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[1]Neuroanatomy and Neurosciences Research Unit, Department of Human Anatomy, Faculty of Basic Medical Sciences, College of Medical Sciences, Ahmadu Bello University (ABU), Zaria; [2]Microscopy and Stereology Research Unit, Department of Human Anatomy, ABU, Zaria; [3]Department of Human Anatomy, Faculty of Basic Medical Sciences, Federal University Wukari, Taraba; [4]Department of Human Anatomy, College of Medical Sciences, Gombe State University, Gombe; [5]Department of Anatomy, Faculty of Basic Medical Sciences, University of Medical Sciences, Ondo; [6]UPM-MAKNA Cancer Research Laboratory, Institute of Bioscience, Universiti Putra Malaysia, Selangor, Malaysia; [7]Department of Basic Medical Sciences, Faculty of Medical and Health Sciences, Newgate University, Minna; [8]Nigerian Defence Academy, Kaduna, Nigeria.

Address for Correspondence:
Sambo Z.S.
Department of Human Anatomy, Faculty of Basic Medical Sciences, College of Medical Sciences, Ahmadu Bello University, Zaria.
zainabsambo16@gmail.com

Original Article

Chloroform fruit extract of *Phoenix dactylifera L.* (Date Palm) has neuroprotective effect against lead acetate-induced neurotoxicity in Wistar rats

[1,2]Agbon A.N., [1]Sambo Z.S., [1]Tukura H.S., [1]Adetoye T.H., [1]Adeola O.A., [1,2]Shuaib Y.M., [1,2,3]Henry R., [4]Mahdi O., [4,6]Bobbo K.A., [5]Enemali F.U., [1,7]Lazarus S.S. and [1,8]Abubakar M.G.

ABSTRACT

Background and aim: Environmental and health hazards posed by lead, a heavy metal contaminant, in water and other media are rising. Different solvent-extract forms of the *Phoenix dactylifera* plant are of vast medicinal benefits. The neuroprotective effect of chloroform fruit pulp extract of *P. dactylifera* (CFPD) was assessed on lead acetate-induced cerebellar and cerebral toxicity in Wistar rats.
Materials and methods: Twenty-four rats were divided into six groups: (A – F; n= 4): the control (group A) was administered distilled water (2 ml/kg p.o); group B received lead acetate (LA, 120 mg/kg body weight p.o) only; group C, received vitamin C (100 mg/kg body weight p.o) as reference drug concomitantly followed by LA (120 mg/kg body weight p.o); groups (D, E, F) received CFPD (125 mg/kg body weight, 250 mg/kg body weight and 500 mg/kg body weight p.o, respectively) concomitantly followed by LA (120 mg/kg body weight). Administrations lasted for 14 days. The neuroprotective effect of CFPD was evaluated using histological (H&E) stained sections of cortical cerebellar and cerebral– (layers III and V) regions as well as biochemical (oxidative stress markers; serum malondialdehyde, superoxide dismutase, catalase, and glutathione peroxidase) assessments.
Results: Results revealed neurodegenerative changes in the LA-treated group's cerebellar and cerebral cortices, including perineuronal vacuolation and gliosis. However, the administration of CFPD remarkably ameliorated LA-induced cerebellar and cerebral changes. Relative to the control, the LA-treated group showed altered serum oxidative stress markers, which were ameliorated ($p<0.05$) with CFPD treatment.
Conclusion: Results suggest that CFPD, especially at a dose of 250 mg/kg, has neuroprotective potential against LA-induced cerebellar and cerebral toxicity in rats which could be attributed to antioxidant properties.

Keywords:
Phoenix dactylifera L; Cerebrum; Cerebellum; Histology; Oxidative stress; Wistar rats

INTRODUCTION

Heavy metals, like mercury, cadmium, and lead are contaminants in the air, soil, and groundwater that pose environmental and health hazards. The potential for biological system uptake, metabolism, and propagation into the food chain poses remarkable health risks (Wani *et al*., 2015; Orr *et al*., 2019). Heavy metal environmental pollutants, particularly lead, are an insidious hazard with the potential to trigger deleterious and irreversible health effects ranging from biochemical, physiological, neurological, and behavioral dysfunctions in both humans and animals (Osemwegiea *et al*., 2017; Wu *et al*., 2018).

Lead toxicity affects virtually all systems of the human body (Ilesanmi *et al*., 2022). The established pathophysiology of lead-triggered tissue injury is elevated production of reactive oxygen species (ROS) which elicits oxidative stress (Flora *et al*., 2012; Carocci *et al*., 2016; Alhusaini *et al*., 2021). The brain contains relatively low levels of endogenous enzymatic defense systems against oxidative stressors (Waggas, 2012), thus is the most vulnerable target to lead toxicity (Cory-Slechta, 1996; Bauchi *et al*., 2016), particularly, the cortical cerebral and cerebellar regions (Ferraro *et al.,* 2009; Korogi *et al*., 2011). Toxic lesions and pathological insults to these brain regions and related circuitry could result in dramatic events manifesting as altered behaviors, reduced accuracy, and flexibility (Stewart and Schwartz, 2007; Manto, 2012; Assi *et al*., 2016; Ben-Azu *et al*., 2021).

Dietary supplements play a vital role in the amelioration of heavy metal toxicity by facilitating their excretion from biological systems (Osemwegiea

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et al., 2017; Ismail, 2017). *Phoenix dactylifera* (known in English as Date Palm, in French as Dattier, and in Hausa (Northern Nigeria) as Dabino (Okere *et al*., 2010)) is a member of the monocot family Arecaceae called "Nakhla" (Chandra *et al*., 1992; Anwar, 2006). *P. dactylifera* is a plant of nutritious values based on its high carbohydrate content, dietary fiber, and essential minerals (Usama *et al*., 2009; Agbon *et al*., 2014a). The plant is of several medicinal value, employed folklorically for the treatment of diverse ailments like inflammation, paralysis, memory disturbances, loss of consciousness, and nervous disorders (Nadkarni, 1976; Saha *et al*., 2017). Broad pharmacological studies on *P. dactylifera* have documented the beneficial properties of the plant against different environmental toxins attributed to powerful and beneficial phytochemical constituents (Al-Qarawi *et al*., 2008; Yasin *et al*., 2015: El-Far *et al*., 2016; Abubakar *et al*., 2024).

