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Lead Acetate-induced Neurotoxicity in Male Wistar Rats: Ameliorative Potentials of Flavonoid-Rich Extract of *Tephrosia bracteolata* Leaves

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Abstract

Lead (Pb) is one of the most common environmental toxicants, exposure to which can cause significant neurotoxicity and an associated decline in brain function. The aim of the study was to determine the ameliorative potentials of flavonoid-rich leaf extract of *T. bracteolata* on lead-acetate-induced neurotoxicity in male Wistar rats. Twenty male Wistar rats were distributed into five groups with four animals apiece. Group 1 rats served as the normal control and were administered distilled water at 5ml/kg b.w. Group 2 rats served as negative control and were administered 50 mg/kg lead-acetate. Groups 3 and 4 were co-administered 50 mg/kg lead-acetate and various doses of the extracts. Group 5 was administered 50 mg/kg ascorbic acid in addition to 50 mg/kg lead-acetate. The study lasted for 28 days. The neuroprotective effect *T. bracteolata* was assessed by measuring the concentration malondialdehyde, enzymatic antioxidant activities of superoxide dismutase, catalase and also the histopathological examination of the brain was carried out. Results showed that the increase in malondialdehyde, the decrease in the activity of the antioxidant enzymes, and the altered histology of the brain induced by lead acetate were mitigated in groups of rats administered various doses of the extract. The extract therefore, could be considered as having protective effect on lead acetate-induced neurotoxicity in Wistar albino rats.

Keywords

Flavonoid, *Tephrosia bracteolata*, lead acetate, neurotoxicity

Introduction

Lead poisoning, a condition resulting from the accumulation of lead in the body, has been recognized as a significant global public health concern for centuries (ATSDR, 2007). Lead is a pervasive environmental toxin that can enter the human body through various routes, including ingestion, inhalation, and dermal exposure. Historically, lead was widely used in various industries, such as plumbing, paints, and gasoline, leading to extensive environmental contamination and human exposure. While substantial efforts have been made to reduce lead exposure over the years, it remains a persistent issue, particularly in areas with aging infrastructure and inadequate regulatory measures.

One of the most alarming aspects of lead exposure is its adverse impact on the nervous system. Lead-induced neurotoxicity is a well-documented consequence of chronic exposure to this heavy metal (Flora *et al.,* 2012). It manifests as a range of neurological and cognitive impairments, especially in children, who are particularly vulnerable due to their developing nervous systems. Cognitive deficits, behavioural abnormalities, decreased IQ, and attention deficits are among the neurological sequel associated with lead exposure. Moreover, the effects of lead-induced neurotoxicity are not confined to childhood but can persist into adulthood, resulting in lifelong impairments (Bellinger, 2008).

The neurotoxic effects of lead are mediated through various mechanisms. One of the primary mechanisms involves lead's interference with neurotransmission by disrupting the release and uptake of neurotransmitters such as dopamine and glutamate (Flora *et al.,* 2012). Additionally, lead exposure leads to the generation of reactive oxygen species (ROS) and oxidative stress, which can damage neuronal structures and impair cellular functions (Flora *et al.,* 2012). These multifaceted mechanisms underscore the complexity of lead-induced neurotoxicity.

Understanding and mitigating the neurotoxic effects of lead is of paramount importance for several reasons. First and foremost, the health and well-being of individuals, particularly children, are at stake (Patrick, 2006). Lead exposure remains a pressing issue in many parts of the world, and its detrimental effects on cognitive development and overall neurological health cannot be underestimated. By comprehensively studying lead-induced neurotoxicity, we can better protect vulnerable populations and develop strategies to limit exposure.

Secondly, lead poisoning poses a significant economic burden on societies. The societal costs associated with the healthcare and educational interventions required for lead-exposed individuals are substantial (Flora *et al.,* 2012). Furthermore, productivity losses due to impaired cognitive function and behavioural issues in affected individuals can have long-lasting economic consequences.

Thirdly, lead pollution persists in the environment, even in countries that have banned or restricted its use. Therefore, understanding the neurotoxic effects of lead is essential for ongoing environmental remediation efforts and the development of effective policies and regulations to prevent further contamination (Silbergeld & Finkelstein, 2001).

In recent years, there has been growing interest in exploring natural remedies for mitigating the effects of lead-induced neurotoxicity. Among the potential candidates, *Tephrosia bracteolata*, a plant indigenous to various regions, has gained attention due to its rich flavonoid content (Mani *et al.,* 2011). Flavonoids are bioactive compounds known for their antioxidant properties and their ability to counteract oxidative stress, a key mechanism underlying lead-induced neurotoxicity (Rahman & Khan, 2009). *Tephrosia bracteolata* has a history of traditional medicinal use and has been investigated for its various pharmacological activities, including its potential neuroprotective effects.

Flavonoids present in *Tephrosia bracteolata* are believed to scavenge free radicals, reduce oxidative damage, and modulate inflammatory responses, all of which are implicated in the neurotoxic effects of lead (Mani *et al.*, 2011). The anti-inflammatory and antioxidant properties of flavonoids have been the subject of numerous studies in the context of neuroprotection. These compounds have shown promise in mitigating neuronal damage and preserving cognitive function in various experimental models of neurotoxicity (Mani *et al.*, 2011).

This research endeavours to explore the neuroprotective potential of *Tephrosia bracteolata*, particularly its flavonoid-rich extract, in ameliorating lead acetate-induced neurotoxicity in male Wistar rats.

Materials and Methods

Materials

All chemicals used were of analytical grade.

Methods

Plant material

The leaves of *T. bracteolata* were collected from a natural habitat and authenticated by an ethnobotanist.

