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Neuroprotective Effects of Aqueous Extract of *Bryophyllum pinnatum* Against Lead Acetate Induced Damage in the Cerebellum of Rats

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ORIGINAL STUDY

Neuroprotective Effects of Aqueous Extract of *Bryophyllum pinnatum* Against Lead Acetate Induced Damage in the Cerebellum of Rats

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ABSTRACT

Lead is a persistent environmental toxin with pronounced neurotoxic effects, particularly on the central nervous system. This study evaluated the impact of lead acetate on the cerebellar cortex of adult Wistar rats and assessed the neuroprotective effects of aqueous Bryophyllum pinnatum extract. Twenty adult Wistar rats (180–220 g) were randomly assigned to four groups (n = 5): Control (distilled water), T1 (0.075 mg/kg lead acetate), T2 (100 mg/kg B. pinnatum), and T3 (lead + B. pinnatum). Treatments were administered orally for 21 days. Cerebellar tissues were processed for biochemical and histological analysis, and data were analyzed using GraphPad Prism v10.1.Lead exposure significantly decreased body weight and cerebellar weight compared to control ($p < 0.01$). Superoxide dismutase (SOD) and catalase (CAT) activities were markedly reduced ($p < 0.0001$), while malondialdehyde (MDA) levels were significantly elevated ($p < 0.0001$), indicating increased lipid peroxidation. Purkinje cell counts were significantly diminished in the lead-treated group ($p < 0.0001$). Histologically, lead induced marked neuronal shrinkage, pyknotic nuclei, and cytoplasmic vacuolation in Purkinje cells. Co-treatment with B. pinnatum significantly improved body and cerebellar weights ($p < 0.01$), restored SOD and CAT activities ($p < 0.001$), reduced MDA levels ($p < 0.0001$), and preserved Purkinje neuron morphology and population ($p < 0.0001$). These results demonstrate that lead acetate induces cerebellar neurotoxicity via oxidative stress mechanisms. B. pinnatum extract effectively mitigates these effects by enhancing antioxidant defense, reducing lipid peroxidation, and maintaining neuronal integrity, underscoring its therapeutic potential against lead-induced neurotoxicity.

Keywords: *Bryophyllum pinnatum*, Lead neurotoxicity, Cerebellar damage, Antioxidant protection, Neuroprotection

1. Background

Lead poisoning represents one of humanity's most persistent health challenges, particularly affecting developing countries where environmental controls may be limited [1]. This toxic trace metal elements infiltrates our environment through deteriorating paint, contaminated soil, and industrial emissions, accumulating in the human body where it disrupts neurological and biological functions [2].

Dietary exposure of lead increases when crops grow in contaminated soil, while inhalation is common near smelting and informal e-waste sites [3]. Absorbed lead enters the bloodstream through the gut or lungs, then distributes to soft tissues including the brain crossing the blood–brain barrier by mimicking calcium [1].

Unlike many toxins that the body efficiently eliminates, lead follows a more sinister path: while small amounts are excreted in urine, the majority

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accumulates in body tissues, particularly the central nervous system (CNS), creating structural changes that persist even after blood lead levels decrease [4].

Lead targets the brain through a devastating cascade of cellular destruction, generating reactive oxygen species (ROS) including superoxide radicals, hydroxyl radicals, hydrogen peroxide, and lipid peroxides that systematically damage cellular materials [5]. Despite decades of research, the complete mechanism of lead's toxic action in the nervous system remains partially understood. Once lead enters the brain, it persists longer than in blood, with some brain regions showing particularly slow clearance times [6].

The brain regions most vulnerable to lead include the prefrontal cortex, cerebellum, and hippocampus. Lead damages these areas at molecular, cellular, and intercellular levels, often resulting in permanent morphological alterations that persist even after lead levels decline [7]. The nervous system appears exceptionally sensitive and represents the chief target for lead-induced toxicity [8].