Although, varying solvent-extract forms of *P. dactylifera* fruit have been reported with antioxidant and neuroprotective properties following heavy metal exposure (Vyawahare *et al*., 2009; Yusuf *et al*., 2017; Lazarus *et al*., 2018; Boudghane *et al*., 2022), little or no studies have reported the neuroprotective potentials of chloroform fruit extract of *P. dactylifera* against lead-induced neurotoxicity. This study evaluated the neuroprotective effect of chloroform fruit extract of *P. dactylifera* on lead-induced cerebellar and cerebral toxicity in Wistar rats using histological and biochemical assessments.

MATERIALS AND METHODS

Plant Material, Plant Extraction and Phytochemical Screening

Dried *P. dactylifera* fruits were obtained from a local market (Samaru market) in Zaria, and validated with a Voucher Specimen Identity: 7130 at the Herbarium Unit of the Department of Biological Sciences, Faculty of Life Sciences, Ahmadu Bello University (ABU), Zaria, Kaduna State, Nigeria.

The method of maceration as described by Agbon *et al*. (2013) for preparing chloroform fruit pulp extract of *P. dactylifera* (CFPD) was adopted. Trease and Evans's (2002) method for qualitative phytochemical screening of secondary metabolites (phenolic and non-phenolic compounds) was adopted. Plant extraction and phytochemical analysis were conducted in the Department of Pharmacognosy and Drug Development, Faculty of Pharmaceutical Sciences, ABU, Zaria.

Drugs and Chemical

Lead acetate (LA), a whitish powdered solute was obtained and used as a neurotoxicant for the experiment. The product is manufactured by British Drug Houses (BDH) Chemicals, Poole, England.

Vitamin C (Emzor Vitamin C) was obtained and used for the experiment as a standard antioxidant to evaluate the activity of CFPD. Emzor Pharmaceutical Industries Limited, Lagos, Nigeria manufactures the product. Chloroform, a colorless, pungent, and volatile solvent was obtained and used as an anesthetic agent and a solvent of plant extraction. The product is manufactured by BDH Chemicals, Poole, England.

Experimental Animals

Twenty-four healthy male Wistar rats (75-125 g) were obtained from the Animal House of the Department of Human Anatomy, Faculty of Basic Medical Sciences, College of Medical Sciences, ABU, Zaria, and housed in the same facility under standard laboratory conditions following internationally accepted principles for laboratory animal use and care as found in the ABU Committee on Animal Use and Care (ABUCAUC) guidelines. The rats were acclimatized for a week before the commencement of the experiments in new wired cages. All the rats were given food (rat chow) and water *ad libitum*; treatment groups were administered CFPD/ lead/ vitamin C in addition to water and food.

Experimental Design

Twenty-four rats were divided into six groups (A - F) of four rats each (n=4): The control group A was administered distilled water (2 ml/kg body weight); group B received LA (120 mg/kg body weight; Sujatha *et al* ., 2011) only; group C, received vitamin C (100 mg/kg; Henry *et al*., 2021) as reference drug concurrently followed by LA (120 mg/kg); groups D, E and F received CFPD (125 mg/kg body weight, 250 mg/kg body weight and 500 mg/kg body weight, respectively; equivalent to 2.5, 5 and 10% LD_{50}- Agbon *et al*., 2014a) concurrently followed by LA (120 mg/kg) for two weeks. All administrations were via the oral route.

Euthanasia and Sample Collection

At the end of the experiment, rats were euthanized using chloroform anesthesia, the cranial cavity was dissected using dissecting scissors and forceps, brains were harvested for subsequent histological tissue processing, and blood samples were collected via jugular vein in 5 ml plain sample bottles and centrifuged using a centrifuging machine to obtain serum for biochemical assay (*See* Figure 1).

Physical Observation

During the experimental period, the rats were observed for any change in physical activity and behavioral patterns, such as playfulness, agility, and eating.

Histological Studies

Harvested rats' whole brains were fixed in Bouin's fluid and processed for light microscopic examination (Optical Microscope; HM-LUX, Leitz Wetzlar, Germany at 25/0.50 × objective) using histological paraffin sections with Hematoxylin and Eosin (H&E) staining in the Histology Unit, Department of Human Anatomy, ABU, Zaria. Light microscopy and micrography were conducted in the Microscopy and Stereology Research Laboratory of the same facility. Tissue sections of the cerebellar cortex and cerebral cortex (layers III and V); composed of neurons critically involved in motor-related functions (Bhuiyan *et al*., 2014) were blindly examined for histopathological changes.