Extraction

Fresh leaves of *T. bracteolata* were rinsed with distilled water to remove all debris, shade-dried for seven days and subsequently pulverized using an electric blender. A known quantity (1.5 kg) of the powder was macerated in 7.5 L of absolute ethanol. After 72 h, the suspension was filtered using a mesh, and then Whatman No 1 filter paper. This procedure was repeated twice and all the filtrates were concentrated in a rotary evaporator set at 45 °C to obtain the crude ethanol extract of *T. Bracteolate* leaves. The flavonoid-rich extract of *T. Bracteolate* leaves was prepared according to the method previously described Chu *et al.*, (2002). Exactly 9 g of the crude extract was dissolved in 60 ml of 10% H_2SO_4 and was hydrolysed by heating on a water bath for 30 min at 100 °C. Thereafter, the mixture was placed on ice for 15 min to allow the precipitation of flavonoids and aglycones. The precipitate (flavonoids/aglycones mixture) was dissolved in 50 ml of 95% ethanol (warmed to 50 °C) in 100 ml volumetric flask and thereafter made up to the mark with the 95% ethanol. This was centrifuged, filtered and the filtrate collected was concentrated using a rotary evaporator to obtain the flavonoid-rich extract of *T. Bracteolate* leaves (FRETB) that was stored in an airtight lightproof container at 4 °C until used.

Experimental animals

Twenty male Wistar rats (200-250 grams) were accommodated in well-ventilated with constant 12-h light 12-h dark cycle. The animals had free access to standard pelletized rat feed and clean water *ad libitum* and were allowed one week of acclimatization.

Experimental design

The animals were weighed and randomly shared into five groups of four animals each. Group 1 served as normal control and were administered5 ml/kg of distilled water. Reproductive toxicity was induced intraperitoneal by administration of Lead acetate-PbA (50 mg/kg) in groups 2 to 5 and treated as follows. Group 2 (PbA only), Group 3 (PbA+5 mg/kg FRETB), Group 4 (PbA+10 mg/kg FRETB) and Group 5 (PbA+50 mg/kg Ascorbic acid) (standard control). PbA was administered once per week while FRETB and Ascorbic acid were administered daily throughout the duration (28 days) of the study.

Sacrifice and Sample Collection

The rats were sacrificed on the 29th day by intraperitoneal injection of 120 mg/kg of sodium thiopentone anesthesia. Brain tissues were collected from each animal and preserved for analyses.

Estimation of Oxidative Stress Biomarkers

Malondialdehyde (MDA) concentration was measured according to the method of Draper and Hadley, (1990). Catalase (CAT) activity was assayed following the method of Aebi (1983) while superoxide dismutase (SOD) activity was assayed via the method of Xin *et al.*(1991).

Histopathological examination of the brain

The effect of treatment on the histology of thebrain of the rats was microscopically evaluated following Hematoxylin and Eosin stain. The organs were fixed in 10% formalin and histopathological examination was carried out according to the method of Drury *et al.* (1967).

Statistical Analysis

All data were expressed as mean ± standard deviation, and statistical differences between means were determined by one- way ANOVA followed by Duncan's post–hoc test for multiple comparison tests using SPSS version 20. Values were considered significant at P≤ 0.05.

Results

Effect of flavonoid-rich extract of *Tephrosia bracteolate* on malondialdehyde concentration in brain tissue of lead acetate- exposed Wistar rats

The result shows that the level of malondialdehyde in the brain tissue was significantly increased in the lead acetate-induced group (group 2) compared with the control rats (P<0.05) but significantly (P<0.05)reduced in the FRETB + lead acetate-induced groups compared to the lead acetate- exposed group (group 2).

