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Ameliorative Effects of Flavonoid-rich Extract of *Tephrosia bracteolata*Leaves on Lead acetate-induced Haematotoxicity, Immunotoxicity and Oxidative Stress in male Wistar Rats

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Abstract

This study evaluated the ameliorative effect of flavonoid-rich leaf extract of *T. bracteolata* on lead-acetate-induced haematotoxicity, immunotoxicity and oxidative stress in male Wistar albino rats. Twenty male Wistar rats were distributed into five groups with four animals apiece. Group 1 served as the control and was given only distilled water throughout the course of the study. Group 2 served as the lead-induced group and was 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. Standard procedures were used to evaluate the hematological indices, immunological and oxidative stress parameters. Exposure of rats to lead acetate revealed a significant decline in hematological parameters and elevated immunological and oxidative stress markers The results also showed that the extracts, especially at high doses, significantly ($p < 0.05$) ameliorated the harmful effects of lead acetate administration on the hematological indices, immunological and oxidative stress parameters. The extract could, therefore, be considered as having protective effect on hematological, immunological and oxidative stress parameters in Wistar albino rats.

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Keywords: Flavonoid-rich extract, *Tephrosia bracteolata* leaves,lead acetate,haematotoxicity, immunotoxicity, oxidative stress

Introduction

Lead exposure has been reported to be toxic to most organs, such as the liver, kidney, heart, brain, testes, and hematopoietic tissues (Assi *et al*., 2016). Exposure to lead can be through various routes- orally through ingesting food and water contaminated with lead, inhalation of polluted air, from dust, burning fuel, and fossil. Due to the colourless and odorless nature of lead, it persists for a longer time in the environment. It can only be detected at a very high concentration, a stage where it becomes harmful to the environment and living organisms including humans. Sources of lead poison include contaminated food and water, lead-containing paint and gasoline, industrial emission (Al-Megrin *et al*., 2019). The toxicity of lead has been reported to cause liver injury, osteoporosis, neurological disorders, and cardiovascular diseases (Alhusaini *et al*., 2019). The accepted mechanism of lead toxicity is oxidative stress (Abdelhamid *et al*., 2020). This is often achieved by generating free radicals and depleting the antioxidant systems. Lead has been reported to replace the cations in enzymes and proteins resulting in loss of activities and functions respectively (Ilesanmi *et al*., 2022).

Some of the macromolecules oxidized by lead include lipids (measured as malonedialdehyde (MDA), reduced glutathione (GSH), and antioxidants such as superoxide dismutase (SOD) and catalase (SOD)). The role of natural products in combatting the toxic effects of heavy metals and other poisonous chemicals is on the rise. Since the major mechanism of lead toxicity is oxidative stress, natural products rich in antioxidants can be a good antidote against lead poison and can be used along with common lead chelators. Several compounds from natural products with confirmed antioxidant activities have been used as an antioxidant agent against lead poisoning (Chen *et al*., 2019). Therefore, this study is aimed at determining the effects of flavonoid-rich extract of *Tephrosia bracteolate* leaves on lead acetate induced perturbations in hematological and oxidative stress parameters in Wistar rats.

Tephrosia bracteolata is a shrub of widespread belonging to the family Fabaceae that grows in uncultivated areas of tropical and warm-temperate regions. There are approximately 400 species included in this genus (Sadam *et al*., 2020). Idakwoji *et al.* (2021) reported the antidiabetic activities of the ethanol extract of *Tephrosia bracteolata* leaves. Similarly, Egharevba *et al.* (2020) also reported the antidiabetic, antioxidant and antimicrobial activities of extracts of *Tephrosia bracteolata* leaves. Other reported biological activities of the plant include anticancer (Hassan *et al*., 2017) and anti-plasmodial activities (Nondo *et al*., 2014).

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-

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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 dis- solved 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. bracteolata*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. Blood samples for serum assay were collected from each animal via cardiac puncture into plain and EDTA-bottles.