Lead disrupts the body's antioxidant defense systems by inhibiting essential enzymes like glutathione through binding to their sulfhydryl groups [8]. This creates a destructive cycle where lead both generates harmful free radicals and simultaneously destroys the body's ability to neutralize them. Exposure occurs primarily through respiratory and gastrointestinal systems, with absorbed lead accumulating in various organs and interfering with physiological processes affecting the central nervous system, blood formation, kidney function, and reproductive health [1]

The cerebellum, nicknamed the "little brain," occupies a vital position in human neurology. Located at the brain's posterior base, this structure accounts for only 10% of brain volume yet houses over 50% of the brain's total neurons [9]. Beyond its traditional role in motor control and posture, the cerebellum acts as a sophisticated modifier, refining motor pathways to create more adaptive and accurate movements [10].

Recent neuroimaging and behavioral studies have revealed the cerebellum's crucial involvement in perception, cognition, and emotion processing, particularly in circumstances requiring predictions or precise timing [11]. Its extensive connections with cortical and subcortical brain centers suggest that cerebellar dysfunction may contribute not only to motor impairments but also to complex neurological and neurodevelopmental conditions [12]. The cerebellum is crucial because it is one of the most lead-sensitive regions of the brain, showing early oxidative injury and structural alterations due to its high metabolic demand and dense neuronal network [7]. Purkinje cells, in particular, are highly vulnerable to toxic insults due to their size, extensive dendritic arborization, and high firing rates; their degeneration is a reliable indicator of cerebellar dysfunction [13].

In searching for effective treatments against lead neurotoxicity, scientists have turned to nature's pharmacy. *Bryophyllum pinnatum*, known as the "life plant" or "miracle leaf," stands out as a promising candidate. In Nigeria, B. pinnatum is widely used for wound healing and infant umbilical cord care [14]. Pharmacological studies have revealed impressive biological activities including immunomodulatory, CNS depressant, analgesic, anti-inflammatory, antimicrobial, antitumor, antiulcer, antidiabetic, anticonvulsant, antioxidant, and antihypertensive properties [15].

The plant's therapeutic effects stem from its rich phytochemical profile, including alkaloids, triterpenes, glycosides, flavonoids, steroids, bufadienolides, lipids, and organic acids [16]. Since lead generates free radicals during pathogenic processes, antioxidant supplementation should theoretically interrupt or minimize lead's damaging effects and enhance traditional chelating agents [17]. The present study investigates whether aqueous B. pinnatum leaf extract can provide meaningful protection against lead-induced cerebellar damage.

2. Methodology

2.1. Plant extraction and screening

Fresh leaves of *Bryophyllum pinnatum* were harvested from herbal centre, Ikenne, Ogun-state, Nigeria, were authenticated in the pharmaceutical department of Olabisi Onabanjo university Sagamu. Two kilograms of *Bryophyllum pinnatum* was cleaned with tap water and air-dried in the dark at room temperature. The dried leaves were pulverized into a fine homogenous powder using an electrical blender (Binatone, United Kingdom). 600g of the powdered was weighed and extracted using Distilled water (1:4 at./vol.) For 72 hours at room temperature (26–28 ˚C) through cold maceration. The solution was filtered through Whatman filter paper (Whatman International, United States), and the filtrate was concentrated to dryness using a rotary evaporator (Laborota 4000–efficient, Germany) at 40–45 ˚C.

2.2. Animal care

Twenty (20) adult Wistar rats of both sexes, aged 6–8 weeks (180–220 g), were obtained from the Animal House, Department of Pharmacology, Ogun State,

Nigeria. The animals were housed and managed at the Animal House of the Department of Anatomy, Olabisi Onabanjo University, Ago-Iwoye, Ogun State, Nigeria, under humane conditions according to the Principle of Laboratory Animal Care (Clark *et al,* 1997) and NIH Guide for the Care and Use of Laboratory Animals. Ethical approval for this study was gotten from University Ethical Review Committee (UERC), Olabisi Onabanjo University, Ago Iwoye (OOU/SCIENG/EC/241282).

The rats were housed in well-ventilated plastic cages having dimensions of 36 cm long × 24 cm wide × 15 cm high. They were maintained under standardized animal house conditions (temperature: 23–25°C; approximately 12 hrs light/12 hrs dark cycle per day) and were fed with standard rat chow (Premier Feed Mills, Nigeria) and given tap water ad libitum.