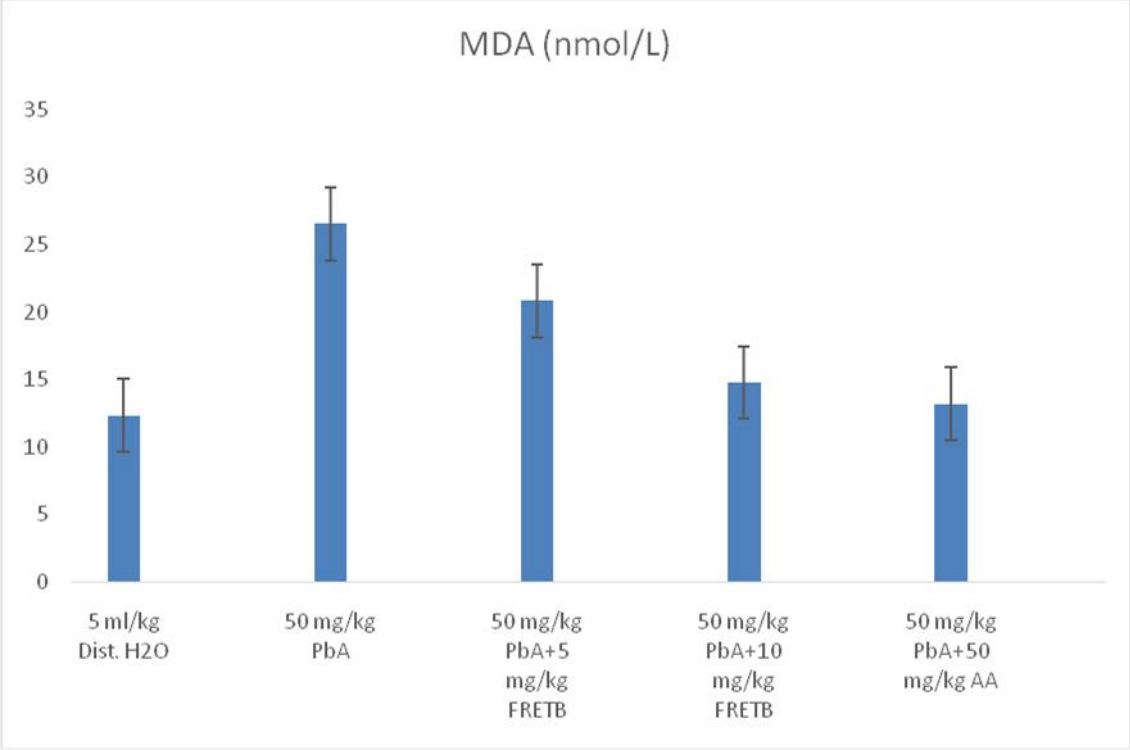

Figure 1.Effect of Flavonoid-rich extract of *Tephrosia bracteolata* leaves (FRETB) on brain tissue malondialdehyde concentrationin lead acetate-induced neurotoxicity in male Wistar. PbA= Lead acetate, FRETB = Flavonoid-rich extract of *Tephrosia bracteolata* leaves, AA= Ascorbic acid

Effect of flavonoid-rich extract of *Tephrosia bracteolata* on superoxide dismutase activity in brain tissue of lead acetate- exposed Wistar rats

The result shows that the superoxide dismutase activity in the brain tissue was significantly increased in the lead acetate-induced group (group 2) compared with the control group ($P<0.05$) but significantly ($P<0.05$)reduced in the FRETB + lead acetate-induced groups compared to the lead acetate-induced (group 2).

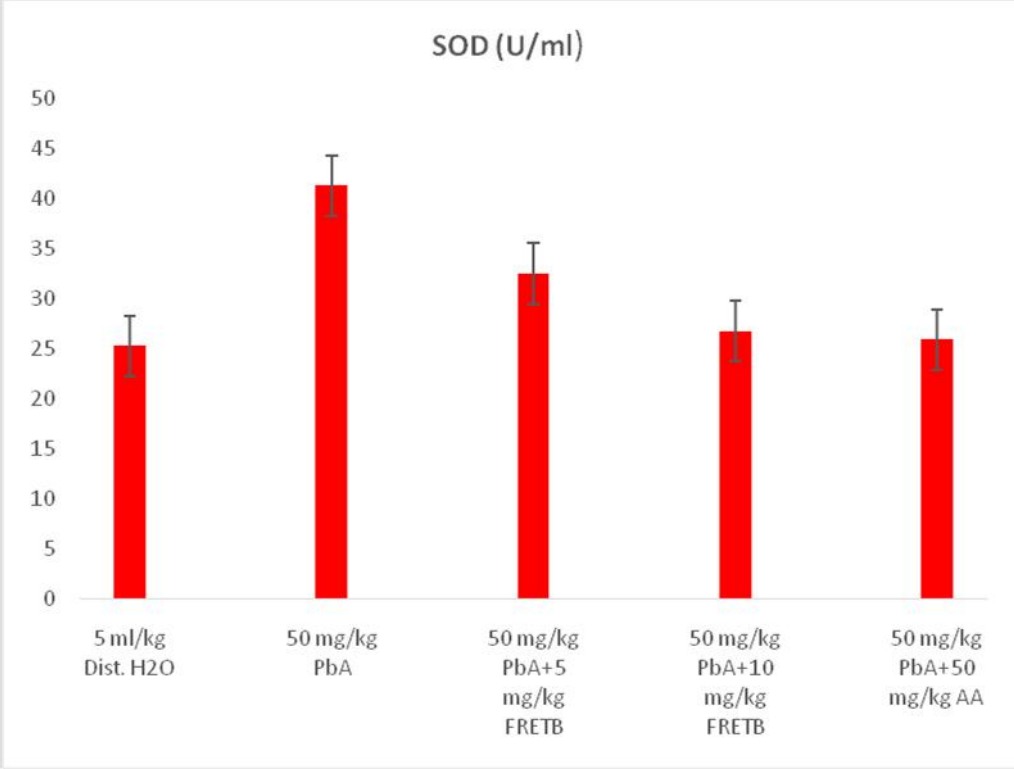

Figure 2.Effect of Flavonoid-rich extract of *Tephrosia bracteolata* leaves (FRETB) on brain tissue superoxide dismutase (SOD) in lead acetate-induced neurotoxicity in male Wistar. PbA= Lead acetate, FRETB = Flavonoid-rich extract of *Tephrosia bracteolata* leaves, AA= Ascorbic acid

Effect of flavonoid-rich extract of *Tephrosia bracteolata* on catalase activity in brain tissue of lead acetate- exposed Wistar rats

The result shows that the catalase activity in the brain tissue was significantly increased in the lead acetate-induced group (group 2) compared with the control group but significantly($P<0.05$) reduced in the FRETB + lead acetate-induced groups compared to the lead acetate-induced (group 2).