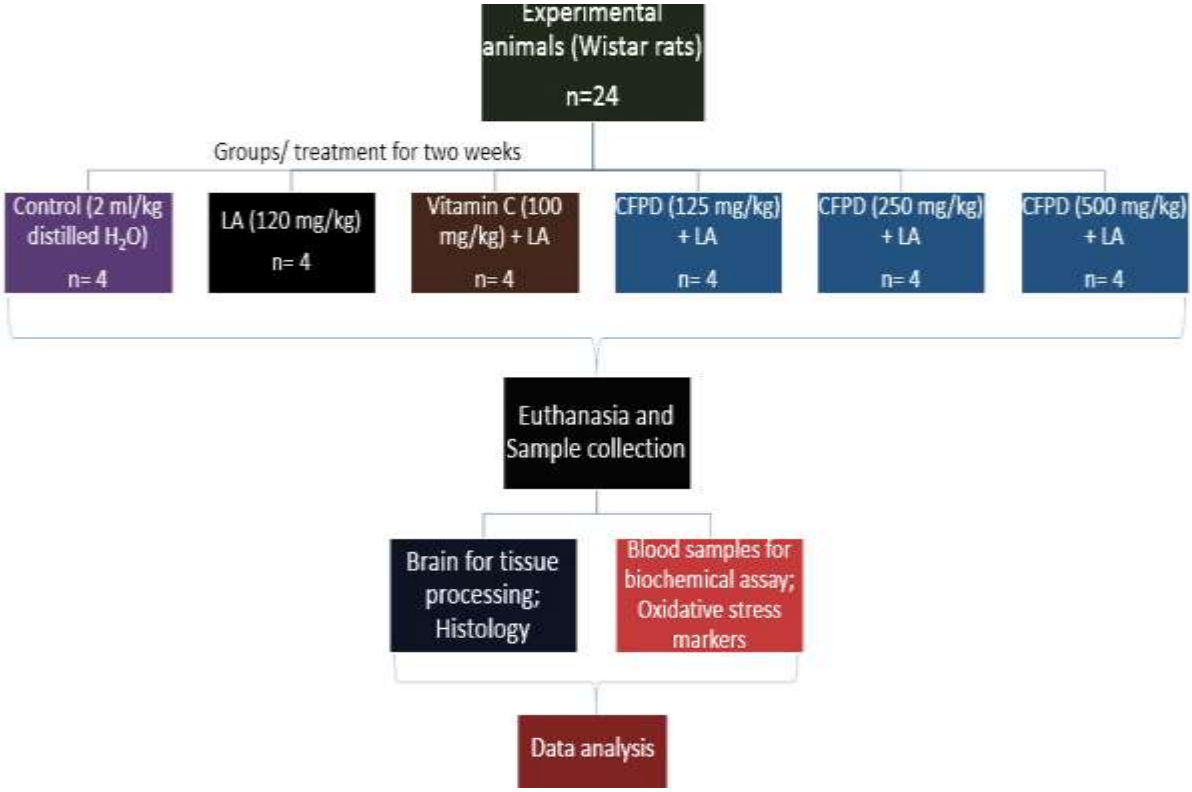

Figure 1: Experimental protocol

Chloroform fruit extract of *Phoenix dactylifera* (CFPD)*;* Lead acetate (LA).

Biochemical Studies

Collected sera from centrifuge blood samples were assayed for oxidative biomarkers (malondialdehyde, MDA; superoxide dismutase, SOD; catalase, CAT and glutathione peroxidase, GPx using assay kits (ELISA Kit; *WKEA Med Supplies Corp, China*). Serum malondialdehyde (MDA) was assayed to estimate lipid peroxidation (LPO) levels. Antioxidant enzymatic activity (SOD, CAT, and GPx; vital component of the antioxidant defense system, inhibiting intracellular injury triggered by free radicals by reacting with ROS (Lee *et al.,* 2007; Sanders *et al*., 2009; Kabeer *et al*., 2019) was assayed using the methods described by Okey and Ayo (2015) in the Department of Chemical Pathology, ABU Teaching Hospital, Shika.

Data Analysis

Data obtained were analyzed using the Statistical Package for the Social Sciences (IBM SPSS *v 21.0* SPSS Inc., Chicago, USA) and Microsoft Office Excel 2013 for charts. Results were expressed as mean ± SEM and the presence of significant differences among means of the groups was determined using one-way ANOVA with the least significant difference (LSD) *post hoc test* for significance. Values were considered significant when $p< 0.05$.

RESULTS

Phytochemical Analysis

Phytochemical analysis of the CFPD produced negative and positive reactions for some secondary metabolites: alkaloids, flavonoids, saponins, and others (Table 1).

Physical Observation

Physical observation of rats revealed normal activity in the control group, while the LA-treated groups expressed sluggishness and reduced playfulness.

Table 1: Phytochemical constituents of chloroform fruit pulp extract of *Phoenix dactylifera*

Constituents	Alkaloid	Cardiac glycoside	Flavonoids	Saponin	Steroid and Tripenone	Tannin
Inference	–	+	–	+	+	–

+ = Positive (Present); **–** = Negative (Absent)

Histological Assessments

In this study, sections of the cortical regions of the cerebellum and cerebrum (layers III and V) of rats were examined for histopathological changes, and the following were observed:

Generally, at a low microscopic magnifying power, the cortical cerebellar region presented with several cerebellar lobules with distinct cellular distribution patterns; molecular and granular (Plate 1). Similarly, the cerebral cortex presented with an organized cellular laminarization with six layers (I – VI); layers III and V are predominantly composed of pyramidal cells (Plate 2).

At a closer (high) magnification, the cerebellar cortex of the control group revealed normal histoarchitectural features with a characteristic appearance of three cortical laminae; an outer molecular layer with distinct neurons, an intermediate Purkinje cell layer, and an inner granular layer (Plate 3A).

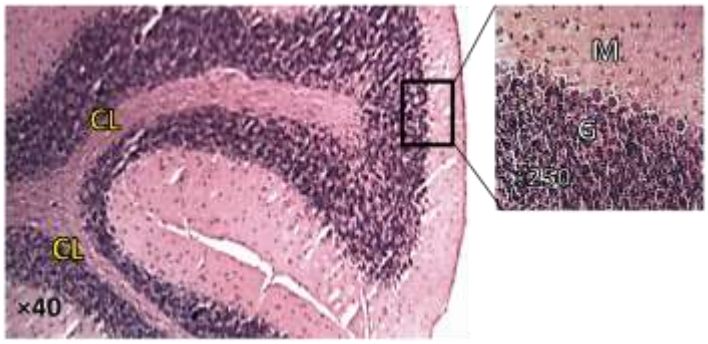

Plate 1: Coronal section of the cerebellum of Wistar rat indicating cortical region. H and E stain.
Cerebellar lobule (CL); Molecular cell layer (M); and Granular cell layer (G).