2.3. Experimental design

Twenty adult Wistar rats (180–220g, both sexes) were randomly assigned to four groups (n = 5 each): Control (distilled water), T1 [Lead acetate (0.075 mg/kg) was freshly prepared each day by dissolving it in distilled water], T2 (100 mg/kg B. pinnatum aqeuos extract), in the combined treatment group (T3), lead acetate was administered first, followed by Bryophyllum pinnatum extract after a 30-minute interval to avoid possible interference during gastrointestinal absorption. All treatments were administered orally daily for 3 weeks.

2.4. Weight change and sacrifice

Animal body weight changes were monitored throughout the study, with final body weight measurements recorded on the last day of the experiment immediately before sacrifice. Following euthanization via cervical dislocation, the brain was carefully extracted under sterile conditions. The Brain tissue was then weighed using a precision electronic balance (Mettler Toledo, Microsep Pty Ltd, Greifensee, Switzerland). All weight measurements were expressed in grams to maintain consistency across data collection parameters.

2.5. Markers of oxidative stress assessment

1g of cerebellar tissue samples were collected and homogenized using phosphate buffered saline in a mortar and pestle. Homogenates were poured into pre-cooled heparinized tubes, placed on ice for 3 hours, then centrifuged using desktop centrifuge model 90–1 (Jiangsu Zhangji Instruments Co., China) at 3000 rpm for 15 minutes. The resulting homogenate was decanted into Eppendorf tubes and stored at –80 °C for subsequent biochemical analysis. Tissue homogenate levels of SOD were assayed by the modified methods as described by Sun et al. [18]; CAT were assayed by the modified methods as described by Sinha [19]; MDA were assayed by the modified methods as described by Gutteridge et al. [20].

2.6. Histopathological examination

Excised Cerebellar tissues were immediately fixed in 10% neutral buffered formalin. After proper fixation, tissues were dehydrated in a graded series of alcohol, cleared in xylene and embedded in paraffin wax using a cassette. For routine histological study, the paraffin-embedded brain tissues were sectioned at 5 μm thickness using an RWD S700A rotary microtome. The slides were deparaffinized in xylene and rehydrated in graded ethanol (100%, 90%, 80%, 70% and 50%) and rinsed in water. Slides were stained in hematoxylin for 5 min and rinsed with water, and counterstained in eosin for general assessment of the cerebellar morphology. The stained slides were then cover slipped using DPX mounting glue directly over the tissue sections. Thereafter, the slides were left overnight to dry for examination under a light microscope.

2.7. Photomicrography and morphometric analysis

Slides were examined under a light microscope (Leica ICC50 W, Germany) at 40x magnifications, with photomicrographs taken at 400x. Image were captured using Amscope 2.0. Purkinje cell quantification was performed using a standardized counting protocol. Three non-overlapping fields were selected per cerebellar section at ×400 magnification, focusing on the mid-vermis region where Purkinje cells are consistently aligned. Counting was conducted manually by two independent observers blinded to group allocation to eliminate bias. Only Purkinje cells with clearly visible soma and nucleus were included. Mean values from the three fields were used for statistical analysis.

2.8. Statistical analysis

Data were expressed as means ± SEM and analyzed using one-way ANOVA followed by Tukey post-hoc test, with significance accepted at $P < 0.05$. All statistical analyses were conducted using GraphPad Prism 10.1.