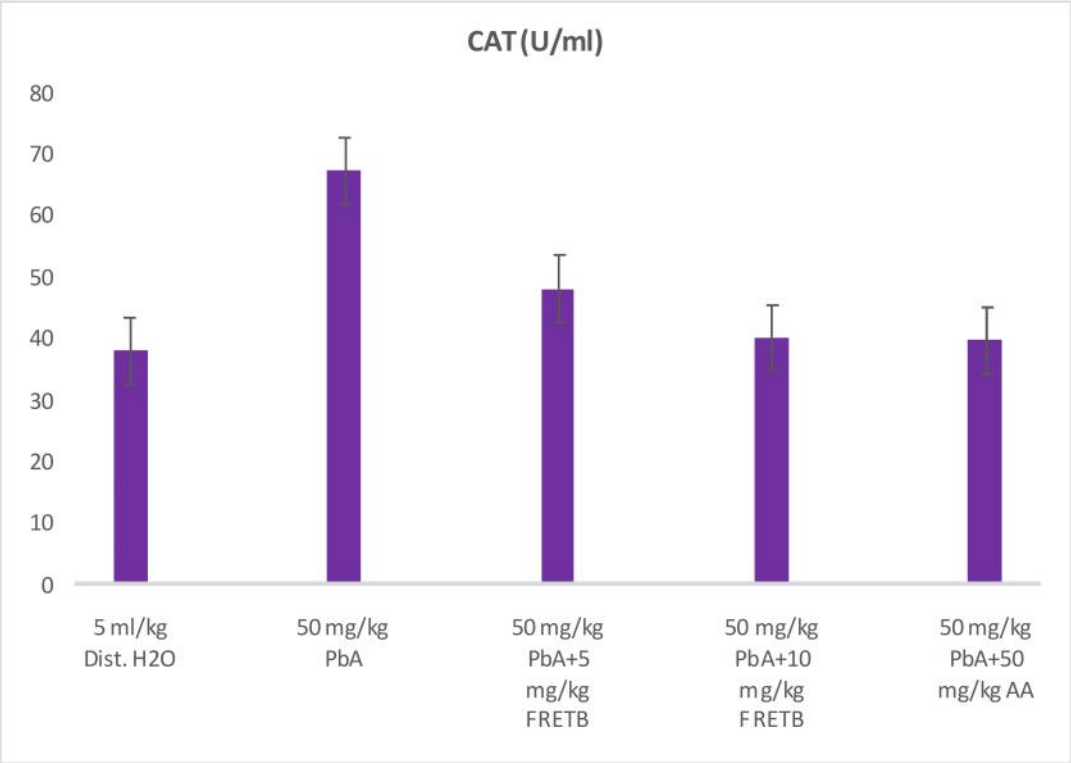

Figure 3. Effect of Flavonoid-rich extract of *Tephrosia bracteolata* leaves (FRETB) on brain tissue catalase (CAT) activity in lead acetate-induced neurotoxicity in male Wistar. PbA= Lead acetate, FRETB = Flavonoid-rich extract of *Tephrosia bracteolata* leaves, AA= Ascorbic acid

Effect of Flavonoid-rich extract of *Tephrosia bracteolata* leaves (FRETB) on histology of the brainin lead acetate-induced renal toxicity in male Wistar Rats

No abnormality was seen in the normal control group (Plate1) which was treated with distilled water (5ml/kg), whereas in group (Plate 2) treated with PbA only, there was neuronal degeneration observed. Groups 3 and 4 (Plates 3&4) treated with FRETB at varied doses and group (Plate 5) treated with ascorbic acid, showed neuronal regeneration in the brain histology.

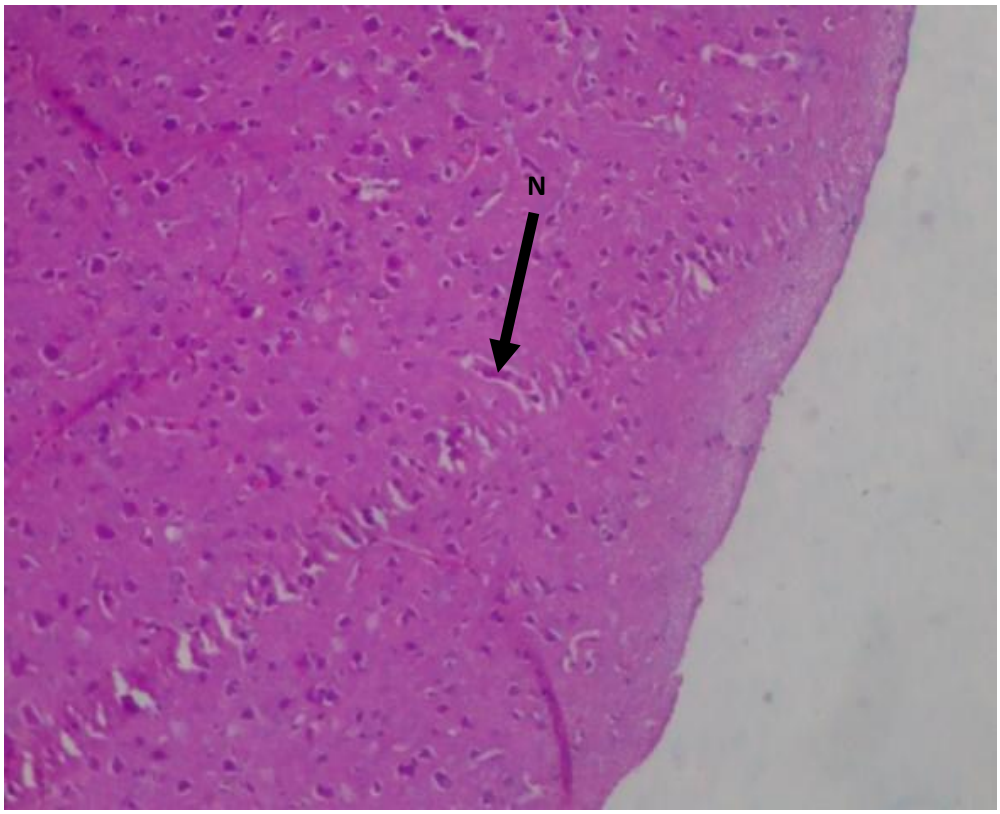

Plate 1. Histologic section of brain tissue of distilled water (5 ml/kg)- treated rat (normal control) showing neuronal cells on a background of neuropil. No abnormalities seen. (HE x 250). N=Neurone

