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Research Article
Hepatoprotective and Nephroprotective Potency of *Ricinodendron heudelotii* Against Acetaminophen-induced Toxicity in Wistar Albino Rats

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Abstract

Background and Objective: The seeds of the plant *Ricinodendron heudelotii* are used in preparation of various meals and eaten for its delicious taste and aroma. Its extract has been used in many Nigerian communities in the treatment of various health disorders. This study evaluated the activity of ethanol seed extracts of *Ricinodendron heudelotii* on acetaminophen-induced hepatic/nephrotoxicity in male Wistar albino rats. **Materials and Methods:** Thirty rats were divided into six groups of six rats each. Five of these groups were induced with acetaminophen. Three of the groups were thereafter treated with different concentrations of the ethanol seed extracts of *Ricinodendron heudelotii*. Treatment was carried out for a period of 21 days, the animals were sacrificed and blood samples were collected for biochemical analysis and histological examinations of the hepatic and renal cells. **Results:** The results obtained revealed an amelioration of the acetaminophen-induced toxicity in the hepatic cells of the experimental animals as seen in the concentrations of total protein, total and conjugated bilirubin, albumin, AST and ALP. The renal function biomarkers tested showed a decrease in the elevated blood urea nitrogen, creatinine levels and the blood electrolytes at all concentrations except 800 mg kg^{-1} b.wt. of extract concentration. The histological examination of the cells also revealed amelioration of the integrity of the cells when treated with the seed extract. **Conclusion:** The results obtained from the study, therefore, suggested that *Ricinodendron heudelotii* ethanol seed extract has an ameliorative/protective potency against acetaminophen-induced toxicity on the hepatic and renal cells.

Key words: Hepatoprotective, nephrotoxicity, nephroprotective, hepatotoxicity, *Ricinodendron heudelotii*, acetaminophen, silymarin

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Liver is the largest organ in the human body and it is responsible for detoxification of xenobiotics and other chemicals via inactivating and metabolizing the substances, thus the vulnerability of the liver to toxicity.

The kidney is a vital organ in the human body, saddled with the function of excretion of metabolic waste as a natural filter of the blood and removal of wastes which are diverted to the urinary bladder[1].

Acetaminophen, commonly called paracetamol is one of the commonly used analgesic-antipyretic drugs. As a common over the counter drug, it is mostly taken without prescription[2] leading to its abuse, hence its toxicity. When taken in over dose, acetaminophen induces hepatotoxicity[2-4] and if significant, can trigger nephrotoxicity[5,6]. This toxicity can be attributed to the metabolism of the drug through glucuronidation and sulfation in the liver, while water soluble metabolites are excreted through the kidney[6].

Silymarin is a polyphenolic component isolated from the fruits and seeds of the milk thistle plant Silybum marianum (Asteraceae family) [7], its use in the prevention and treatment of liver diseases has gained world-wide acceptance[8]. Silymarin extract contains approximately 65-80% flavonolignans (silybin A, silybin B, isosilybin A, isosilybin B, silychristin and silydianin), a small proportion of flavonoids and approximately 20-35% fatty acids and polyphenolic compounds, which possess a range of metabolic regulatory effects[7].

The need for complementary and alternative medicine via natural products in ameliorating toxicity in human body is necessary as presently no drug is available for exciting liver function, proffer protection to the liver and revitalize hepatic cells[8]. Also, natural products are cost efficient, readily available, with little or no side effects.

Ricinodendron heudelotii has been reported to be a therapeutic plant[9] due to the presence of bioactive compounds in it. This study was aimed at evaluating the hepato and nephroprotective potency of *Ricinodendron heudelotii* seed extract in acetaminophen-induced hepatic and nephrotoxicity.

MATERIALS AND METHODS

Study area: This study was carried out in the laboratory and animal house of Biochemistry Department, University of Port Harcourt, from April-August, 2017.

Plant collection: The seeds of *Ricinodendron heudelotii* were obtained from mile 3, market in Port Harcourt Rivers state, Nigeria.

Preparation of plant extract: The seeds were cleaned and ground into fine powder with the aid of grinding machine. About 1000 g of the powdered seed was weighed, transferred into a big conical flask and soaked with 2000 mL of ethanol for 72 h. The mixture was agitated manually by shaking for better extraction. After 72 h, the mixture was filtered using whatman filter paper (Whatman qualitative filter paper No. 1 Camlab, UK) and the clear filtrate was concentrated by heating with a water bath at a temperature of 80°C. The extract was stored in a sample bottle in aliquots at 4°C until required for use[9].