Estimation of Haematological and Immunological Parameters

Haematological parameters (red blood cell (RBC), haemoglobin (HB), packed cell volume (PCV), white blood cell (WBC), neutrophil (N), lymphocytes (L), monocytes (M) and platelets) were carried out following the method described by Dacie and Lewis, (1991).

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).

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 bracteolata* leaves (FRETB) on haematological parameters in lead acetate-exposed male Wistar rats

Table 1 shows that RBC, Hb and PCV concentration of untreated lead acetate- exposed group was significantly ($P<0.05$) lower than all the treatment groups. The result also indicates a decrease in platelet concentration in lead acetate-exposed group compared to normal control. However, FRETB and ascorbic acid –treated groups showed significant ($p<0.05$) increase in RBC, Hb and PCV concentration relative to lead acetate induced untreated group (group 2).

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Table 1: Effect of Flavonoid-rich extract of *Tephrosia bracteolata* leaves (FRETB) on haematological parameters in lead acetate-exposed male Wistar rats

Group/ Treatment	RBC ($x10^9$/L)	Hb (g/L)	PCV (%)	Plat ($x10^9$/L)
Group 1 (5 ml/kg Dist. H_2O)	220.21 ± 11.21^b	12.16 ± 2.41^b	51.26 ± 3.28^b	820.23 ± 96.15^a
Group 2 (50 mg/kg PbA)	175.17 ± 16.32^a	10.14 ± 1.25^a	40.21 ± 4.15^a	815.28 ± 85.44^a
Group 3 (50 mg/kg PbA+5 mg/kg FRETB)	180.22 ± 13.18^a	12.32 ± 1.39^b	42.32 ± 4.18^a	820.32 ± 90.21^a
Group 4 (50 mg/kg PbA+10 mg/kg FRETB)	217.14 ± 17.15^b	12.88 ± 1.25^b	50.52 ± 6.51^b	822.17 ± 94.11^a
Group 5 (50 mg/kg PbA+50 mg/kg AA)	214.16 ± 18.21^b	12.36 ± 1.43^b	50.12 ± 6.23^b	818.46 ± 79.30^a

Mean values having different lowercase alphabets as superscripts are considered significant ($p<0.05$) along the columns. 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 immunological parameters in lead acetate-exposed male Wistar

The effect of effect of FRETB on immunological parameters in lead acetate induced Wistar rat is shown in table 2. No significant difference was observed in the immunological parameters following lead acetate exposure.

Table 2: Effect of Flavonoid-rich extract of *Tephrosia bracteolata* leaves (FRETB) on immunological parameters in lead acetate-exposed male Wistar

Group/ Treatment	WBC ($x10^9$/L)	Neu (%)	Lymp (%)	Mono (%)
Group 1 (5 ml/kg Dist. H_2O)	5.46 ± 1.40^a	51.23 ± 5.25^a	22.67 ± 2.34^a	26.10 ± 2.36^a
Group 2 (50 mg/kg PbA)	5.28 ± 1.28^a	52.34 ± 9.59^a	21.35 ± 3.23^a	26.31 ± 2.58^a
Group 3 (50 mg/kg PbA+5 mg/kg FRETB)	5.32 ± 1.26^a	51.44 ± 8.23^a	21.26 ± 1.29^a	27.30 ± 2.74^a
Group 4 (50 mg/kg PbA+10 mg/kg FRETB)	5.17 ± 1.33^a	50.34 ± 8.15^a	22.18 ± 1.35^a	27.48 ± 2.44^a
Group 5 (50 mg/kg PbA+50 mg/kg AA)	5.23 ± 1.45^a	50.24 ± 7.22^a	22.24 ± 1.46^a	27.52 ± 2.93^a

Mean values having the same lowercase alphabets as superscripts are considered non-significant ($p>0.05$) along the columns. PbA= Lead acetate, FRETB=Flavonoid-rich extract of *Tephrosia bracteolata* leaves, AA= Ascorbic acid

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Effect of Flavonoid-rich extract of *Tephrosia bracteolata* leaves (FRETB) on oxidative stress biomarkers in lead acetate-exposed male Wistar