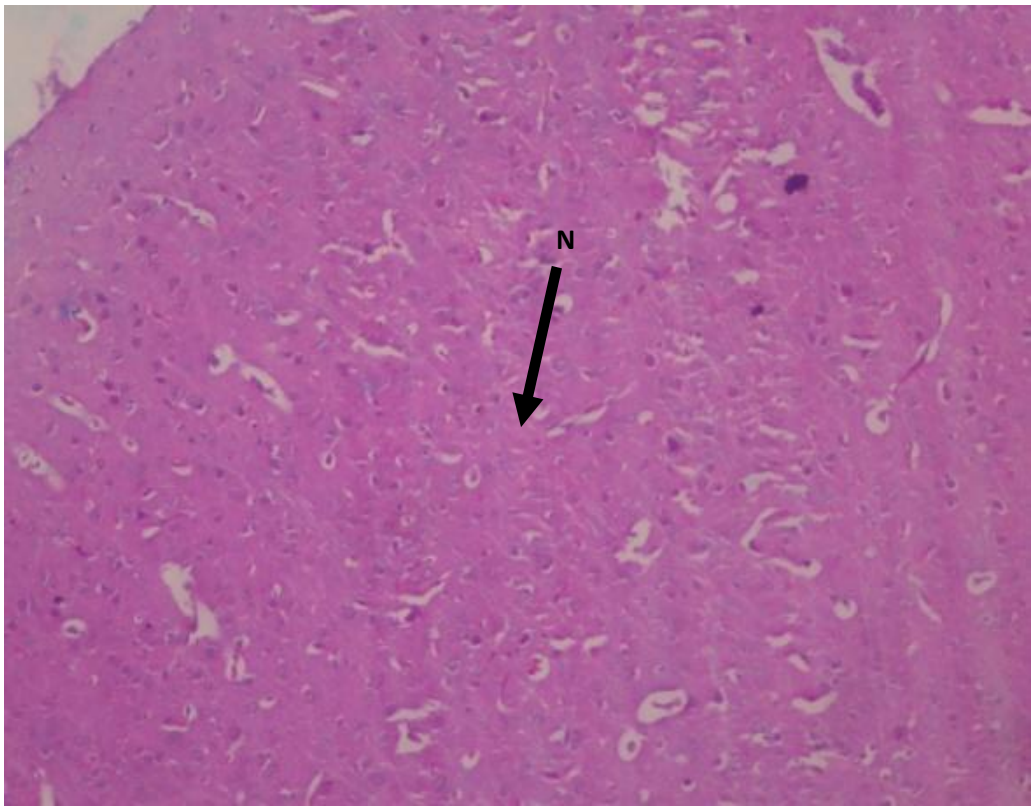

Plate 2. Histologic section of brain tissue of PbA (50 mg/kg)- treated rat showing degenerated neuronal cells on a background of neuropil. (HE x 250). N=Neurone, PbA= Lead acetate

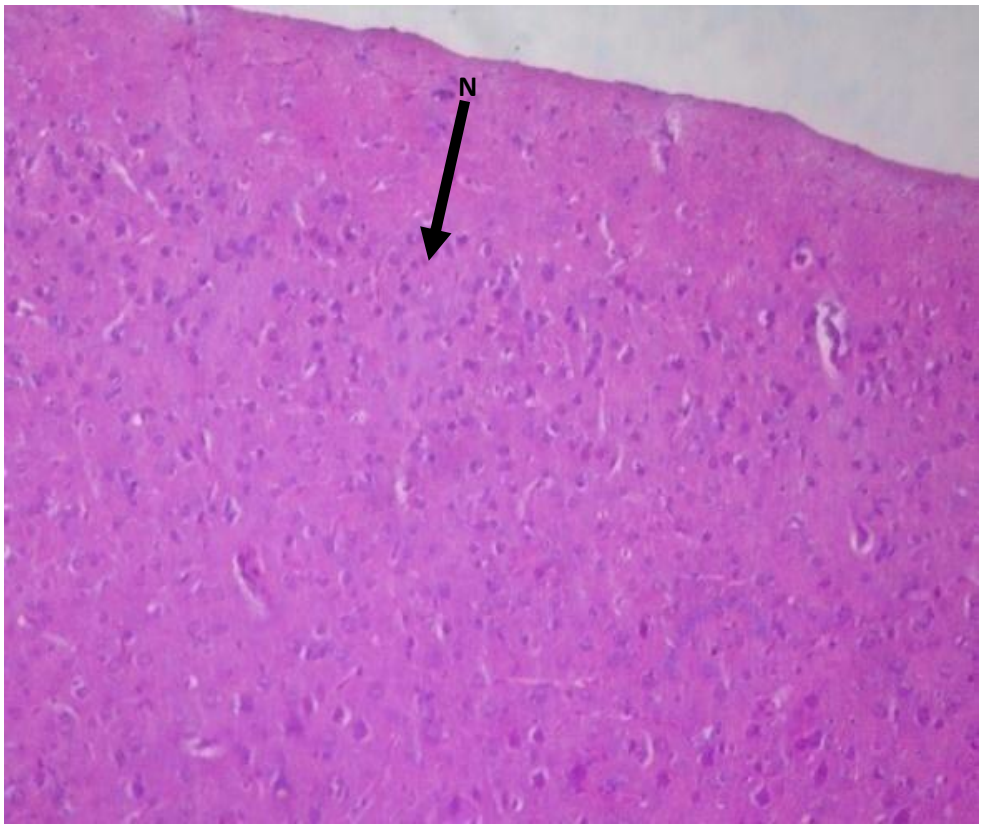

Plate 3. Histologic section of brain tissue of PbA (50 mg/kg) + FRETB (5 mg/kg)- treated rat showing neuronal cells on a background of neuropil. No abnormalities seen. (HE x 250). N=Neurone,PbA= Lead acetate, FRETB=Flavonoid-rich extract of *Tephrosia bracteolata* leaves

