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Protective Effects of Flavonoid-rich extract of *Tephrosia bracteolata* leaves on lead acetate-induced hepatotoxicity in male Wistar Rats

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Abstract

This study investigated the ameliorative effects of flavonoid rich extract of *T. bracteolata* (FRETB)on the hepatic function in rats exposed to lead acetate poisoning. Hepatotoxicity was induced intraperitoneal by administration of Lead acetate-PbA (50 mg/kg) while FRETB and Ascorbic acid were administered daily throughout the duration (28 days) of the study. The protective effects of FRETB on the liver were investigated by evaluating the serum activities of aspartate transaminase (AST), alanine transaminase (ALT) and alkaline phosphatase (ALP). Also, the serum levels of bilirubin, total protein and albumin as well as histological studies on the liver tissues were investigated. Administration of lead acetate showed significant ($p<0.05$) increase in serum activities of ALT, AST and ALP. There was also an increase in the concentration of serum bilirubin with a corresponding decrease in total protein and albumin concentrations. Histological examination of the liver also showed hepatic necrosis.However, FRETB at 10 mg/kg significantly ($p < 0.05$) reduce the activities of AST, ALT and ALP. Also, bilirubin concentrations were reduced while there was an increase in serum concentrations of total protein and albumin. This finding suggests that the flavonoid-rich extract of *Tephrosia bracteolata* leaves may ameliorathe deleterious effects of lead on the liver.

Keywords: Flavonoid-rich, *Tephrosia bracteolata*, lead acetate, hepatotoxicity, Wistar Rats

Introduction

Lead is a highly toxic heavy metal found in the environment that has been used by humans since ancient times, due to its unique properties. It is one of the most common heavy metals on Earth, and it is highly persistent in the environment. As a result, lead contamination is a major problem for the environment and human health. Although lead has been used in a variety of products, including gasoline, paint, and batteries, its use has been gradually restricted due to its well-documented adverse health effects (Mahaffay, 1990). Despite these restrictions, lead exposure remains a significant problem, with approximately two billion people worldwide estimated to be at risk.

Lead can cause liver damage when ingested. The liver is particularly susceptible to lead toxicity because it is responsible for clearing lead from the blood. Ingestion of lead acetate can lead to a number of liver complications, including hepatomegaly (enlarged liver), jaundice, and hepatic encephalopathy (a brain disorder caused by liver failure). In severe cases, it can lead to liver failure and even death. In addition to liver damage, lead acetate can also cause other serious health problems, such as kidney damage, anaemia, and nervous system damage. Lead-induced hepatotoxicity is a complex process involving several different mechanisms. The main mechanism involves the binding of lead to sulfhydryl groups in the liver, which disrupts normal cellular functions and leads to oxidative stress. Lead also interferes with the metabolism of essential fatty acids, and inhibits the activity of several enzymes that are important for liver function. In addition, lead acetate can induce the production of inflammatory cytokines, which further contributes to liver damage. Finally, lead acetate can affect the transport of bile acids, which can lead to cholestasis (obstruction of bile flow). The long-term effects of lead acetate-induced hepatotoxicity can be quite serious. Even after the acute toxicity has resolved, the liver can remain damaged and lead can continue to accumulate in the body, causing chronic effects. These long-term effects include fibrosis (scarring of the liver), cirrhosis (severe scarring), and hepatocellular carcinoma (liver cancer). In addition, lead acetate exposure can lead to cognitive impairment, anemia, and hypertension. Children are particularly vulnerable to the long-term effects of lead exposure, as it can impair their neurological development.

The treatment for lead poisoning consists of dimercaprol and succimer (Park *et al.*, 2008). However, this treatment is inadequate and alternative treatment is sought for. Medicinal plants are currently considered for their potential abilities to manage heavy metal poisoning. This study investigated the ameliorative effects of flavonoid-rich extract of *Tephrosia bracteolata*on lead acetate-induced hepatotoxicity in male Wistar Rats.

