidant anti- on the cerebrum, cerebellum, and hippocampus of male Wistar rats.

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Introduction

Neurotoxicity refers to any adverse effect on the nervous system, caused by either a physical, chemical or biological agent thereby inhibiting the ability of an organism to live or adapt to its surrounding [1]. The deleterious effect arising from short-term exposure to heavy metals like lead and aluminium may be compensated by the brain.

Recently there has been a global increase in neurological disease in both developed and developing countries due to heavy metal environmental pollutants with attendant increase in mortality and morbidity. Oxidative stress has been recognized to be a major indirect mechanism of heavy metal neurotoxicity [2]. The induction of oxidative stress is characterized by increased levels of reactive oxygen species (ROS) such as superoxide (O^{2-}) and hydroxyl (•OH) radicals, hydrogen peroxide (H_2O_2), and lipid peroxide [2]. Modern pharmaceutical industry is founded on compounds identified in medicinal plants [3]. Various extracts and drugs of plant origin have shown promise in the treatment of a range of neurological diseases, and many studies have demonstrated how the antioxidant properties of natural products help to mitigate the toxicity of heavy metal poising. *Mondora myristica* also called calabash, Jamaica or African nutmeg is a tropical plant that belongs to the *Annonaceae* family. This less studied and under-exploited plant is extensively distributed in Africa, Asia, Australia as well as Central and South America (4) It is used to manage so many ailments like arthritis, and stomach aches. Previous studies have reported the antioxidant properties of *M. myristica* seeds [5-6].

To date, however, there remains a paucity of information on the investigation into the possible protective effects of *M. myristica* low-doses heavy metal mixture neurotoxicity rat models.

Materials and Methods

Sample identification

Dried fruit *Mondora Myristica* was bought from the local market in Port Harcourt, Rivers State, Nigeria. It was identified and authenticated in the Department of Pharmacognosy, Faculty of Pharmacy, University of Port Harcourt, Rivers State Nigeria.

Sample processing and extraction

The dried *Mondora Myristica* was milled into fine powder. After weighing the powder, the extract was prepared using a cold maceration method. One gram of the powder was dissolved in 500ml of deionized water and left covered for 24 hours. After 24 h, the mixture was strained, the marc was pressed, and the extract was filtered and stored in the refrigerator at 4 °C. Fresh extracts were prepared every three days.

Experimental design

Six groups of six animals each were used for the study. Group 1 was treated with deionized water and Group 2 animals received only lead acetate and aluminum at the doses of 20 mg/kg b.wt, and 35mg/kgb.wt, group 3 received 100 mg of *M. myristica* only Group 4-6 received 100, 200 and 400mg/kg of *M. myristica* p.o. and lead acetate and aluminium at the doses of 20 mg/kg b.wt, and 35mg/kgb.wt rally for 42 days. Animals were sacrificed for 24 h under ethyl ether anaesthesia after the last treatment. The brain was perfused, excised and preserved in 10 % formalin for histopathological study. All the experimental procedures were performed according to the committee for control and supervision of experiments on animals, and norms and approved by the University of Port Harcourt Nigeria, Ethical Committee.

Antioxidant assay

The cerebral cortex, cerebellum and hippocampus were dissected and minced into small pieces and homogenized with ice-cold 0.05 M potassium phosphate buffer (pH 7.4) to make 10 % homogenates. The homogenates were centrifuged at 6000 rpm for 15 mins at 4 °C. The supernatant was collected for the estimation of catalase (CAT) activity using hydrogen peroxide as substrate according to the method of Clairborne (Clairborne 1995) [7]. Superoxide dismutase (SOD) was assayed by the method described by (Misra and Fridovich 1972) [8]. Glutathione-S-transferase (GST) was assayed by the method of Habig et al. 1974[9]. Reduced glutathione (GSH) was determined at 412 nm using the method described by Sedlak and Lindsay 1996 [10]. Lipid peroxidation was quantified as malondialdehyde (MDA) according to the method described by Ohkawa et al. 1978 [11]and the MDA level was calculated according to the method of Todorova et al.[2005[12]and expressed as µmol MDA/mg protein.

Histopathological studies

The different brain regions from all the experimental groups were fixed in 10 % formaldehyde, dehydrated in graded alcohol, cleared in xylene, and then embedded in paraffin. Microtome sections (5µm thick) were prepared from each brain sample and stained with toluidine blue dye. The sections were lastly photographed beneath the light microscope attached to the camera and examined for histopathological findings.