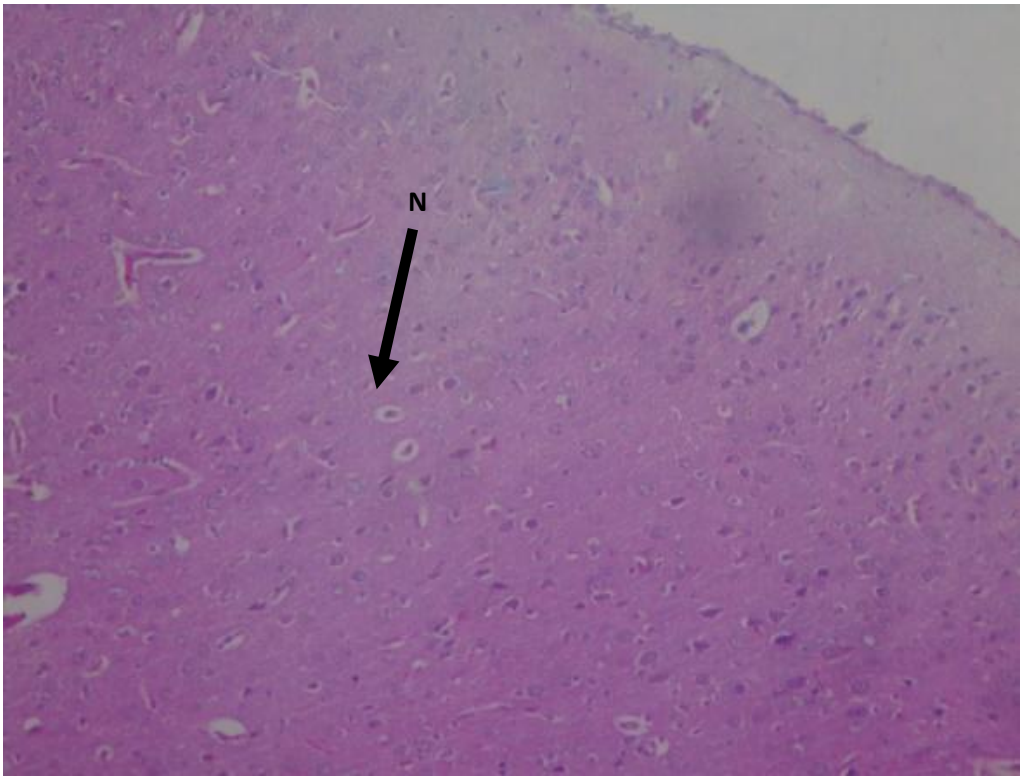

Plate 4. Histologic section of brain tissue of PbA (50 mg/kg) + FRETB (10 mg/kg)- treated rat showing neuronal cells on a background of neuropil. No abnormalities seen. (HE x 250). N=Neurone,PbA= Lead acetate, FRETB=Flavonoid-rich extract of *Tephrosia bracteolata* leaves

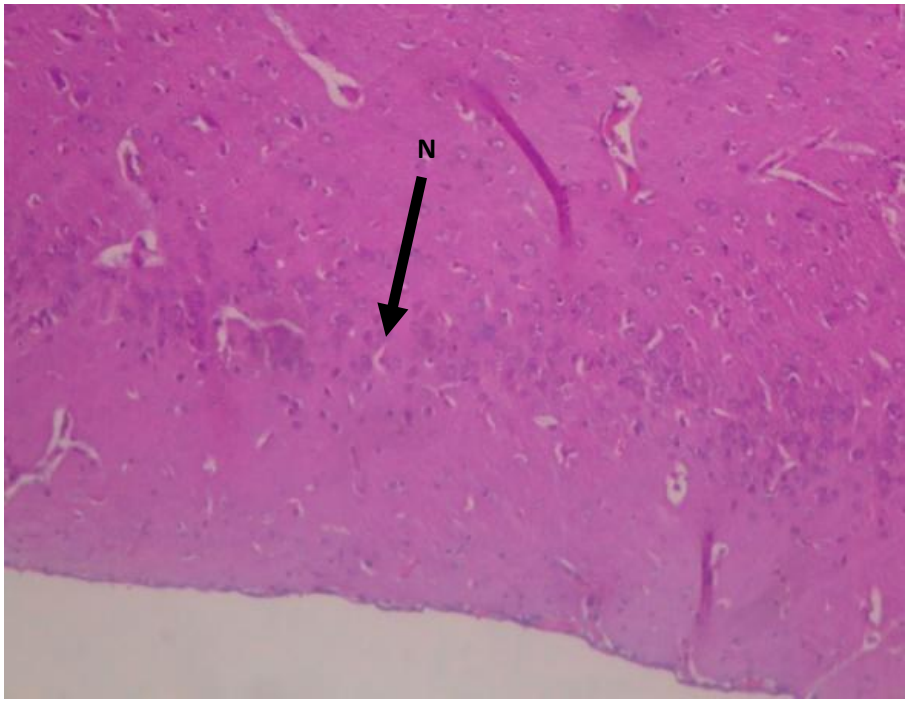

Plate 5. Histologic section of brain tissue of PbA (50 mg/kg) + AA (5 mg/kg)- treated rat (standard control) showing neuronal cells on a background of neuropil. No abnormalities seen. (HE x 250). N=Neurone,PbA= Lead acetate, AA= Ascorbic acid