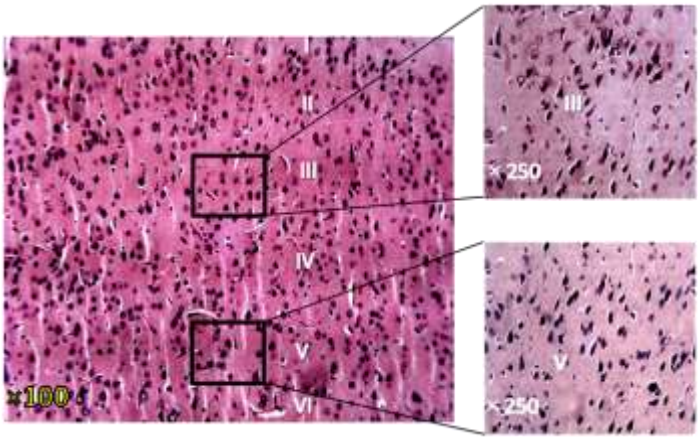

Plate 2: Coronal section of the cerebral cortex of Wistar rat indicating layers. H and E stain
Layers I -VI (I - VI).

The cerebellar cortex of the LA (120 mg/kg)-treated group showed histoarchitectural distortions including perineuronal vacuolations and gliosis compared to the control group (Plate 3B). The cerebellar cortex of vitamin C (100 mg/kg) +LA- and CFPD+LA -treated groups revealed mild histoarchitectural distortions compared to the LA-treated group. Remarkable histoarchitectural preservation was observed in the CFPD (250 mg/kg) +LA --treated group compared to the vitamin C+LA and control groups (Plates 3C-F).

Histological features of the cerebral cortex revealed characteristic pyramidal and stellate cells, amongst other populations of cells in the control group (Plates 4A and 5A). Relative to the control, the LA (120 mg/kg)-treated group showed distorted histoarchitecture of layers III and V of the cerebral cortex; neurodegenerative changes like pyknotic nuclei, chromatolysis, perineuronal vacuolation, and gliosis (Plates 4B and 5B). Relative to the histoarchitectural distortions observed in the LA-treated group, the cerebral cortex of vitamin C+LA- and CFPD+LA-treated groups revealed mild distortions. Histoarchitectural preservation was observed in CFPD+LA-treated groups in a dose-dependent fashion (Plates 4C - F and 5C - F).

Biochemical Studies

The serum MDA levels showed no significant difference ($p>0.05$) in all the groups when compared to the control group (Figure 2). A significant increase ($p<0.05$) in serum SOD activity was observed in CFPD (250 mg/kg) +LA (120 mg/kg)-treated group when compared with the vitamin C+LA and control groups (Figure 3). In the serum CAT activity, LA -treated group revealed a significant decrease ($p<0.05$) in CAT activity when compared to the control. The CFPD (250 mg/kg) +LA -treated group showed significantly increased ($p<0.05$) CAT activity when compared to the control and vitamin C+LA groups (Figure 4). Similarly, in the serum GPx activity, LA-the treated group showed significantly decreased ($p<0.05$) GPx activity compared to the control, while CFPD (250 mg/kg) +LA -treated group showed a significant increase ($p<0.05$) in GPx activity compared to the vitamin C+LA and control groups (Figure 5).

DISCUSSION

In this study, preliminary phytochemical screening of CFPD was carried out and, the neuroprotective effect of CFPD against LA-induced neurotoxicity was evaluated by the assessment of Wistar rats' physical activity, cortical cerebellar and cerebral histopathological changes, and alteration in the activity of oxidative stress biomarkers.

Qualitative phytochemical analysis of CFPD revealed the presence of saponins, steroids, and tripenone which have been reported to exert neuroprotective actions in *in vivo* and *in vitro* models of neurological disorders (Chen *et al*., 2015; Hwang *et al*., 2015; Qian *et al*., 2016; Agbon *et al*., 2021). The observed absence of flavonoid suggests low flavonoid content in the sample (CFPD); minimum extraction of certain sub-types of flavonoid concentration has been reported with the solvent, chloroform (Ghasemzadeh *et al*., 2011; Dixon and Gupta, 2017; Sundar *et al*., 2017). This suggests the activities of phytochemicals other than flavonoid, which have been emphasized with *P. dactylifera* fruit extracts neuroprotective properties (Rice-Evans, 2001; Pujari *et*