Table 3 shows the effects of flavonoid- rich extract on antioxidant status of lead acetate induced oxidative stress in male Wistar rats. The data obtained shows the MDA concentration of the untreated lead acetate- exposed group (group 2) was significantly higher compared to the normal control rat (group 1). After 28 days of treatment with the standard drug and flavonoid-rich extract of *T. bracteolate* (group 4 and 5) resulted in a significantly ($p<0.05$) lower MDA concentration relative to the untreated group. The decline in MDA was observed to be dose-dependent and comparable to that of the normal control group as shown in table 3. The result also indicated a significantly ($p<0.05$) increase SOD and CAT activities of the untreated group (group 2) as compared to the normal control. Most striking from the treatment groups are significant ($p<0.05$) decrease of SOD and CAT of the rats treated with flavonoid rich extract of *Tephrosia bracteolata* and ascorbic acid (group 4 and 5) when compared to the untreated group.

Table 3: Effect of Flavonoid-rich extract of *Tephrosia bracteolata* leaves (FRETB) on oxidative stress biomarkers in lead acetate-exposed male Wistar

Group/ Treatment	MDA (nmol/ml)	SOD (U/ml)	CAT (U/ml)
Group 1 (5 ml/kg Dist. H_2O)	15.23±2.11[a]	22.04±3.34[a]	33.35±2.46[a]
Group 2 (50 mg/kg PbA)	22.46±2.15[b]	31.99±3.65[b]	50.95±3.40[b]
Group 3 (50 mg/kg PbA+5 mg/kg FRETB)	20.35±2.67[b]	28.48±3.46[b]	48.72±2.33[b]
Group 4 (50 mg/kg PbA+10 mg/kg FRETB)	14.56±2.23[a]	22.30±2.69[a]	35.95±3.47[a]
Group 5 (50 mg/kg PbA+50 mg/kg AA)	14.18±2.57[a]	21.75±2.72[a]	35.23±.54[a]

Mean values having different lowercase alphabets as superscripts are considered significant ($p<0.05$) along the columns. PbA= Lead acetate, FRETB=Flavonoid-rich extract of *Tephrosia bracteolata* leaves, AA= Ascorbic acid

Discussion

Lead is a ubiquitous environmental and industrial pollutant that has been detected in nearly all phases of environment and biological system. Its persistence in human and animal tissues has quite often been associated with considerable health risks (Juberg et al., 2017). Ascorbic acid is probably the most widely studied vitamin when it comes to the prevention of lead-induced oxidative stress. Its property of quenching ROS along with metal chelation makes it a potential detoxifying agent for lead (Das and Saha, 2010). However, the therapeutic and prophylactic use of plant extracts to ameliorate lead-induced organ damage has been severally explored (Adikwu *et al.*, 2013).

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In the hematological study, the results showed a significant decrease in the hematological parameters, including the RBC count, Hb concentration, PCV, and platelet concentration in the lead-exposed rats compared to controls. The results of this study were consistent with the findings of previous studies (Haridy et al., 2014; Obafemi et al., 2019). According to Manser et al. (2019), low-level exposure to inorganic lead in workplace can have harmful effect on certain types of the blood cells, reduce hemoglobin production, and cause reduced lifespan and function of red blood cells. The mechanisms of lead-induced hematological alterations in rats could be due to lead-related RBC membrane fluidity that leads to increased erythrocyte hemolysis rates (Mannem, 2014; Ray, 2016), lead interference with the heme synthesis pathway, such as the downregulation of -aminolevulinic acid dehydratase (ALAD), resulting in low Hb concentration and the interference of lead with iron and copper metabolism in the RBCs (Obafemi et al., 2019). Moreover, its effect on ALAD has been used clinically to gauge the degree of lead acetate poisoning (Ray, 2016). These effects of lead on erythrocyte and its inhibition on heme biosynthetic process may contribute to the significantly ($p < 0.05$) low PCV, RBC, and hemoglobin levels in the lead-induced group when compared with the other groups in the study. This situation was, however, reversed in the extracts and reference drug treated-groups even though the lower doses of FRETB did not show much effect in this regard.