Discussion

Lead exerts some of its neurotoxic effects by promoting oxidative damage and peroxidation of the lipids in the cell membranes, thus compromising cellular functions by impairing the physicochemical properties, fluidity, and integrity of cell membranes, thereby increasing the cell vulnerability to lipid peroxidation and cell death (Al-Quraishy *et al.,* 2016). Both animal and human studies have suggested that exposure to PbA is associated with increased oxidative stress and a heightened incidence of neurotoxicity. 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. Antioxidants exert their effects through mechanism that initiate peroxidation, chelating metals, breaking free radical chain reactions and reducing concentration of O_2. As strong free radical scavengers, they can act as very effective neuroprotective agents against lead-induced oxidative stress.

The presence of these phytochemicals' tannins and flavonoids in the leaf and fruit extracts of *T. bracteolata* have accounted for the antioxidant activity (Arguoru *et al*., 2016). *T. bracteolata* may be stimulating Malondialdehyde synthesis, thereby maintaining intracellular Malondialdehyde levels and scavenging reactive oxygen species (Ercal *et al.,* 1996). In addition, it has a lot of micronutrients and can also act as metal chelators. Nutritional factors are often mentioned as important modifiers of lead metabolism and lead toxicity (Ahamed *et al*., 2006). This intrinsic quality has attracted widespread interest in clinical nutrition and medicinal research.

This study confirmed that intoxication of rats with Lead acetate disrupts the redox balance, as indicated by a reduction in SOD and CAT activities. These findings are in agreement with previous reports that have demonstrated that Pb disrupts redox homeostasis (Akande *et al.*, 2016; Dkhil *et al.*, 2016; Hasanein *et al.,* 2016). Furthermore, MDA, CAT and SOD are potential targets for Pb neurotoxicity because these biomarkers depend on other necessary co-factors

(cations) for their proper molecular structure and function (Dua *et al.,* 2016). Interestingly, however, *T. bracteolata* partly ameliorated the disruptive effects of Lead acetate on the antioxidant enzyme system. The enhancement of antioxidant enzyme activities could be explained by either a compensatory mechanism of *T. bracteolata* against oxidative stress, or antioxidant gene overexpression, or both (Hashish *et al.,* 2015).

The data in the results shows that Pb^{2+} concentration in the brain tissue was significantly elevated in the Lead acetate-induced group (Group II) compared with the control rats ($P < 0.05$). However, significantly reduced Pb2+ concentration in the brain was determined in the FRETB+ Lead induced groups compared to the Lead acetate-induced group (Group II) ($P < 0.05$).

The results of this study provide compelling evidence for the ameliorative effect of the flavonoid-rich extract of *T. bracteolata* on lead acetate-induced neurotoxicity, particularly in mitigating oxidative stress. Oxidative stress is a pivotal mechanism underlying the neurotoxic effects of lead, and the alterations in oxidative stress biomarkers observed in this study shed light on the potential neuroprotective mechanisms of the extract.

Malondialdehyde (MDA) is a widely recognized biomarker of lipid peroxidation, a process in which free radicals attack and damage the lipid components of cell membranes. Lead-induced neurotoxicity is often associated with increased oxidative stress, leading to elevated MDA levels due to heightened lipid peroxidation (Flora *et al.*, 2012). In our study, the observed decrease in MDA levels among rats treated with the flavonoid-rich extract of *T. bracteolata* is a remarkable finding. It suggests that the extract effectively mitigates lipid peroxidation, indicating its potential to protect neuronal membranes from oxidative damage. This reduction in MDA levels signifies the extract's role in alleviating one of the central mechanisms through which lead impairs neuronal function.

The decrease in MDA levels could be attributed to the extract's antioxidant properties. Flavonoids, such as those found in *T. bracteolata*, are renowned for their ability to scavenge free radicals, including those involved in lipid peroxidation (Neha *et al.,* 2019). By neutralizing free radicals and inhibiting their attack on cell membranes, the extract helps maintain the structural integrity of neurons and prevents the disruption of membrane functions. This protective effect on lipid structures underscores the extract's potential as a neuroprotective agent against lead-induced oxidative damage.

Additionally, the reduction in MDA levels may have broader implications for overall brain health. Elevated MDA levels are associated with a range of neurodegenerative diseases, including Alzheimer's and Parkinson's diseases, where oxidative stress plays a critical role (Butterfield & Halliwell, 2019). The extract's ability to lower MDA levels suggests its potential therapeutic relevance beyond lead-induced neurotoxicity, making it a promising candidate for interventions targeting various neurodegenerative conditions.