Tephrosia bracteolata, a plant native to the tropical regions of Africa, is known for its many beneficial properties. It is considered a valuable resource in West Tropical Africa due to its numerous applications in traditional medicine, agriculture, and other areas (Dalziel, 1987). The plant has been used to treat various ailments such as malaria, skin infections, and stomach disorders. It is also known for its beneficial properties in agriculture, such as repelling pests and increasing crop yield. Overall, *Tephrosia bracteolata* is a valuable resource in West Tropical Africa and its uses have been recognized by local communities for generations (Evans *et al.*, 1985).

Materials and Methods

Materials

Spectrometer (RS232 Mercers Row Industries, UK), Refrigerator (ffr-in-1285-34 newline; Nigeria), Electronic water bath (SBS30, Shakers company, UK), (Analytical weighing balance PB3002_5, Mettler Toledo, Switzerland), Centrifuge (5m800b Sorgifriend, Switzerland).

Methods

Plant material

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

Extraction

Freshleaves 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. bracteolata*leaves. The flavonoid-rich extract of *T. bracteolata*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 cages in the Animal House Unit of the Depart of Biochemistry, Prince Abubakar Audu University, Anyigba, 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 weekof 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 the plain bottle

Estimation of Liver Function Biomarkers

Serum activities of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were assessed using the method of Reitman and Frankel, (1957). Alkaline phosphatase (ALP) activity was determined using the method of Kind and King, (1954).Total bilirubin (TB) and direct bilirubin (DB) were determined following the method of Jendrassik and Grof, (1938). Total protein (TP) concentration was determined using the Biuret method, Daumas, (1975) while albumin concentration was determined through the method of Spencer and Price, (1971).

Histopathological examination of the Liver

The effect of treatment on the histology of the liver 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 $P \leq 0.05$.

Results

Effect of Flavonoid-rich extract of *Tephrosia bracteolata* leaves (FRETB) on serum enzyme activities in lead acetate-induced hepatotoxicity in male Wistar

The effect of flavonoid-rich extract of *Tephrosia bracteolata* leaves (FRETB) on serum enzyme activities in lead acetate-induced hepatotoxicity in male Wistar Rats is shown in Table 1. The result showed significant ($p<0.05$) increases in serum AST, ALT and ALP following exposure to lead acetate compared to the normal control rats. Treatment with FRETB led to significant ($p<0.05$) decrease in the activity of these enzymes.The most notable reduction was found in the 10mg/kg FRETB and ascorbic acid-treated groups (groups 5 and 6 respectively) which were comparable to the normal control group.

Table 1: Effect of Flavonoid-rich extract of *Tephrosia bracteolata* leaves (FRETB) on serum enzyme activitiesin lead acetate-induced hepatotoxicity in male Wistar

Group/ Treatment	AST (IU/L)	ALT (IU/L)	ALP (IU/L)
Group 1 (5 ml/kg Dist. H_2O)	43.50±4.92[a]	43.23±4.16[a]	30.49±3.18[a]
Group 2 (50 mg/kg PbA)	60.15±3.49[c]	58.15±5.22[c]	37.23±4.26[c]
Group 3 (50 mg/kg PbA+5 mg/kg FRETB)	51.23±5.22[b]	49.77±6.18[b]	31.46±2.14[b]
Group 4 (50 mg/kg PbA+10 mg/kg FRETB)	41.18±4.19[a]	40.91±6.21[a]	30.44±3.23[a]
Group 5 (50 mg/kg PbA+50 mg/kg AA)	41.26±3.28[a]	39.28±4.16[a]	30.26±3.19[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 serum bilirubin levels in lead acetate-induced hepatotoxicity in male Wistar

Table 2 shows the effect of flavonoid-rich extract of *Tephrosia bracteolata* leaves (FRETB) on serum concentration of bilirubin in lead acetate-induced hepatotoxicity in male Wistar Rats. Result showed significant ($p<0.05$) increases in serum concentration of bilirubin following exposure to lead acetate compared to the normal control rats. Treatment with FRETB led to significant ($p<0.05$) decrease in concentration of both total and direct bilirubin.