Statistical analysis

The biochemical outcomes were displayed as mean ± SD analyzed using SPSS (Statistical Package for Social Sciences). Statistical variations between groups were studied via applying one-way ANOVA sequentially to Tukey's post hoc assay. A p-value < 0.05 was regarded as significant.

Results

The effect of *M. myristica* on the oxidative stress markers of lead and aluminum-treated Wistar rats on the cerebral cortex is shown in **Figure1**.

Lead/Aluminium treatment (Group 2 caused a decrease in antioxidant enzymes namely Superoxide dismutase (SOD), Catalase (CAT), reduced glutathione (GSH) and Glutathione-S-transferase (GST) when compared with the normal control group, whereas Gps 4-6 that received heavy metal mixture and *M. myristica* had significant increased antioxidant enzymes namely Superoxide dismutase (SOD), Catalase (CAT), reduced glutathione (GSH) and Glutathione-S-transferase (GST) when compared with toxic control (metal mixture). Heavy metal mixture treatment caused an increase in malondialdehyde (MDA) when compared with control, whereas Gps 4-6 that received heavy metal mixture and Mondora myristica had a significant decrease in malondialdehyde (MDA) when compared with control.

The effect of *M. myristica* on the oxidative stress markers of lead and aluminum treated Wistar rats on the cerebral cerebellum is shown in **Figure 2**.

Lead/Aluminium treatment (Group 2 caused a decrease in antioxidant enzymes namely Superoxide dismutase (SOD),

Catalase (CAT), reduced glutathione (GSH) and Glutathione-S-transferase (GST) when compared with the normal control group, whereas Gps 4-6 that received heavy metal mixture and *M. myristica* had significant increased antioxidant enzymes namely Superoxide dismutase (SOD), Catalase (CAT), reduced glutathione (GSH) and Glutathione-S-transferase (GST) when compared with toxic control (lead acetate only). Heavy metal mixture treatment caused an increase in malondialdehyde (MDA) when compared with control, whereas Gps 4-6 that received heavy metal mixture and *Mondora myristica* had a significant decrease in malondialdehyde (MDA) when compared with control.

The effect of M. myristica on the oxidative stress markers of lead and aluminium-treated Wistar rats on the hippocampus is shown in **Figure 3**.

Lead/Aluminium treatment (Group 2 caused a decrease in antioxidant enzymes namely Superoxide dismutase (SOD), Catalase (CAT), reduced glutathione (GSH) and Glutathione-S-transferase (GST) when compared with the normal control group, whereas Gps 4-6 that received heavy metal mixture and M. myristica had significant increased antioxidant enzymes namely Superoxide dismutase (SOD), Catalase (CAT), reduced glutathione (GSH) and Glutathione-S-transferase (GST) when compared with toxic control (lead acetate only). Heavy metal mixture treatment caused an increase in malondialdehyde (MDA) when compared with control, whereas Gps 4-6 that received heavy metal mixture and *Mondora myristica* had a significant decrease in malondialdehyde (MDA) when compared with control

Figure 3 is the histological examination of cerebrum-stained Toluidine blue (×400). The control group (Figure 3a) showed intact neuronal cells with no degeneration whereas in the heavy metal mixture treated group, there was neuronal degeneration evidenced by scanty cells (Figure 3b). Group treated with M myristica only, the neuronal cells in various layers appear intact with increased regeneration (Figure 3c). The concurrent treatment with *M. myristica* showed neuronal regeneration in cerebral histology (Figure 3d -f,) evidenced by reduced cell vacuolation.

Figure 4 is the histological examination of hippocampus-stained Toluidine blue (×400). The control group (Figure 4a) CA 1 region showed intact neuronal cells with no degeneration whereas in the heavy metal mixture treated group, there was neuronal degeneration evidenced by cytoplasmic vacuolation and scanty cells (Figure 4b). Group treated with *M myristica* only, the neuronal cells in various layers appear intact with increased regeneration (Figure 4c). The concurrent treatment with *M. myristica* showed neuronal regeneration in cerebral histology (Figure 4d -f,) evidenced by reduced cell vacuolation.