Catalase (CAT) is a pivotal antioxidant enzyme responsible for breaking down hydrogen. The remarkable increase in Catalase (CAT) activity observed in rats treated with the flavonoid-rich extract of *Tephrosia bracteolata* underscores the extract's potent antioxidative capacity. CAT plays a pivotal role in dismantling hydrogen peroxide (H_2O_2), a highly reactive species that can cause oxidative damage when left unchecked (Neha *et al.,* 2019). Decreased CAT activity is often a hallmark of conditions characterized by oxidative stress, as it reflects an impaired ability to neutralize H_2O_2.The elevation in CAT activity observed in this study aligns with the extract's broader antioxidative potential. Flavonoids, such as those found in *Tephrosia bracteolata*, are adept at scavenging a spectrum of reactive oxygen species, including H_2O_2 (Spagnuolo *et al.,* 2018). The enhanced CAT activity reflects the extract's role in fortifying the cellular defenses against oxidative stress, efficiently converting H_2O_2 into harmless water and oxygen. This detoxification of H_2O_2 contributes significantly to the overall

reduction in oxidative stress observed in treated rats.Furthermore, the augmentation of CAT activity has implications beyond lead-induced neurotoxicity. Various neurodegenerative diseases, such as Alzheimer's and Parkinson's, are characterized by heightened oxidative stress, which overwhelms the antioxidative defenses (Neha *et al.,* 2019). The extract's ability to enhance CAT activity hints at its potential as a therapeutic agent for managing oxidative stress in these debilitating conditions. By bolstering CAT-mediated detoxification, the extract holds promise in mitigating oxidative damage to neurons, thereby preserving cognitive function and neuronal integrity.

Superoxide Dismutase (SOD) is an essential antioxidant enzyme responsible for the conversion of superoxide radicals (O_2^-) into less harmful molecules, such as hydrogen peroxide (H_2O_2) and oxygen. In the context of oxidative stress, a decrease in SOD activity is frequently observed due to the overwhelming presence of superoxide radicals (Neha *et al.,* 2019). The observed elevation in SOD activity in rats treated with the flavonoid-rich extract of *T. bracteolata* highlights its potential in reducing oxidative stress.The heightened SOD activity is particularly noteworthy as superoxide radicals can initiate a cascade of oxidative reactions within cells, including lipid peroxidation and protein oxidation (Flora *et al.,* 2012). By efficiently neutralizing superoxide radicals, the extract effectively halts the propagation of oxidative damage. This prevention of further damage is pivotal for preserving the functional integrity of neurons and maintaining normal cellular processes. Moreover, the enhancement of SOD activity aligns with the extract's broader antioxidative potential. Flavonoids, such as those found in *Tephrosia bracteolata*, are known for their ability to scavenge various reactive oxygen species and reduce overall oxidative stress (Spagnuolo *et al.,* 2018). The increase in SOD activity highlights the extract's role in fortifying the cellular defense mechanisms against oxidative stress. This elevation in SOD activity extends its potential to conditions characterized by heightened oxidative stress, making the extract a candidate for interventions in various neurodegenerative diseases and oxidative stress-related disorders.

The histological evaluation of brain sections from experimental animals provides valuable insights into the structural alterations and cellular changes induced by lead toxicity and how these are mitigated by the flavonoid-rich extract. The brain, being a vital organ, is highly susceptible to oxidative harm in response to lead acetate toxicity. Plates 1 through 5 present histological examinations of the brains of the experimental animals utilized in this study. Notably, the examination revealed that the brains of the untreated group exposed to lead exhibited degenerated neuronal cells set against a backdrop of disrupted neuropil. These observations strongly suggest that the toxic effects of lead acetate have a detrimental impact on the structural integrity of the brain in these animals.

The normal control group (Plate 1, distilled water-5ml/kg) showed intact neuronal cells with no degeneration whereas in toxic PbA only treated group, there was neuronal degeneration evidenced by cytoplasmic vacuolation. The concurrent treatment with the aqueous leaf extract of *Tephrosia bracteolata* dose dependently showed neuronal regeneration in brain histology as showed in Plate 3 (50mg/kg PbA + 5mg/kg FRETB) & Plate 4(50mg/kg PbA + 10mg/kg FRETB) with no abnormalities seen. However, it is noteworthy that in the groups treated with PbA (50 mg/kg) + FRETB (10 mg/kg) and ascorbic acid, a striking improvement in brain histology was observed when compared to the untreated groups, with no abnormalities detected. This absence of organ lesions in both the control and treated groups strongly suggests a protective effect of the flavonoid-rich extract of *Tephrosia bracteolata* leaves on vital organs. The mechanisms underlying this protection by FRETB likely revolve around its potent antioxidant and anti-inflammatory properties, which can effectively counteract the oxidative stress and inflammation induced by lead acetate toxicity. Antioxidants, as key players, play a pivotal role in inhibiting and scavenging free radicals.

As supported by the findings of Idakwoji *et al.*, (2021), the *T. bracteolata* extract contains a substantial amount of antioxidant phytochemicals such as phenols, tannins, and flavonoids. These compounds are known for their relatively high antioxidant activity, enabling them to effectively scavenge the free radicals generated by lead acetate, ultimately leading to the restoration of the deleterious effects. These observations align with the results obtained from the biochemical parameters assessed in this study, further reinforcing the notion that the flavonoid-rich extract from *Tephrosia bracteolata* leaves holds significant promise in protecting vital organs from the detrimental impact of lead acetate toxicity.

Conclusion

This study provides compelling evidence that the Flavonoid-rich extract of *Tephrosia bracteolata* leaves holds significant promise as a neuroprotective agent against lead acetate-induced neurotoxicity s. The extract's ability to ameliorate neuronal degeneration, reduce oxidative stress, and preserve brain histology highlights its multifaceted neuroprotective mechanisms. Lead acetate exposure was shown to induce neurotoxicity in the male Wistar rats, resulting in decreased antioxidant enzymes activity, Catalase (CAT),Superoxide Dismutase (SOD) and Malondialdehyde (MDA) and histological signs of brain's neuronal cells degeneration. These findings have important implications not only in the context of lead toxicity but also in the broader field of neurodegenerative diseases characterized by oxidative stress.

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