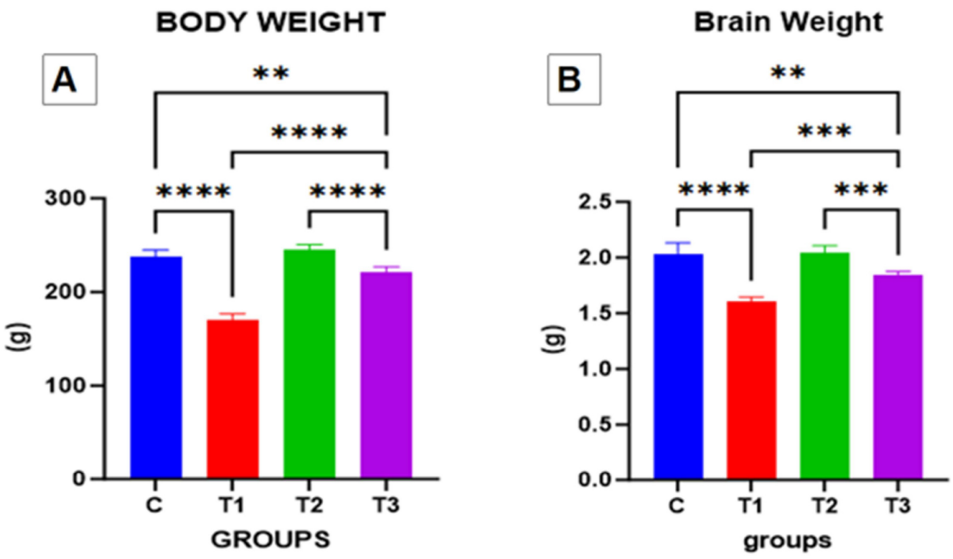

Fig. 1. Showing weght changes across the experimnetal rats. Control (distilled water), T1 (0.075 mg/kg lead acetate), T2 (100 mg/kg B. pinnatum extract), and T3 (combined lead acetate + B. pinnatum) .All data were expressed as Mean ± SEM and analyzed using one-way ANOVA with Tukey's Multiple Comparison Test (GraphPad Prism 10.1, $p < 0.05$).

3. Results

3.1. Weight change

A: The body weight measurements across experimental groups revealed significant alterations following the three-week treatment period (Fig. 1). Animals in the control group (C), which received distilled water, maintained normal weight gain patterns throughout the study duration. In contrast, rats treated with lead acetate alone T1, demonstrated statistically significant weight reduction compared to the control group ($p < 0.05$). Rats in the plant extract-only group T2, exhibited weight patterns similar to control animals. The combined treatment group T3, demonstrated statistically significant improvement in body weight compared to the lead-only group (T1, $p < 0.05$)

B: The cerebellar weight measurements across experimental groups demonstrated significant tissue-specific effects of lead exposure and B. pinnatum intervention. Rats treated with lead acetate alone (T1, 0.075 mg/kg) showed statistically significant cerebellar weight reduction compared to all other experimental groups ($p < 0.05$). Animals in the combined treatment group (T3), which received both lead acetate and B. pinnatum extract, demonstrated significantly increased cerebellar weight compared to the lead-only group (T1, $p < 0.05$).

3.2. Oxidative stress biomarkers

A: The superoxide dismutase (SOD) activity measurements revealed significant oxidative stress alterations across experimental groups. Rats exposed to lead acetate alone (T1) demonstrated statistically significant reduction in cerebellar SOD levels compared to the control group ($p < 0.05$). The intervention with *Bryophyllum pinnatum* aqueous extract effectively restored antioxidant capacity in lead-exposed animals. The combined treatment group (T3) showed significantly increased SOD levels compared to the lead-only group (T1, $p < 0.05$).

B: The catalase (CAT) activity measurements demonstrated significant antioxidant enzyme alterations across experimental groups. Rats exposed to lead acetate alone (T1) showed statistically significant reduction in cerebellar catalase levels compared to the control group ($p < 0.05$). The combined treatment group (T3) demonstrated statistically significant increase in catalase levels compared to the lead-only group (T1, $p < 0.05$).

C: The malondialdehyde (MDA) levels across experimental groups revealed significant lipid peroxidation changes indicative of oxidative damage. Rats exposed to lead acetate alone (T1) demonstrated statistically significant elevation in cerebellar MDA levels compared to the control group ($p < 0.05$). The combined treatment group (T3) showed significantly decreased MDA levels compared to the lead-only group (T1, $p < 0.05$).

3.3. Histomorphometry of purkinje cell population

3.4. Photomicrograph of the Cerebellum

C: Normal cerebellar architecture with intact Purkinje cells and well-organized ML, PL, and GL.