Inducement of toxicity: Thirty six Wistar albino rats were used for the study. They were weighed and allowed to acclimatize for 14 days. Hepatotoxicity and nephrotoxicity were induced in the animals using 750 mg kg^{-1} b.wt. acetaminophen via gavage for a period of 3 days after which the animals were confirmed toxic[10].

Acute and sub-acute oral toxicity studies: Acute toxicity study was performed according to the OECD guidelines No. 420. The experimental animals were grouped into three containing six animals. Animals were observed periodically for the symptoms of toxicity and death within 24 h and then daily for 14 days. *Ricinodendron heudelotii* seed was administered orally at a single dose level of 300 mg kg^{-1} b.wt. to animals for sighting study step-I. In Sighting study step-II, the seed extract was administered orally at a single dose level of 2000 mg kg^{-1} b.wt. oral to animals. The altered autonomic effects (lacrimation, salivation, piloerection) central nervous system effect (tremors, convulsion, drowsiness) skin, body weight, food consumption, water consumption and mortality were observed. The maximum dose tested (2000 mg kg^{-1}) for LD_{50}. From the LD_{50}, doses of 400, 600 and 800 mg kg^{-1} b.wt. were selected and considered[11,12].

Experimental design: The 36 albino rats were divided into six groups of six rats per group. The treatment procedures were as follows[13]:

- **Group 1 (Control):** Feed+Water only
- **Group 2 (Positive control):** Feed+Water+750 mg kg^{-1} acetaminophen+40 mg kg^{-1} b.wt. silymarin

- **Group 3 (Negative control):** Feed+Water+750 mg kg^{-1} b.wt. acetaminophen
- **Group 4:** Feed+Water+750 mg kg^{-1} b.wt. acetaminophen +400 mg kg^{-1} b.wt. *Ricinodendron heudelotii* ethanol seed extract
- **Group 5:** Feed+Water+750 mg kg^{-1} b.wt. acetaminophen +600 mg kg^{-1} b.wt. *Ricinodendron heudelottii* ethanol seed extract
- **Group 6:** Feed+Water+750 mg kg^{-1} b.wt. acetaminophen +800 mg kg^{-1} b.wt. *Ricinodendron heudelottii* ethanol seed extract

Collection of blood and liver samples: At the end of the experiment, the animals were anaesthetized in 10% chloroform vapour and whole blood collected by direct cardiac puncture from each animal into ice cold lithium heparinized bottles and centrifuged. The plasma was collected and used for enzyme/biochemical assay. The animals were dissected and the liver was quickly removed. The largest lobe was divided into two parts which were then used as follows[14]: The liver function biomarkers checked include; Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Alkaline Phosphatase (ALP), Total Protein (TP), Total Bilirubin (TB), Albumin (ALB) and Conjugated Bilirubin (CB).

Assessment of hepatoprotective activity: The serum levels of total protein, bilirubin, albumin and activities of ALT, AST and ALP were determined by using Randox assay kits (Randox Laboratories US, Ltd., 515 Industrial Boulevard, Kearneysville, West Virginia).

Assessment of nephroprotective activity: The blood urea nitrogen, creatinine and blood electrolytes were determined using the Randox assay kits (Randox Laboratories-US, Ltd., 515 Industrial Boulevard, Kearneysville, West Virginia).

Histological analysis: For histopathological studies of the liver, liver tissues were cut in small pieces and immersed in neutral buffered formalin for 24 h. The fixed tissues were processed routinely, embedded in paraffin, sectioned, deparaffinized and rehydrated using the standard techniques[15]. The extent of acetaminophen-induced necrosis was evaluated by assessing the morphological changes in the liver sections stained with Hematoxylin and Eosin (H and E) by using standard techniques[15].

Histopathological studies of the kidney were performed. Pieces of the kidney from each group were fixed immediately in 10% neutral formalin for a period of at least 24 h, dehydrated in graded (50-100%) alcohol, embedded in paraffin wax, cut into 4-5 μm thick sections and stained with H and E[15]. The sections were evaluated for the pathological symptoms of nephrotoxicity such as; necrosis, fatty infiltration, fibrosis, lymphocyte infiltration and blood vessel congestion.