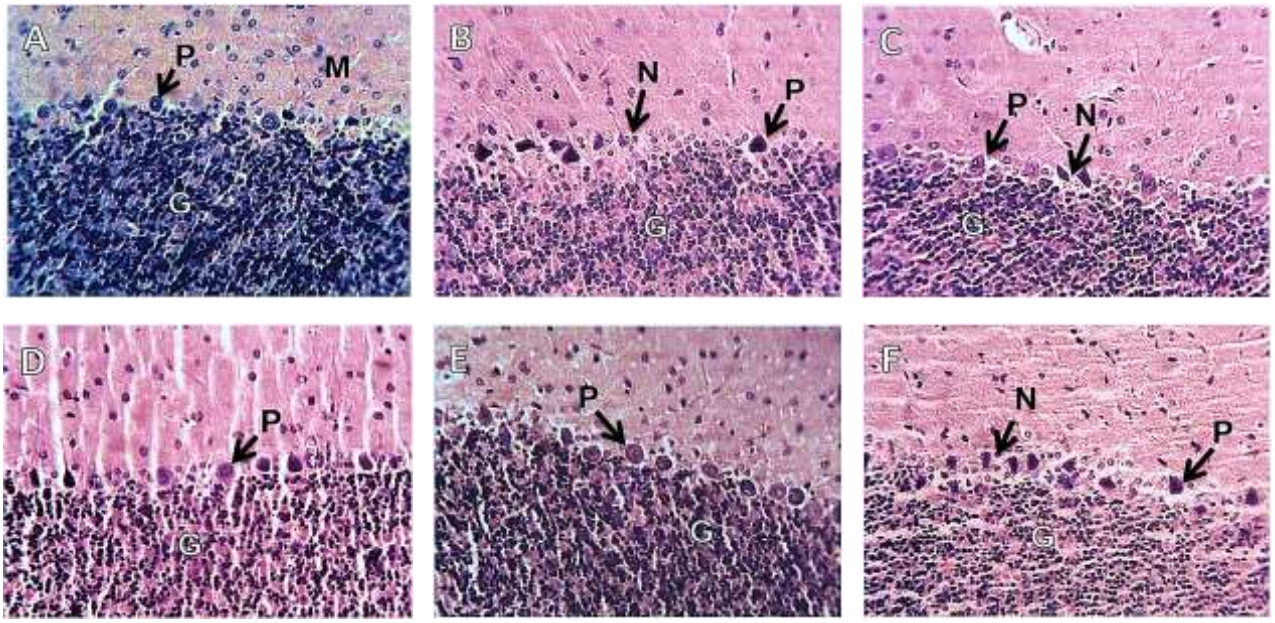

Plate 3: Section of the cerebellar cortex of Wistar rat. H and E stain (Mag ×250). **A**= control (2 ml/kg distilled water) group with normal histoarchitecture of the cerebellar cortex. Purkinje cell layer (P); Molecular cell layer (M); and Granular cell layer (G); **B**= Group administered lead acetate (120 mg/kg) with distortion in the histoarchitecture of the cerebellar cortex; Purkinje cell layer (P); Granular cell layer (G); Perineuronal vacuolation, gliosis (N); **C**= Group administered vitamin C (100 mg/kg) and lead acetate (120 mg/kg) with mild distortion in the histoarchitecture of the cerebellar cortex; Purkinje cell layer (P); Granular cell layer (G); Perineuronal vacuolation (N); **D**= Group administered CFPD (125 mg/kg) and lead acetate (120 mg/kg) with mild distortion in the histoarchitecture of the cerebellar cortex; Purkinje cell layer (P); and Granular cell layer (G); **E**= Group administered CFPD (250 mg/kg) and lead acetate (120 mg/kg) with normal histoarchitecture of the cerebellar cortex; Purkinje cell layer (P); and Granular cell layer (G); **F**= Group administered CFPD (500 mg/kg) and lead acetate (120 mg/kg) with mild distortion in the histoarchitecture of the cerebellar cortex; Purkinje cell layer (P); Granular cell layer (G), Perineuronal vacuolation (N).

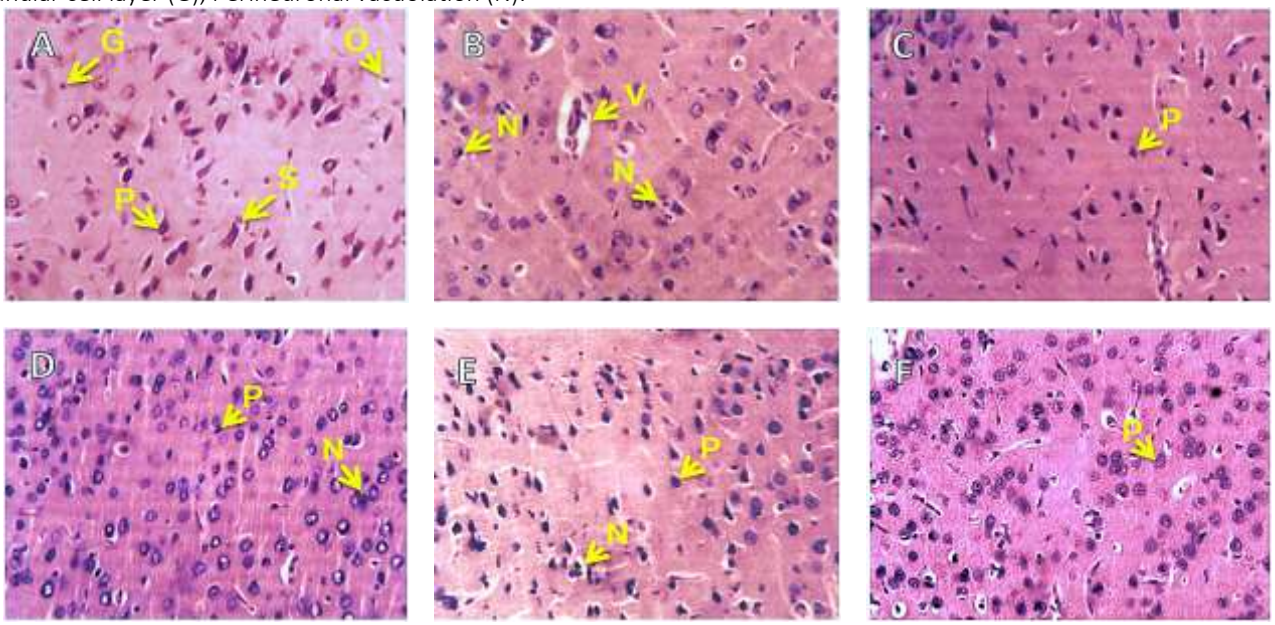

Plate 4: Section of the cerebral cortex (layer III) of Wistar rat. H and E stain (Mag ×250). **A**= Control (2 ml/kg distilled water) group with normal histoarchitecture of the cerebral cortex. Pyramidal cell (P); Stellate cell (S); and Glia cell (G); Oligodendrocyte (O); **B**= Group administered lead acetate (120 mg/kg) with distortion in the histoarchitecture of the cerebral cortex. Vessel (V); Pyknotic necrosis, gliosis (N); **C**= Group administered vitamin C (100 mg/kg) and lead acetate (120 mg/kg) with normal histoarchitecture of the cerebral cortex. Pyramidal cell (P); **D**= Group administered CFPD (125 mg/kg) and lead acetate (120 mg/kg) with mild distortion in the histoarchitecture of the cerebral cortex. Pyramidal cell (P); Chromatolysis, gliosis (N); **E**= Group administered CFPD (250 mg/kg) and lead acetate (120 mg/kg) with mild distortion in the histoarchitecture of the cerebral cortex. Pyramidal cell (P); Gliosis (N); **F**= Group administered CFPD (500 mg/kg) and lead acetate (120 mg/kg) with normal histoarchitecture of the cerebral cortex. Pyramidal cell (P).