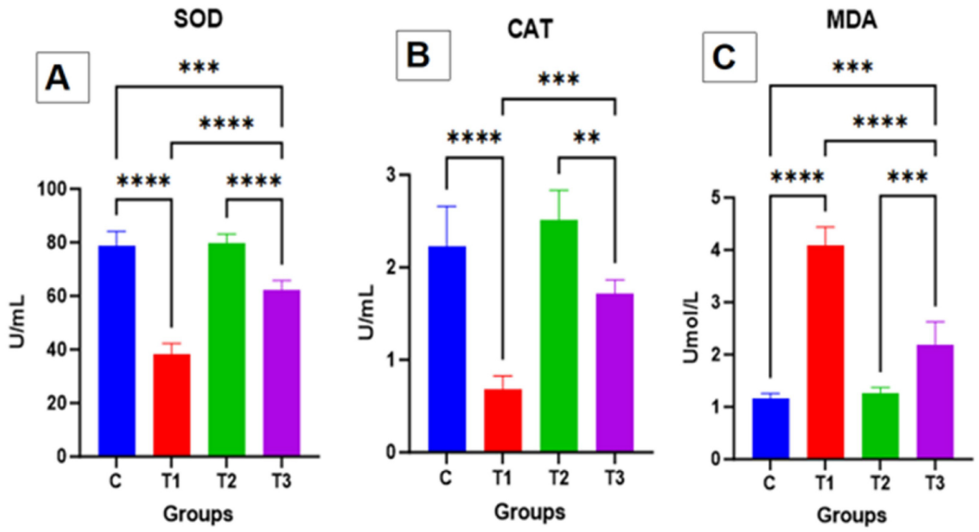

Fig. 2. Oxidative stress parameters across the experimental groups. Control (distilled water), T1 (0.075 mg/kg lead acetate), T2 (100 mg/kg B. pinnatum extract), and T3 (combined lead acetate + B. pinnatum). All data were expressed as Mean ± SEM and analyzed using one-way ANOVA with Tukey's Multiple Comparison Test (GraphPad Prism 10.1, $p < 0.05$).

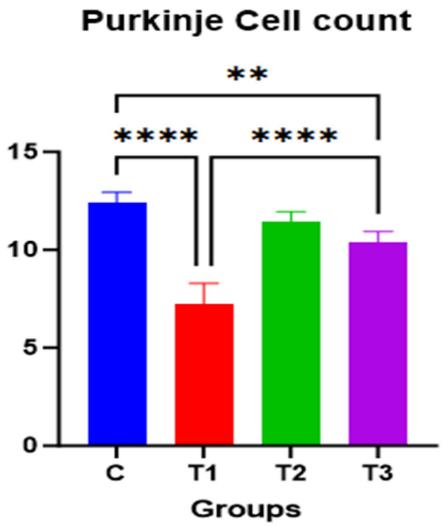

Fig. 3. The Purkinje neuron population analysis revealed significant structural damage in the cerebellar cortex across experimental groups. Rats exposed to lead acetate alone (T1, 0.075 mg/kg) demonstrated statistically significant reduction in Purkinje neuron count compared to the control group ($p < 0.05$). The combined treatment group (T3) showed significantly increased Purkinje neuron population compared to the lead-only group (T1, $p < 0.05$), demonstrating that B. pinnatum extract effectively preserved cerebellar neuronal integrity. All data were expressed as Mean ± SEM and analyzed using one-way ANOVA with Tukey's Multiple Comparison Test (GraphPad Prism 10.1, $p < 0.05$).

T1: Lead-exposed cerebellum showing distorted and reduced Purkinje cells with disrupted layer organization.

T2: *B. pinnatum* exposed cerebellum section showing the distinct cortical layers of the cerebellum with normal cells of purkinje, Golgi cells and Stellate cells

T3: Combined treatment with Lead acetate and *Bryophyllum pinnatum* showing the distinct cortical layers of the cerebellum with normal cells of purkinje, Golgi cells and Stellate cells.

4. Discussion

The present study demonstrated significant body weight alterations following lead exposure and B. pinnatum intervention. Animals in the control group maintained normal weight gain patterns throughout the treatment period, while lead acetate-exposed rats showed marked weight reduction (Fig. 1A), indicating the systemic toxic effects of lead exposure. Group T3 exhibited weight recovery of treatment, demonstrating the ameliorative effect of B. pinnatum on lead-induced weight loss. This protective effect against lead-induced body weight reduction aligns with previous studies showing that antioxidant interventions can preserve normal physiological function during heavy metal exposure [21].