Statistical analysis: Values were given as mean±standard deviation. Data was statistically analyzed using one-way analysis of variance (ANOVA).

RESULTS AND DISCUSSION

The result of Table 1 for the acute toxicity study indicates no abnormality and sign of toxicity of the ethanol seed extract of *Ricinodendron heudelotii* at the doses of 300 and 2000 mg kg^{-1} b.wt. on the experimental animals, rather, an increment in the body weight of the animals were observed at both doses.

The doses of 400, 600 and 800 mg kg^{-1} b.wt. used in the experiment were selected for formulation based on the results of acute and sub-acute toxicity study[16]. The experimental animals gained weight, gained appetite, produced less urine and stool, etc. The increase in body weight of the animals also agrees with the study of previous researches[16] that reported an increase in body weight of experimental animals when administered doses of Hydroalcoholic Polyherbal Formulation (HAF). The weight gain may be due to the fatty acids and oil found in the seed of *Ricinodendron heudelotii*[17].

The hepatic function test result as revealed in Table 2 showed significant changes in the total protein values in all experimental groups. A Decreasing variations were observed in the concentrations of the hepatic function biomarkers: AST, ALT, ALP, TB, CB and ALB levels, while a decrease was observed in the treatment groups. The dosage of 400 mg kg^{-1} b.wt. of extract decreased the serum level of AST while the dosage of 800 mg kg^{-1} b.wt. extract elevated the AST serum level. The

Table 1: Acute toxicity study of the seed extract of *Ricinodendron heudelotii* on the experimental animals

Acute toxicity sign	300 mg kg^{-1} b.wt. (n = 3)	2000 mg kg^{-1} b.wt. (n = 3)
Lacrimation	No	No
Salivation	No	No
Piloerection	No	No
Drowsiness	No	No
Tremors	No	No
Convulsion	No	No
Skin	Normal	Normal
Body weight	Increased	Increased
Food consumption	Normal	Normal
Water consumption	Normal	Normal
Mortality	No	No

Table 2: Effect of *Ricinodendron heudelotii* ethanol seed extract on hepatic function of Wistar albino rats

Groups	AST (U L^{-1})	ALT (U L^{-1})	ALP (U L^{-1})	TP (g L^{-1})	ALB (g L^{-1})	TB (µmol L^{-1})	CB (µmol L^{-1})
1	193.00±8.19^{ab}	48.67±12.58^{a}	66.00±19.00^{a}	83.67±4.16^{a}	37.33±0.58^{a}	20.93±2.80^{a}	12.20±1.20^{ab}
2	95.67±2.89^{ab}	39.00±4.00^{a}	62.67±11.06^{a}	87.33±2.52^{ab}	43.67±0.58^{b}	16.07±1.09^{a}	8.90±0.69^{a}
3	106.00±13.12^{ab}	48.00±7.55^{a}	61.67±11.93^{a}	89.67±2.52^{abc}	40.00±2.00^{ab}	19.13±2.80^{a}	12.60±1.83^{ab}
4	90.67±2.89^{a}	47.33±11.50^{a}	60.33±18.93^{a}	93.33±1.53^{bc}	38.67±1.53^{a}	18.57±8.04^{a}	10.53±2.55^{ab}
5	92.33±20.75^{ab}	45.00±17.69^{a}	63.33±1.16^{a}	95.00±2.00^{c}	43.00±1.00^{b}	24.07±1.91^{a}	13.80±1.39^{b}
6	125.33±5.03^{b}	41.67±1.53^{a}	64.33±21.01^{a}	95.67±1.16^{c}	43.00±2.00^{b}	24.67±1.16^{a}	14.20±0.69^{b}

Values are expressed as Mean±Standard deviation, values with different superscripts show significant difference at 0.05 level, Values with the same super scripts shows no significant difference at the same level, ALT: Alanine Aminotransferase, AST: Aspartate aminotransferase, ALP: Alkaline phosphatase, TP: Total protein, TB: Total bilirubin, ALB: Albumin and CB: Conjugated bilirubin

Table 3: Effect of *Ricinodendron heudelotii* ethanol seed extract on the Blood urea nitrogen and creatinine of Wistar albino rats