Figure 5 is the histological examination of cerebellum-stained Toluidine blue (×400). The control group (Figure 5a) showed intact Purkinje, molecular and granular with normal whereas in the heavy metal mixture treated group, there was granular cell degeneration evidenced by cytoplasmic vacuolation and scanty cells (Figure 5b). Group treated with *M. myristica* only, the neuronal cells in various layers appear intact with increased regeneration (Figure 5c). The concurrent treatment with *M. myristica* showed neuronal regeneration in cerebellum histology (Figure 5 d -f,) evidenced by reduced cell vacuolation.

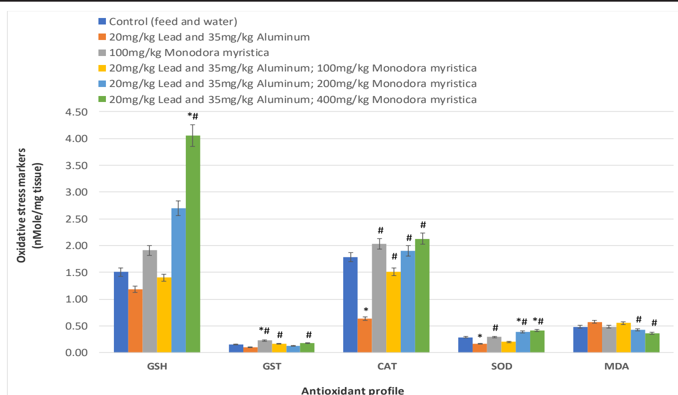

Figure 1: Effect of *Monodora myristica* on the oxidative stress markers of the cerebral cortex.
*Each value represents mean±SD, Values marked with an asterisk (*) differ significantly from the control value (*p < 0.05) while those marked with (#) differ significantly from lead only group (#p < 0.05).*
CATA: Catalase; GSH: Reduced Glutathione; SOD: Superoxidase dismutase; GPX: Glutathione Peroxidase; MDA: Malondialdehyde.

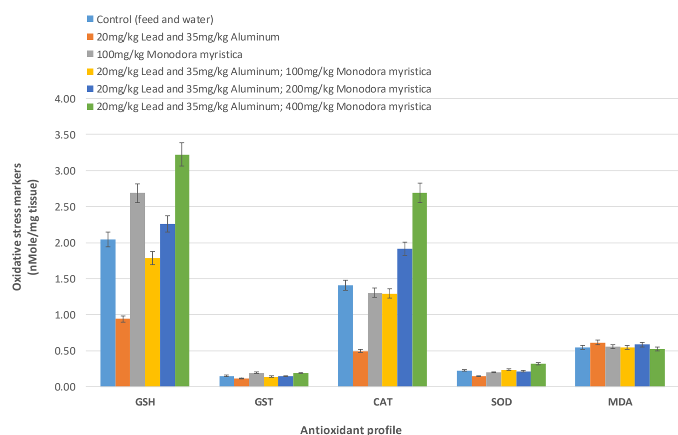

Figure 2: Effect of *Monodora myristica* on the oxidative stress markers of the cerebellum.
Each value represents mean ± SD, Values marked with asterisk (*) differ significantly from control value (*p < 0.05) while those marked with (#) differ significantly from lead only group (#p < 0.05).
CATA: Catalase; GSH: Reduced Glutathione; SOD: Superoxidase dismutase; GPX: Glutathione Peroxidase; MDA: Malondialdehyde.

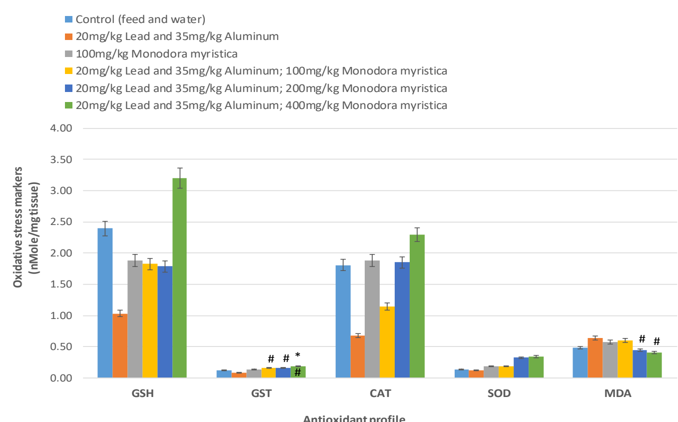

Figure 3: Bar chart showing the effect of *Monodora myristica* on the oxidative stress markers of the Hippocampus. Each value represents mean ± SD, Values marked with asterisk (*) differ significantly from control value (*p < 0.05) while those marked with (#) differ significantly from lead only group (#p < 0.05)
CATA: Catalase; GSH: Reduced Glutathione; SOD: Superoxidase dismutase; GPX: Glutathione Peroxidase; MDA: Malondialdehyde.