Table 2: Effect of Flavonoid-rich extract of *Tephrosia bracteolata* leaves (FRETB) on serum bilirubin levelsin lead acetate-induced hepatotoxicity in male Wistar

Group/ Treatment	Tbil (µmol/L)	Dbil (µmol/L)
Group 1 (5 ml/kg Dist. H_2O)	5.53±1.01[a]	2.28±0.11[a]
Group 2 (50 mg/kg PbA)	5.28±1.33[a]	2.43±0.27[a]
Group 3 (50 mg/kg PbA+5 mg/kg FRETB)	5.77±1.24[a]	2.18±0.19[a]
Group 4 (50 mg/kg PbA+10 mg/kg FRETB)	5.81±1.15[a]	2.73±0.16[a]
Group 5 (50 mg/kg PbA+50 mg/kg AA)	5.26±1.26[a]	2.32±0.16[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

Effect of Flavonoid-rich extract of *Tephrosia bracteolata* leaves (FRETB) on serum protein concentration in lead acetate-induced hepatotoxicity in male Wistar

Table 3 shows the effect of flavonoid-rich extract of *Tephrosia bracteolata* leaves (FRETB) on serum concentrations of total protein and albumin in lead acetate-induced hepatotoxicity in male Wistar Rats. Result showed significant ($p<0.05$) decrease in serum concentrations of total protein and albumin following exposure to lead acetate compared to the normal control rats. Treatment with FRETB led to significant ($p<0.05$) increase in concentration of both total protein and albumin compared to the negative control (Group 2).

Table 3: Effect of Flavonoid-rich extract of *Tephrosia bracteolata* leaves (FRETB) on serum protein concentration in lead acetate-induced hepatotoxicity in male Wistar

Group/ Treatment	TP (g/dl)	ALB (g/dl)
Group 1 (5 ml/kg Dist. H_2O)	73.13±6.83[b]	37.40±1.28[b]
Group 2 (50 mg/kg PbA)	50.26±4.49[a]	23.21±2.80[a]
Group 3 (50 mg/kg PbA+5 mg/kg FRETB)	69.27±6.49[b]	38.38±1.13[b]
Group 4 (50 mg/kg PbA+10 mg/kg FRETB)	71.16±5.33[b]	37.16±2.58[b]
Group 5 (50 mg/kg PbA+50 mg/kg AA)	71.93±5.28[b]	37.29±2.15[b]

Mean values having different lowercase alphabets as superscripts are consideredsignificant ($p<0.05$) 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 histology of the liver in lead acetate-induced hepatotoxicity in male Wistar Rats

Plates 1 to 5 shows the result of the histopathological assessment of the liver tissues of the treated lead acetate-exposed Wistar rats.