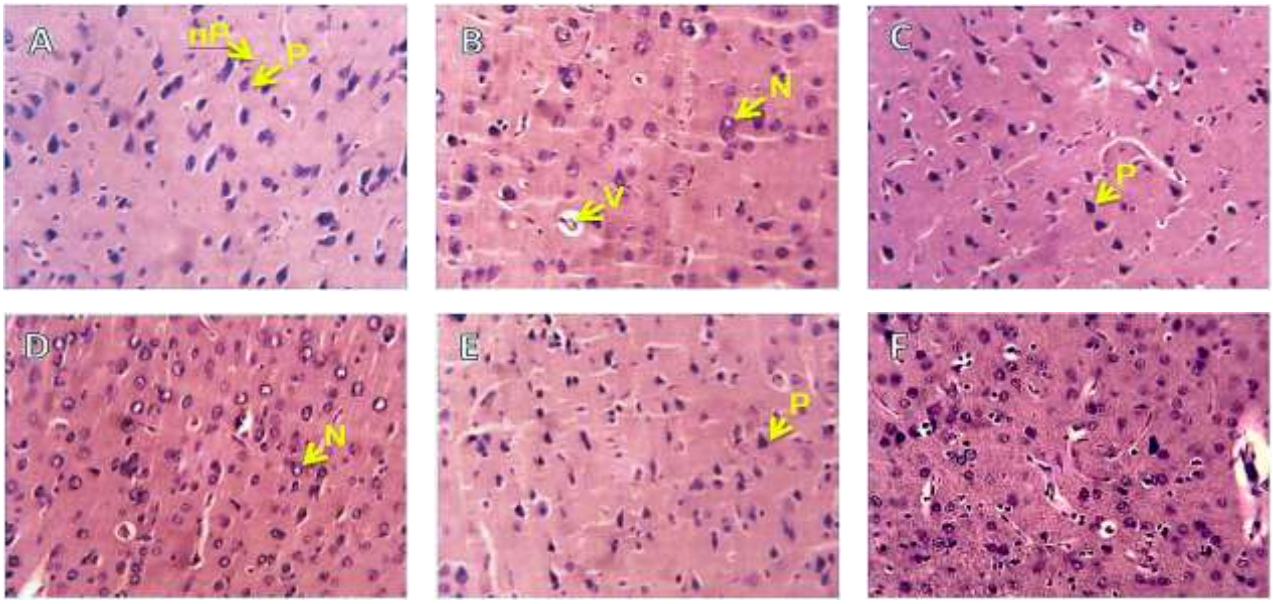

Plate 5: Section of the cerebral cortex (layer V) of Wistar rat. H and E stain (Mag ×250). **A**= Control (2 ml/kg distilled water) group with normal histoarchitecture of the cerebral cortex. Pyramidal cell (P); Neuronal process (nP); **B**= Group administered lead acetate (120 mg/kg) with distortion in the histoarchitecture of the cerebral cortex. Vessel (V); Pyknotic nuclei, chromatolysis, and gliosis (N); **C**= Group administered vitamin C (100 mg/kg) and lead acetate (120 mg/kg) with normal histoarchitecture of the cerebral cortex. Pyramidal cell (P); **D**= Group administered CFPD (125 mg/kg) and lead acetate (120 mg/kg) with mild distortion in the histoarchitecture of the cerebral cortex. Pyramidal cell (P); Pyknotic necrosis, gliosis (N); **E**= Group administered CFPD (250 mg/kg) and lead acetate (120 mg/kg) with normal histoarchitecture of the cerebral cortex. Pyramidal cell (P); Gliosis (N); **F**= Group administered CFPD (500 mg/kg) and lead acetate (120 mg/kg) with normal histoarchitecture of the cerebral cortex.

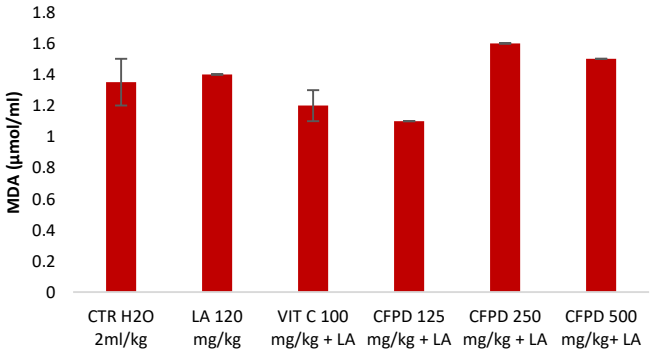

Figure 2: Effect of CFPD on serum malondialdehyde (MDA) levels in Wistar rats. n=4; mean ± SEM; One way ANOVA *LSD post hoc test* p>0.05 when compared with the control. **CTR**= Control (H_2O, distilled water); **LA**= Lead acetate; **VIT C**=Vitamin C; **CFPD**= Chloroform fruit extract of *Phoenix dactylifera.*