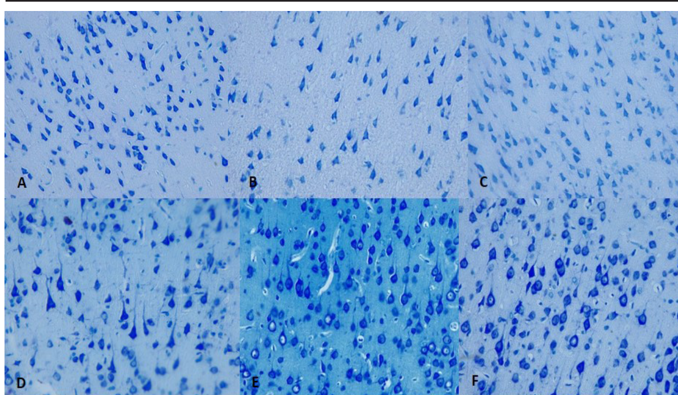

Figure 3a: Histological examination of Cerebrum stained with Toluidine blue (×400).
Fig 3a Control; 3 b Pb+AL ; 3c; *M m* only; 3 d Pb+AL+M.m 100mg/kg; 3e Pb+AL+M.m 200mg/kg;4 f Pb+AL+M.m 400mg/kg;

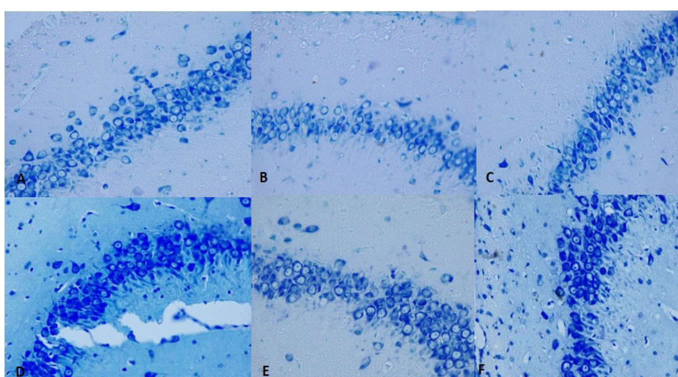

Figure 4: Histological examination of Hippocampus -stained Toluidine blue (×400).
Fig 4a Control; 4b Pb+AL *&Al*; 4c; *M m* only; 4d Pb+AL+M.m 100mg/kg; 4e Pb+AL+M.m 200mg/kg;4 f Pb+AL+M.m 400mg/kg.

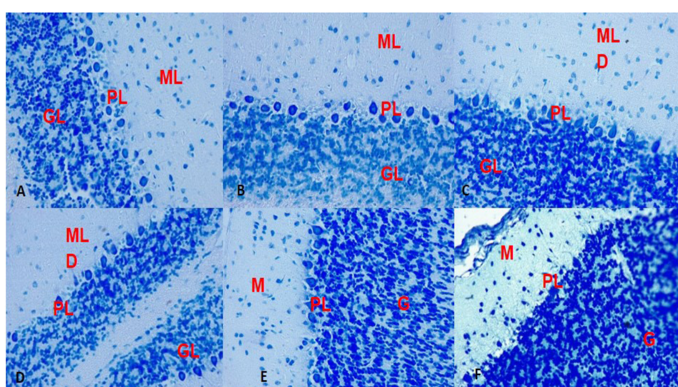

Figure 5: Histological examination of cerebellum stained with Toluidine blue (×400).
ML: molecular layer; PL: Purkinje layer; G: Granular layer
Figure 5a Control; 5b Pb+AL*/*; 5c; *M m* only; 5d Pb+AL+M.m 100mg/kg; 5e Pb+AL+M.m 200mg/kg;5f Pb+AL+M.m 400mg/kg;

Discussion

Heavy metals exert some of their neurotoxic effects by promoting oxidative damage and peroxidation of the lipids in the cell membranes, thus compromising cellular functions by impairing the physiological functions, fluidity, and integrity of cell membranes, thereby increasing the cell vulnerability to lipid peroxidation and cell death [13]. Both animal and human studies have suggested that exposure to heavy metal mixtures are associated with increased oxidative stress and a heightened incidence of neurotoxicity [1]. Numerous natural products are effective antioxidants and many medicinal plants with a long history of use in folk medicine in different countries against a variety of diseases have turned out to be rich sources of antioxidants (14,15). Recently, great interest has been given to naturally occurring antioxidants which played prominent roles in inhibiting both free radicals generation and oxidative chain reactions within tissues and membranes (16).