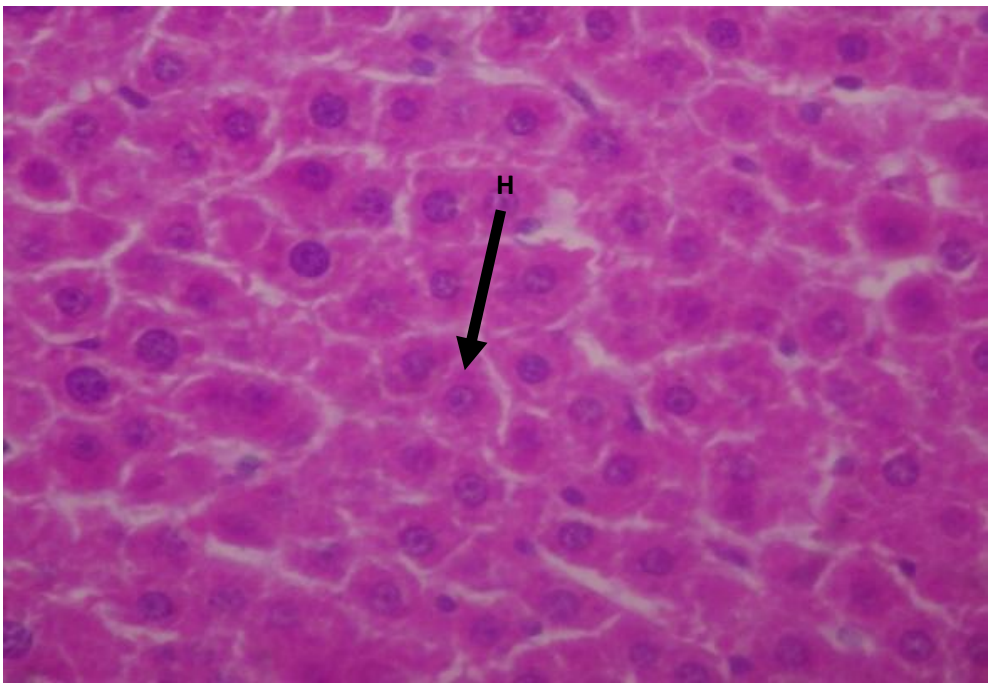

Plate 1. Histologic section of liver tissue of distilled water (5 ml/kg)- treated rat (normal control) showing parallel radially arranged plates of hepatocytes. No abnormalities are seen. (HE x 250). H= Hepatocytes

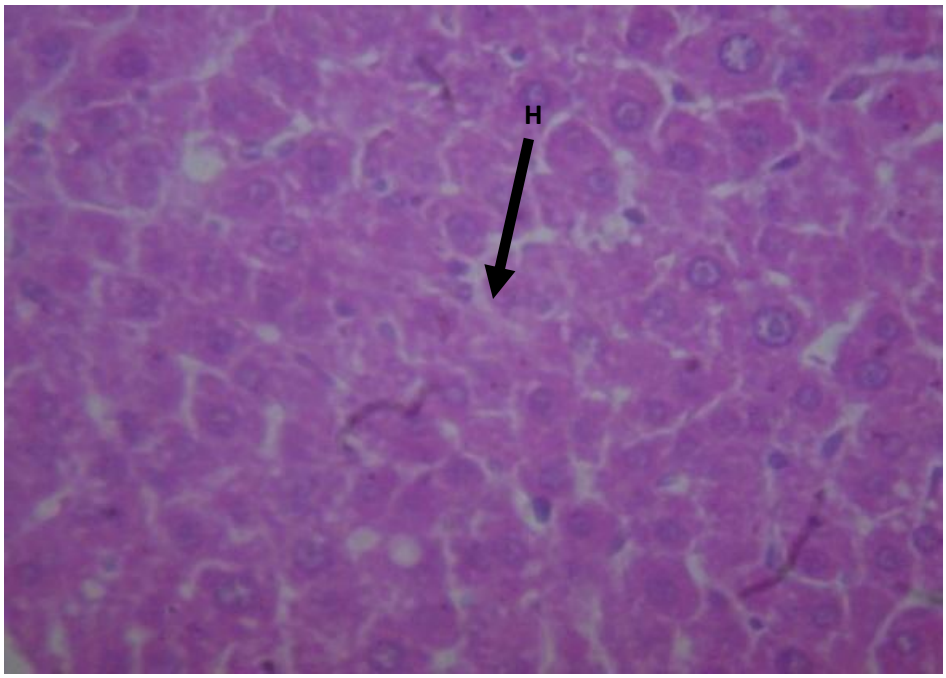

Plate 2. Histologic section of liver tissue of PbA (50 mg/kg)- treated rat showing massive necrotized hepatocytes. (HE x 250). H= Hepatocytes, PbA= Lead acetate