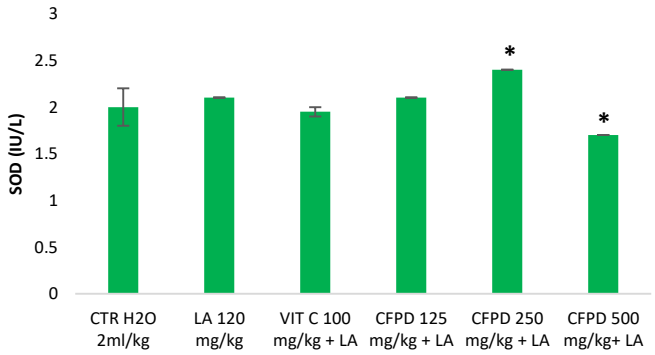

Figure 3: Effect of CFPD on serum superoxide dismutase (SOD) activity in Wistar rats. n=4; mean ± SEM; One-way ANOVA LSD post hoc test *=p<0.05 when compared with the control. **CTR**= Control (H_2O, distilled water); **LA**= Lead acetate; **VIT C**=Vitamin C; **CFPD**= Chloroform fruit extract of *Phoenix dactylifera.*

al., 2011; Agbon et al., 2014b). Saponins act as neuroprotective agents via anti-inflammatory, antioxidant, and antiapoptotic pathways. Moreover, modulation of neurotransmitters and neurotrophic factors, Ca^{2+} influx attenuation, tau phosphorylation inhibition, and neural network regeneration have been reported as possible mechanisms (Zhou et al., 2009; Luo *et al*., 2011; Sun *et al*., 2014; Chen *et al*., 2015). Steroids' neuroprotective mechanisms involve neurons, glial cells, and blood vessels of the central nervous system; steroids reduce reactive gliosis by acting on microglia and astroglia and pro-inflammatory cytokines release (Garcia-Segura and Balthazart, 2009).

Altered physical activity and behavioural patterns, such as reduced agility and social interaction exhibited by LA-treated rats are suggestive of treatment-related toxicity. *In vivo* studies on response to toxins associated with altered physical activity like sluggishness and loss of appetite are indicative of drug-related toxicity (Toma *et al*., 2009; Lazarus *et al*., 2018).

Exposure to lead adversely affects human and animal health (Patrick, 2006; Assi *et al*., 2016; Harshitha *et al.,* 2024). Lead is highly toxic and interrupts the body's neurological, biological, and

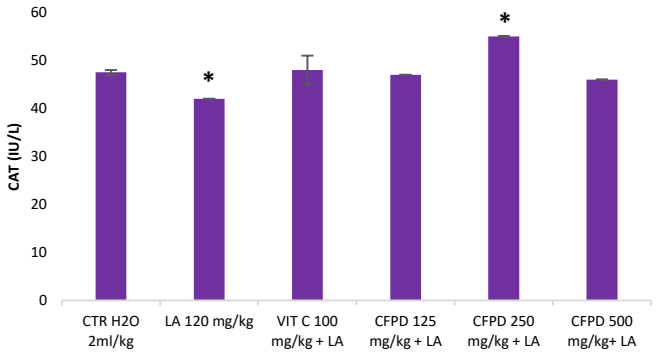

Figure 4: Effect of CFPD on serum catalase (CAT) activity in Wistar rats. n=4; mean ± SEM; One way ANOVA LSD post hoc test *=p<0.05 when compared with the control. **CTR**= Control (H_2O, distilled water); **LA**= Lead acetate; **VIT C**=Vitamin C; **CFPD**= Chloroform fruit extract of *Phoenix dactylifera.*

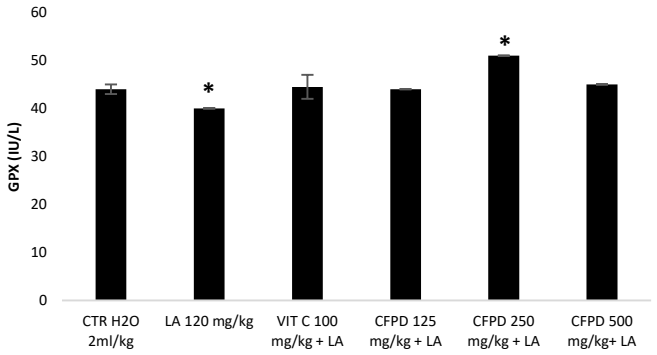

Figure 5: Effect of CFPD on serum glutathione peroxidase (GPx) activity of Wistar rats. n=4; mean ± SEM; One way ANOVA LSD post hoc test *=p<0.05 when compared with the control. **CTR**= Control (H_2O, distilled water); **LA**= Lead acetate; **VIT C**=Vitamin C; **CFPD**= Chloroform fruit extract of *Phoenix dactylifera.*

cognitive functions (Elombah and HRW, 2012; Bauchi *et al*., 2016). Histopathological changes in cortical cerebellar and cerebral regions of the LA-treated rat are indications of drug-related neurotoxicity (Kalantaripour, 2012; Arora *et al*., 2024). Heavy metals such as lead, mercury, cadmium, and arsenic can trigger nervous tissue damage (Amal and Mona, 2009; Butt *et al*., 2018; Eze *et al*., 2021). Mechanisms of lead-triggered tissue injury include elevated production of ROS; superoxide radicals, hydrogen peroxide, and hydroxyl radicals, thus, eliciting oxidative stress which results in the cell membrane and DNA damage (Sharma *et al*., 2010; Singh *et al*., 2018). Findings are in line with the reports of Yusuf *et al*. (2017) and Henry *et al*. (2021) who observed degenerative changes as histoarchitectural distortions including satellitosis, perineuronal vacuolation, and cytoplasmic shrinkage of Purkinje cells in the cerebellar cortex of lead-exposed rats.

Mild histoarchitectural distortion, compared to the severe neurodegenerative changes in the LA-treated group, observed as preserved histoarchitecture of cerebellar and cerebral cortices of rats treated with vitamin C is suggestive of ameliorative activity. This is in agreement with the report of Ibegbu *et al*. (2013); ascorbic acid (vitamin C) ameliorated cortical cerebral damage in heavy metal-exposed rats. Kumar *et al*. (2018) reported that ascorbic acid participates in several beneficial cellular functions like antioxidant protection and the scavenging of free radicals (Teleanu *et al*., 2019).