Groups	Blood Urea Nitrogen (mmol L^{-1})	Creatinine (µmol L^{-1})
1	5.10±0.56^{a}	134.67±9.50^{a}
2	10.73±0.25^{b}	152.00±24.00^{a}
3	5.47±1.20^{a}	136.67±7.00^{a}
4	4.93±0.91^{a}	130.00±1.53^{a}
5	4.10±0.70^{a}	118.00±7.55^{a}
6	4.00±1.55^{a}	112.33±23.63^{a}

Values are expressed as Mean±Standard deviation, values with different superscripts show significant difference at 0.05 level, values with the same super scripts shows no significant difference at the same level

Table 4: Effect of *Ricinodendron heudelotii* ethanol seed extract on nephrotic function of Wistar albino rats

Groups	Na^{+} (mmol L^{-1})	K^{+} (mmol L^{-1})	HCO_3^{-} (mmol L^{-1})	Cl^{-} (mmol L^{-1})
1	113.00±2.00^{ab}	6.10±0.27^{ab}	24.67±3.06^{a}	33.67±2.52^{a}
2	111.67±3.06^{ab}	7.83±1.77^{bc}	26.67±1.16^{a}	31.00±1.00^{a}
3	103.00±6.00^{a}	4.87±1.12^{a}	29.33±1.16^{a}	50.67±18.50^{a}
4	109.00±2.00^{ab}	5.40±0.30^{ab}	26.00±3.46^{a}	35.00±2.65^{a}
5	111.67±6.51^{ab}	9.43±0.50^{c}	29.33±1.16^{a}	43.33±9.50^{a}
6	130.33±19.50^{b}	12.40±1.28^{d}	25.33±1.16^{a}	33.00±2.00^{a}

Values are expressed as Mean±Standard deviation, values with different superscripts show significant difference at 0.05 level, values with the same super scripts shows no significant difference at the same level

reversal of increased serum level maybe due to the prevention of leakage of intracellular enzymes by its stabilizing activity. This is in agreement with the commonly accepted view that serums levels of transaminases return to normal with healing of hepatic parenchyma and the regeneration of hepatocytes[18]. Also, this study is in accordance with the findings showing a decreased activity of AST, ALT, ALP and increased content of TP and albumin levels in CCl_4 induced hepatotoxicity when treated with aqueous extract of *Mangifera indica* stem bark[18]. Based on the results obtained it can be inferred that the seed extract of *Ricinodendron heudelotii* has some protective effect on the liver as seen by the reduction in the level of the hepatic enzymes, which also supports that *Gongronema latifolium* and *Piper guineense* leaf extracts have some protective effect on the liver evident by reduction in serum liver enzymes[19].

A decrease in blood urea concentration was observed in all experimental groups when compared with the control group as shown in Table 3. This agrees with the findings in previous study[20] which revealed reduction in blood urea concentration in normal doses when compared with the control group while in low doses, it increased. The blood creatinine showed no significant difference at $p \leq 0.05$, however, a decreasing variation was observed in the groups treated with *Ricinodendron heudelotii* ethanol seed extract. The result of this study supported the renal protective effect of therapy of Hydroalcoholic Polyherbal Formulation (HAF) showing a maximum decrease in Blood Urea Nitrogen (BUN) and serum creatinine when administered with HAF[16].

Electrolytes imbalance is a common finding in complications of liver and kidney damage. The blood electrolytes concentration as seen in Table 4 showed results for sodium (Na), potassium (K), chloride (Cl^{-}) and bicarbonate (HCO_{3-}). Chloride and Bicarbonate showed no significant difference at $p \leq 0.05$, when compared to the control groups. There were variations in group 4, 5 and 6, with group 5 having the highest level of bicarbonate and chloride ion. Also Sodium showed no significant difference at $p \leq 0.05$ confidence level in all the groups when compared with the normal control. It was observed that as the concentration of the ethanol seed extract of *Ricinodendron heudelotii* increased, the level of sodium and potassium also increased. Potassium showed an