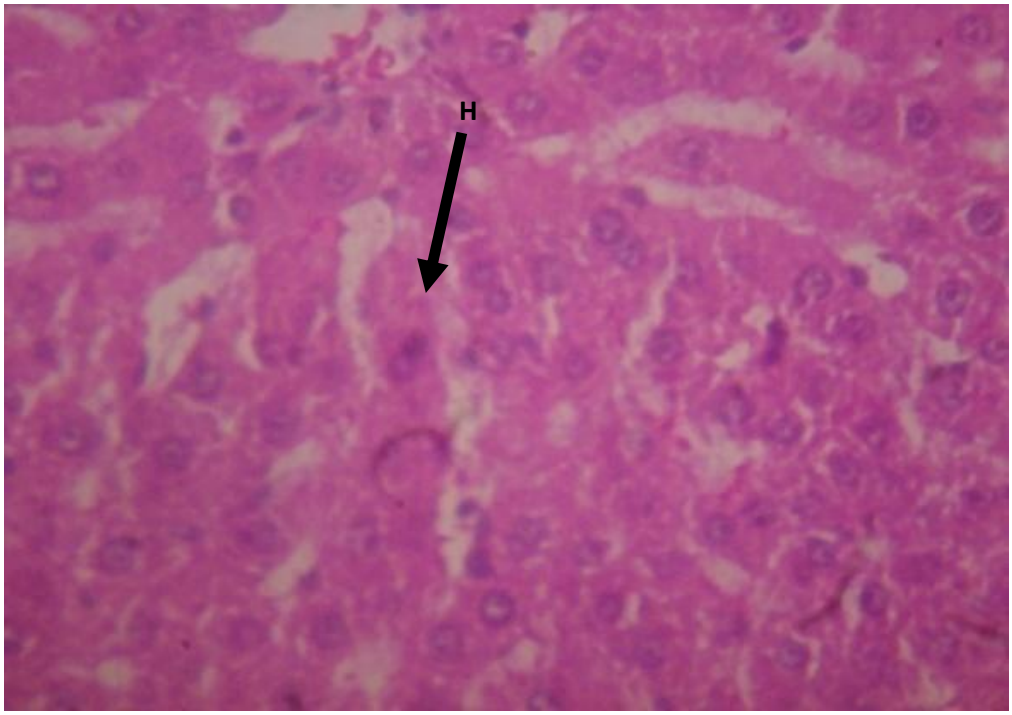

Plate 3. Histologic section of liver tissue of PbA (50 mg/kg) + FRETB (5 mg/kg)- treated rat showing gradual restoration of hepatocytes. (HE x 250). H= Hepatocytes,PbA= Lead acetate, FRETB=Flavonoid-rich extract of *Tephrosia bracteolata* leaves

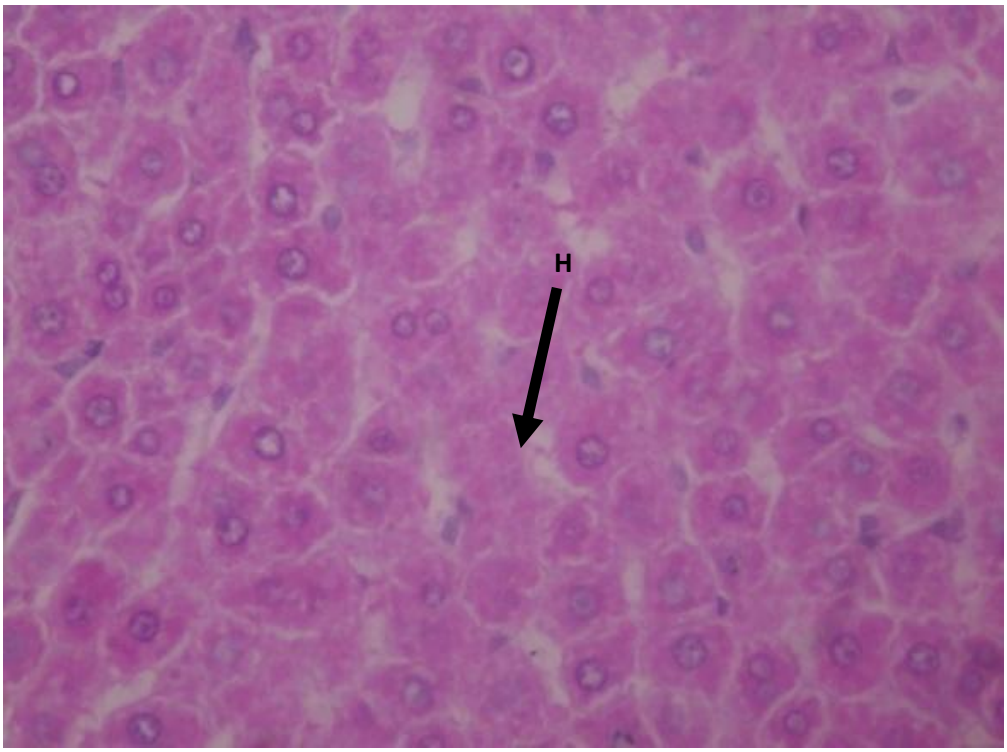

Plate 4. Histologic section of liver tissue of PbA (50 mg/kg) + FRETB (10 mg/kg)- treated rat showing parallel radially arranged plates of hepatocytes. No abnormalities are seen. (HE x 250). H= Hepatocytes,PbA= Lead acetate, FRETB=Flavonoid-rich extract of *Tephrosia bracteolata* leaves