Histological features of CFPD-treated rats demonstrated preservation of the cortical cerebellar and cerebral parenchyma and cytoarchitecture of neurons. This suggests that CFPD has ameliorative activity against lead-acetate-induced histological changes. These findings are consistence with the reports of Edobor *et al*. (2021) and Henry *et al*. (2021) which demonstrated preserved histoarchitectural features of the cerebral and cerebellar cortices following treatment with fruit pulp extracts of *P. dactylifera* in Wistar rats exposed to environmental neurotoxins. Wan Ismail and Mohd Radzi (2013) reported that treatment with *P. dactylifera* fruit extracts greatly reduced neuronal damage in the form of shrinkage, atrophy, and necrosis of neurons and increased the levels of endogenous antioxidants in the brain of rats. Agbon *et al*. (2021) reported remarkable neuroprotection following heavy metal-induced degenerative changes by the preservation of brain cytoarchitectural features comparable to a referenced antioxidant drug. The polyphenolics including saponins, found in many plant extracts, are strong ROS scavengers, antioxidants, and protectors of neurons from lethal damage (Pujari *et al*., 2011) and can chelate metal ions (Komaki *et al*., 2015). Thus, CFPD can potentially preserve neuronal cytoarchitectural features following lead-triggered changes in observed brain regions.

In this study, oxidative stress markers (MDA, SOD, CAT, and GPx) were assayed in serum. LPO levels, expressed by MDA concentration, showed elevation in the lead-treated groups compared to the control. LPO is a free radical-related process that is potentially detrimental, eliciting tissue damage resulting from cellular components and membrane disruption (Himakar *et al*., 2010; Auza *et al*., 2017) and, involved in oxidative stress, which plays an essential role in neuronal degeneration (Rao and Purohit, 2011). In this study, the vitamin C-treated group revealed ameliorative potentials by depressed levels of LPO relative to the control which could be attributed to its antioxidant activity. Antioxidants can eliminate ROS and derivatives, acting as defence regulators or inhibitors of reactive entity production (Mut-Salud *et al*, 2016). Vitamin C plays a pivotal role in neutralizing free radicals; acting both intracellularly and extracellularly to combat free radical damage (Young and Woodside, 2001; Pawar *et al*., 2016).

Biological systems defend themselves against the detrimental effects of activated species by free radical scavenging activity and chain reaction terminator enzyme systems like SOD, CAT, and GPx (Semiz and Sen, 2007; Uma *et al.,* 2012; Jomova *et al.,* 2024). Lead and other heavy metals having serious health implications have been reported to alter enzymatic antioxidant activity (Moreira *et al.,* 2010; Abdulazeez *et al*., 2024) by direct binding with enzymes' thiol group which leads to distortion in their three-dimensional conformations (Sharma *et al*., 2014). In this study, serum CAT and

GP_X activity levels decreased remarkably in the lead-treated group when compared to the control which is suggestive of treatment-induced oxidative stress. Lead is a potent thiol-binding agent that potentially decreases glutathione (GSH) levels and elicits lipid, protein, DNA, and RNA oxidation by elevating ROS levels (Clarkson, 1997; Valko *et al*., 2005; Flora *et al*., 2008). GPx activity is tied to glutathione reductase which regulates reduced GSH levels (Bompart *et al.,* 1990). GPx enzyme catalyzes the reduction of ROS by utilizing GSH as a reducing reagent, thereby preventing free radical formation. Thus, several deleterious effects result from reduced activity of these enzymes owing to the accumulation of superoxide radicals and hydrogen peroxide, linked with neurodegenerative diseases (Khan *et al.,* 2012). This finding is in line with the reports of Durak *et al*. (2010) and Kim *et al*. (2015).

In this study, enzymatic antioxidant activity levels of the vitamin C-treated group were comparable to the control and, were remarkably increased in CFPD-treated groups, especially at a dose of 250 mg/kg. Vitamin C, an established antioxidant, is an excellent source of electrons thus, can donate electrons to free radicals such as hydroxyl and superoxide radicals and extinguish their reactivity (Bindhumol *et al.,* 2003; Salehi *et al*., 2018).

Relatively higher levels of antioxidant enzymatic activity in the CFPD-treated group reflect enhanced antioxidant activity, facilitating detoxification of lead-induced toxicity (Lu, 2013). Thus, it is suggestive of CFPD neuroprotective effects through its antioxidant activities. Exogenous antioxidants, especially from dietary sources, have been associated with great stability between free radicals and antioxidant status. This aids in diminishing oxidative stress and reducing the risk of disease-related conditions (Kumar *et al*., 2016). Findings are consistent with reports on extracts of medicinal plants exerting neuroprotective effects against heavy metal-induced oxidative stress through antioxidant activities (El-Tarras *et al*., 2016; Gombeau *et al*., 2019; Phukan *et al*., 2019). Findings are in agreement with the reports on the neuroprotective properties of extracts of *P. dactylifera* against chemically triggered oxidative stress-neurotoxicity, probably by mechanisms that enhance antioxidant defense systems (Mohamed *et al*., 2016; Agbon *et al*., 2017; Budaye *et al*., 2018; Essa *et al*., 2019). Phenolic substances including saponins are considerably potent antioxidants. Phytochemicals with antioxidant properties have been associated with reduced symptoms of neurodegeneration and toxicity in an animal model; (Hwang *et al*., 2015; Hussain *et al*., 2020). Thus, CFPD has the potential to alleviate systematic oxidative stress triggered by lead intoxication by increasing the activities of serum antioxidant enzymes such as SOD, CAT, and GPx.

Conclusion

Chloroform fruit extract of *Phoenix dactylifera*, especially at a dose of 250 mg/kg, has the potential to ameliorate lead acetate-induced neurodegenerative changes in the cerebellar and cerebral cortices of Wistar rats. Neuroprotective properties could be consequent to the phytochemicals with antioxidant properties present in the plant extract.

Conflict of Interest

No conflict of interest

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