Lead acetate exposure resulted in significant brain weight reduction compared to control animals (Fig. 1B), indicating tissue-specific damage and potential atrophy in this critical brain region. The intervention with B. pinnatum extract effectively prevented brain weight loss, with the combined treatment group showing significantly preserved brain weight compared to the lead-only group. This neuroprotective effect on organ weight preservation suggests that B. pinnatum helps maintain normal brain architecture and cellular integrity against lead-induced tissue damage [13].

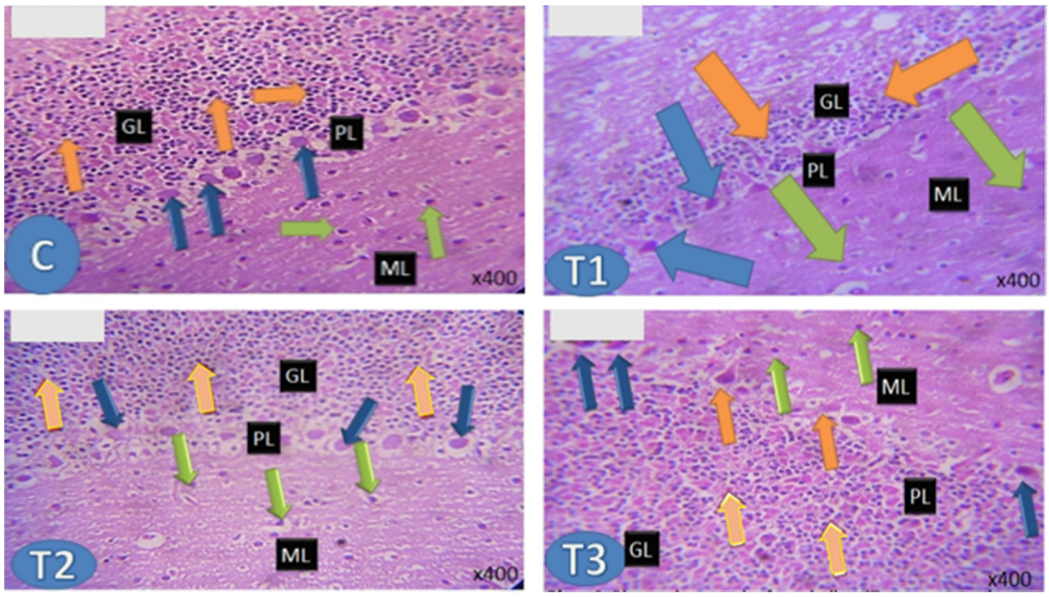

Fig. 4. Hematoxylin and eosin–stained sections of the cerebellar cortex (×400) across experimental groups. C = Control; T1 = Lead acetate (0.075 mg/kg); T2 = Bryophyllum pinnatum extract (100 mg/kg); T3 = Lead acetate + B. pinnatum. Each panel shows the three cerebellar cortical layers; molecular layer (ML), Purkinje layer (PL), and granular layer (GL). Blue arrows indicate Purkinje cells, yellow arrows indicate Golgi cells, and green arrows indicate stellate cells.

The neurotoxic effects of high-level lead exposure have been proven in both animals and humans, where damage involves peripheral and central nervous systems [8]. Many factors account for the neurotoxic effects of lead, including integrity of the blood-brain barrier, lead-binding proteins, cellular scavengers (e.g., glutathione), and interactions with other micronutrients [22]. In the present study, lead acetate exposure significantly depleted both superoxide dismutase (SOD) and catalase activities in cerebellar tissue (Fig. 2), confirming oxidative stress as a primary mechanism of lead neurotoxicity in accordance with the study by Neha et al. [23].

Changes in antioxidant enzymes observed in this study can be explained by the generation of reactive oxygen species and depletion of antioxidant reserves. Lead exposure inactivates glutathione molecules (important endogenous antioxidants) by binding to their sulfhydryl groups directly [24]. The intervention with B. pinnatum extract successfully restored both SOD and catalase activities in lead-exposed animals, demonstrating the plant's comprehensive antioxidant protective mechanism. This restoration of antioxidant enzyme function supports the plant's ability to counteract lead-induced oxidative damage and preserve cellular defense systems.