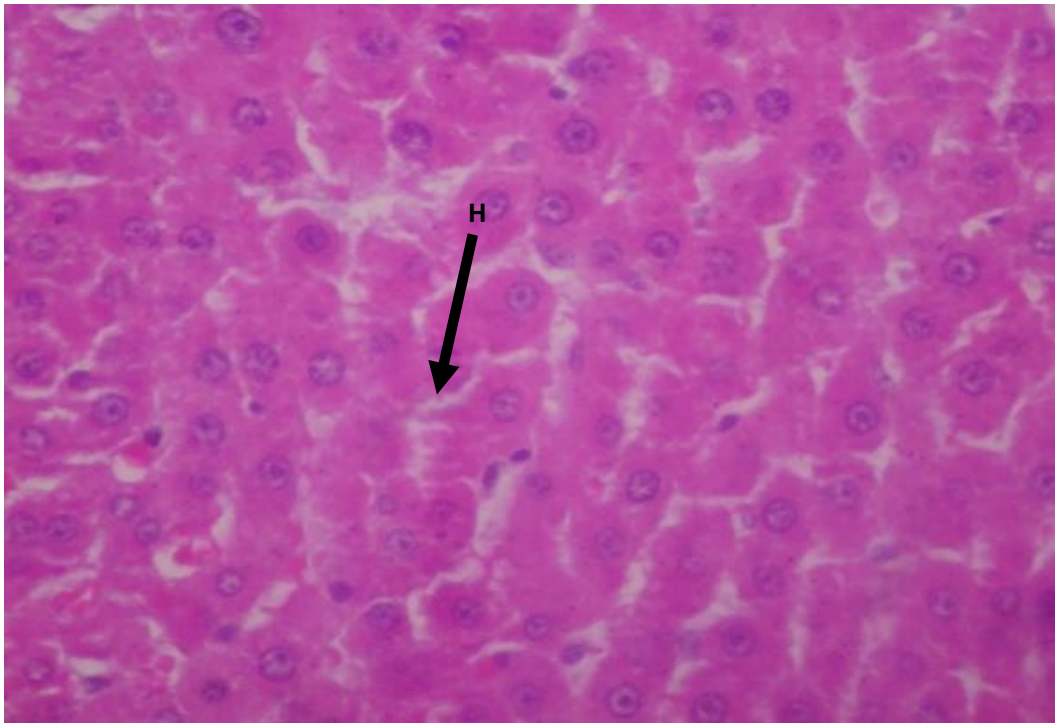

Plate 5. Histologic section of liver tissue of PbA (50 mg/kg) + AA (5 mg/kg)- treated rat (standard control) showing parallel radially arranged plates of hepatocytes. No abnormalities are seen. (HE x 250), H= Hepatocytes,PbA= Lead acetate, AA= Ascorbic acid

Discussion

The main pathological effects of lead acetate-induced hepatotoxicity include oxidative stress, inflammation, fibrosis, and decreased liver function. Oxidative stress occurs when the liver is exposed to excess free radicals, which can damage cells and tissues. Inflammation is a result of the liver's immune response to the damage caused by lead acetate. Fibrosis is the excessive accumulation of scar tissue in the liver, which can lead to decreased liver function (Chakrabarti *et al.*, 2019). The decreased liver function that can occur as a result of lead acetate-induced hepatotoxicity can manifest in several ways. For example, the liver may become less able to filter toxins from the blood, leading to a build-up of toxins in the body. The liver may also become less able to synthesize proteins and other substances that are important for maintaining health. In severe cases, lead acetate-induced hepatotoxicity can even lead to liver failure (Saif, 2017). One of the key molecular mechanisms is the activation of a family of transcription factors called nuclear factor-kappa B (NF-κB). NF-κB is a key regulator of inflammation and cell survival, and it can be activated by oxidative stress and other factors. Once activated, NF-κB can trigger the production of pro-inflammatory cytokines and other inflammatory molecules (Kaur et al., 2016). This can lead to the chronic inflammation and fibrosis that are characteristic of lead acetate-induced hepatotoxicity.