Antioxidants exert their effects via several basic mechanisms, which include scavenging the species that initiate peroxidation, quenching singlet oxygen, chelating metals, breaking free radical chain reactions, and reducing the concentration of O_2. As powerful free radical scavengers, they can act as very effective neuroprotective agents against heavy metal-induced oxidative stress. The presence of alkaloids, saponin, tannins, flavonoids and phenols in varying quantities in the aqueous extract of *M. myristica* seeds has accounted for its antioxidant property [17].

Exposure to heavy metals has been reported to cause oxidative stress and cause neurotoxicity. An increase in MDA with a concomitant decrease in the activities of SOD and CAT and decreased GSH levels was observed in the study of the protective effect of natural antidotes like curcumin against a heavy metal mixture of neurotoxicity [18]. Our observation of increased malondialdehyde (MDA) by heavy metal mixture treatment in rat brain and a significant decrease in total antioxidants confirm the role of oxidative stress. This is consistent with earlier studies [2]. Lead treatment of the rats increased cerebral tissue (L-MDA) levels as compared with the *Mondora myristica* extract treated groups ($p<0.05$) and a decrease in antioxidant glutathione, glutathione peroxidase, catalase and superoxide dismutase activity which had been reported by others [19 -20) which coincides well with the present study.

In this study, there were severe neurochemical and biochemical; changes in the brain resulting from exposure to low dose heavy metal mixture of Pb, Al. Rats treated with only low dose heavy metal mixture 20 mg/kg $PbCl_2$, Al 35mg/kg body weight for 42 days showed oxidative stress marked by an increase in MDA content and a decrease in the activities of CAT, SOD and GSH. These observations are in line with the works of Radwan et al. [21] who reported that exposure to a heavy metal caused a marked elevation in MDA level and a decrease in SOD, CAT and GSH contents in the brain. Our findings are also consistent with the previous works of Karaca and Eraslan [22] and Abdel Moneim [23] which reported that exposure to heavy metals could lead to reactive oxygen species (ROS) generation, causing an elevation in MDA level, sulfhydryl depletion, changes of antioxidant cellular defenses and DNA damage. The elevation in the lipid peroxidation marker could be from an overproduction of the superoxide anions which stifle the antioxidant enzymatic system [24]. The decreased activities of SOD and CAT levels may be because of the binding of the heavy metals with the sulfhydryl group of these enzymes and the substitution of endogenous redox metals which changes these enzyme configurations leading to their inhibition [25]. The depletion in the GSH content may be attributed to the use of GSH in scavenging the generated free radicals. The combined effect of increased MDA and decreased SOD, CAT and GSH in our present study could lead to neurodegeneration as a result of heavy metal mixture exposure. Nevertheless, the results suggested that treatment with varying dose *Mondora myristica* (100, 200 and 400 mg/kg body weight) significantly alleviated the brain oxidative status induced by heavy metal mixture exposure. This could be ascribed to its antioxidant properties.

The present research is also in line with a study done by Baty et 2020 on the neuroprotective role of luteolin against lead acetate-induced cortical damage in rats [26]. The biochemical results together with histopathological observations indicated heavy metal mixture induced neuronal damage which was restored with the natural product M. myristica treatment.

M. myristica seed is a rich source of flavonoids which have been shown to exhibit both antioxidant and anti-inflammatory properties [9]. M. myristica has strong antioxidant effects which ameliorated brain damage caused by heavy metal intoxication in experimental rats in a dose-dependent manner by improving the antioxidant defense systems as well as mitigating lipid peroxidation associated with heavy metal toxicity [13]. This is consistent with our study. M. myristica essential oils were found to reduce stress-related disorders like depression significantly restoring the hippocampal redox balance state and attenuating heavy metal-induced oxidative damage which is inconsistent with this present study on restoring oxidative enzymes [27].

Conclusion

The findings from this study showed that aqueous seed extract of *M. myristica* administration could suppress oxidative stress and neuroinflammation and reinstate the brain histological architecture. Given this *M. myristica* seed can be used for the management of heavy metal mixture-induced neurotoxicity.

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