Table 2 presents the effect of flavonoid rich extract *T. bracteolata* treatment on hematological parameters in lead-induced toxicity in rats. The result shown an increase in the neutrophil and monocytes concentration of lead acetate induced untreated group (group 2) when compared to the normal control group. This result is consistent with another study, which also showed a lead-induced increase in lymphocytes count (Shah and Altindog, 2020). Exposure to lead acetate can lead to an increase in monocytes count and neutrophil count in the blood (Tajudeen *et al*., 2019). This is often a response to inflammation and the body's attempt to defend against the toxic effects of lead acetate. Elevated monocytes and neutrophil counts can be indicative of an inflammatory response, although are not specific to lead acetate toxicity and can be seen in various other inflammatory conditions as well (Ahamed and Siddiqui, 2017).

However, a decrease in WBC and lymphocytes concentration in lead acetate induced untreated group (group 2) in relative to the normal control was observed. This decrease suggests that lead acetate might have an immunosuppressive effect, weakening the immune system's ability to function optimally. This can be problematic because a compromised immune system can lead to increased susceptibility to illnesses and prolonged recovery times. Following flavonoid rich extract of *T. bracteolata* administration at various concentration, restoration of immunological counts back to the physiological levels were observed. This result suggests that FRETB can reduce the inflammatory responses that are induced by lead toxicity.

Lead acetate-induced oxidative stress is mostly rooted in lipid peroxidation and disturbance of the prooxidant–antioxidant balance by generation of reactive oxygen species (Bechara, 2014). Lipid peroxidation a reactive oxygen species mediated mechanism, has been implicated in the pathogenesis of various liver injuries and subsequent liver fibrogenesis in experimental animals and humans (Mervat et al., 2022). The ability of lead to induce Lipid peroxidation is predicated on its strong affinity for thiol groups of amino acids, especially cysteine. Lead may, therefore, affect the antioxidant defense via inhibiting the functional thiol groups of enzymes, such as SOD and CAT (Patrick, 2016). This fact might be the reason for the significantly ($p < 0.05$) lower SOD and CAT levels in the serum of lead-induced rats when compared with the normal and treated groups as shown in Table 3.3. This result is in line with the findings of Tajudeen *et al*. (2019) who reported a decrease in SOD and CAT activities in lead acetate induced rats. Furthermore, MDA level is also an important marker of lipid peroxidation in biological systems. Lead is known to produce oxidative

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damage by enhancing peroxidation of lipid membranes and LPO is deleterious process solely carried out by free radicals (Halliwell and Gutteridge, 2019). From the result obtain in Table 3.3, it was observed that MDA level in the lead-induced group was significantly ($p < 0.05$) higher than all the other groups in this study.

However, the results of this study (Table 2) showed a significant ($p<0.05$) reduction in serum MDA concentration of lead acetate-induced rats treated with graded doses of flavonoid rich extract of *T. bracteolata*. This indicates that administration of the extracts led to a reduction in the level of lipid peroxidation. The observed decrease in the oxidative stress status of the treated rats could be attributed to the presence of polyphenolic phytocompounds such as flavonoids, tannins, and phenolic classes highly present in flavonoid rich extract of *T. bracteolata*. The antioxidant activities of many plants have been linked to the presence of alkaloids, flavonoids, tannins, saponins, steroids, and other phenolic compounds (Asmat *et al*., 2016). A possible mechanism by which the extract increased the activities of these enzymes could be at molecular level by increasing the expression of messenger RNA of these enzymes contrary to what was obtainable in the oxidative stress condition as reported by Sindhu *et al.* (2014).

Conclusion

In this study, the restorative potential of flavonoid-rich extract derived from *Tephrosia bracteolata* leaves on lead acetate-induced haematotoxicity, immunotoxicity, and oxidative stress in male Wistar rats was investigated. The elevation of haematological and immunological parameters as well as oxidative stress markers clearly demonstrates the toxic influence of lead acetate on the health of the Wistar rats. However, the Administration of the flavonoid-rich extract from *Tephrosia bracteolata* leaves exhibited a remarkable restorative effect indicating its potential as a promising therapeutic agent in mitigating the adverse effects of lead acetate exposure.

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