Malondialdehyde levels revealed significant oxidative damage following lead exposure, with elevated MDA indicating increased lipid peroxidation and cellular membrane damage (Fig. 2). The combined treatment with B. pinnatum effectively reduced MDA levels compared to lead-only exposure, demonstrating successful prevention of lead-induced lipid peroxidation. Zhu et al. [25] and Mattson et al. [26] reported that mitochondrial dysfunction and distortion have been recorded in many neurodegenerative diseases associated with oxidative damage. The reduction in MDA levels, combined with restoration of antioxidant enzymes, confirms the protective mechanism of B. pinnatum against lead-induced oxidative stress.

The antioxidant activity of B. pinnatum is attributed to its rich content of flavonoids, phenolic acids, and bufadienolides, which exert free radical-scavenging and metal-chelating actions [15]. These phytochemicals enhance endogenous antioxidant defenses by upregulating SOD and catalase activities and preserving glutathione pools, thereby counteracting Pb-induced ROS generation [27]. Flavonoids in B. pinnatum can also inhibit lipid peroxidation by stabilizing cell membranes and interrupting chain-reaction oxidation [28]. Collectively, these mechanisms explain the significant reduction in MDA levels and restoration of antioxidant enzymes observed in the T3 group.

In the present study, lead-induced damage and disorganization in Purkinje cells were evident (Fig. 3). By light microscopy, they appeared shrunken with distorted shapes, and their nuclei appeared irregular (Fig. 4). Ultrastructural examination proved Purkinje cell damage in the form of irregular euchromatic nuclei, rarified cytoplasm, small dense mitochondria with destroyed or dilated cristae, and cells

surrounded by empty spaces. Alterations in granular cells included increased condensation of nuclear chromatin, nuclei surrounded by shells of vacuolated cytoplasm, and mitochondria with destroyed cristae. These findings are in agreement with Engin, [29], who reported that when rats received lead acetate in their drinking water for 60 days, degeneration in neuronal cells was evident. The histological findings were also similar to those reported by Fakunle et al. [30].

Conversely, animals treated with both lead and B. pinnatum revealed marked improvement in the altered histological architecture of the cerebellar cortex. With light microscopy, the Purkinje, molecular, and granular cell layers appeared almost normal, while electron microscopy showed Purkinje cells with euchromatic nuclei, normal prominent nucleoli, strands of rough endoplasmic reticulum in the cytoplasm, and some dilated Golgi cisternae around the nucleus (Fig. 4). The significant preservation of Purkinje neuron population in the combined treatment group demonstrates that B. pinnatum provides substantial structural neuroprotection at the cellular level.

The comprehensive results demonstrate that B. pinnatum's neuroprotective mechanism operates through multiple pathways: restoration of antioxidant enzyme activities (SOD and catalase), reduction of lipid peroxidation (decreased MDA), preservation of neuronal architecture, and maintenance of cerebellar tissue integrity. This multi-target approach effectively counteracts lead's toxic effects, which primarily involve oxidative stress generation, antioxidant depletion, and subsequent neuronal damage.

5. Conclusion

Aqueous Bryophyllum pinnatum extract significantly counteracted lead-induced oxidative stress, restored endogenous antioxidant enzymes, reduced lipid peroxidation, preserved cerebellar weight, and maintained Purkinje neuron population and morphology. These findings indicate that B. pinnatum provides multi-pathway neuroprotection against lead-induced cerebellar toxicity and may represent a promising natural adjunct in mitigating heavy-metal–associated neurodegenerative risks.

Acknowledgment

None.

Conflict of interest

The authors declared no conflict of interest.

Ethical Approval

This study received approval from Ethical Review Committee (UERC), Olabisi Onabanjo University, Ago Iwoye (OOU/SCIENG/EC/241282) and conducted in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

Data availability

The authors confirm that the data supporting the findings of this study are available within the article.

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This research received no external funding.

Author contribution

Conceptualization and Methodology: Bamgbose O.A, Akanji D.O; Supervision: Fakunle P.B; Formal analysis, Investigation, Data curation: Taiwo-Ola D.O, Akanbi B.A, Odubela K.O; Writing Original draft: Bamgbose O.A. Akanbi B.A; Writing, Reviewing and Editing: All author's read and approved the final writing.

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