The result of this study showed that flavonoid-rich extract of *Tephrosia bracteolata* significantly reduced the levels of AST ($p<0.05$) in rats with lead acetate-induced renal toxicity. This suggests that FRETB may have a protective effect on the liver, as AST is an important enzyme for liver function. This study found that FRETB also significantly reduced the levels of ALT ($p<0.05$) in rats with lead acetate-induced renal toxicity. ALT is another enzyme that is important for liver function, so this finding further supports the hypothesis that FRETB may have a protective effect on the liver. Result from this study shows again that FRETB significantly reduced the levels

of ALP ($p<0.05$) in rats with lead acetate-induced renal toxicity. ALP is an enzyme that is produced in the liver, but it is also found in other organs, such as the kidneys. Therefore, the reduction in ALP levels suggests that FRETB may have a protective effect on both the liver and the kidneys.The outcome of the analysis on the serum enzyme activities in this study suggest that FRETB may have a beneficial effect on lead acetate-induced renal toxicity.

The results of this study further suggests that the flavonoid-rich extract of *Tephrosia bracteolata* leaves may protect the liver from damage caused by lead acetate-induced renal toxicity. This was evident with the significant reduction in serum bilirubin levels ($p<0.05$) in rats treated with the extract. This finding is important because it indicates that the extract may have the potential to reduce the risk of liver damage caused by lead acetate exposure.

For total protein (TP), the results of the study were similar to the results for serum protein concentration. Lead acetate-induced renal toxicity significantly reduced the levels of TP, but FRETB significantly reversed this effect ($p<0.05$). This suggests that FRETB may be effective in restoring normal TP levels in the body. As for albumin (ALB), the results were similar to those for TP. Lead acetate-induced renal toxicity significantly reduced the levels of ALB, but treatment with FRETB significantly reversed this effect ($p<0.05$).

Histological analysis of the liver revealed that lead acetate-induced renal toxicity caused a number of changes, including hepatocyte degeneration, infiltration of inflammatory cells, and an increase in collagen fibres. However, treatment with FRETB partially or completely reversed these changes ($p<0.05$). These results suggest that FRETB may have a protective effect on the liver, preventing or reversing the damage caused by lead acetate-induced renal toxicity.

The phytochemicals present in the plant especially the flavonoids might have acted as hepatoprotective agents promoting liver regeneration and improving the function of liver cells. The flavonoids may be stimulating the production of proteins that help to protect liver cells from damage and promote their repair. These effects may be mediated by the activation of certain signalling pathways, such as the Nrf2/ARE pathway or the TGF-β1/Smad3 pathway. The flavonoids in FRETB may be working at the level of gene expression to promote the production of protective proteins. Flavonoids can act as epigenetic modulators, meaning they can influence the way DNA is packaged and expressed. They can bind to certain proteins called histones, which are responsible for organizing DNA into chromatin. By binding to histones, flavonoids can alter the expression of genes, including those that code for proteins that protect the liver.

Conclusion

In conclusion, the flavonoid-rich extract of *Tephrosia bracteolata* leaves showed ameliorative effects in acetate-induced hepatotoxicity in rats. The extract was found to reduce the serum activity of alanine aminotransferase, aspartate aminotransferase and alkaline phosphase. Also, the extract reduced serum bilirubin level and restored the level of total protein and albumin. The study also showed that the extract had a beneficial effect on the histology of the liver tissues. Based on these findings, it can be concluded that the flavonoid-rich extract of *T.bracteolata* may be an effective agent for protecting against lead-induced hepatotoxicity.

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