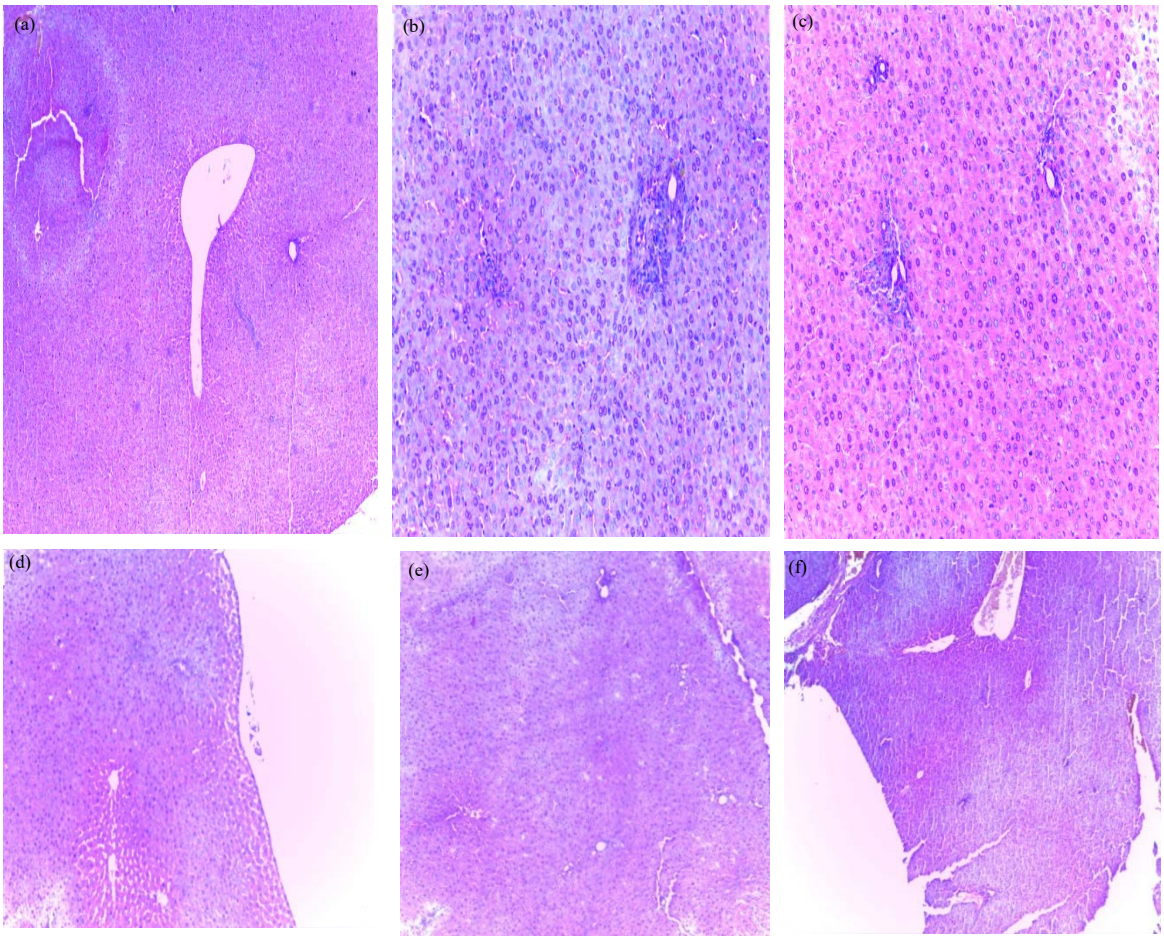

Fig. 1(a-f): Photomicrograph of hepatic cells of experimental Wistar albino rats, (a) Central vein, portal tracts, hepatocytes and sinusoids with no histological change (Group 1), (b) Periportal inflammation (Group 2), (c) Obvious distorted cell with periportal inflammation (Group 3), (d) Sinusoidal dilatation (Group 4), (e) No obvious histological change with portal tracts and hepatocytes (Group 5) and (f) No obvious histologic change with dilated vein and hepatocytes (Group 6) H and E 400X

increasing significant difference in group 5 and 6 when compared with the normal control at $p<0.05$ confidence level. Hyperkalemia or excess potassium in the blood, occurs in cases of renal failure because the kidneys lose the ability to excrete the mineral. This result supported the findings that oral administration of the *Cassia occidentalis* L. extract at a daily dose of 30 mg kg^{-1} for three weeks caused significant increase in serum potassium concentration compared with control[21].

The histological examination of the hepatic and renal cells of experimental animals as shown in Fig. 1a-f and 2a-f, respectively revealed no obvious histological changes in the hepatic and renal cells in groups 1, 3, 4, 5 and 6 which are the control group, standard drug group and the groups administered the seed extracts at 400, 600 and 800 mg kg^{-1} b.wt., respectively. However, a distortion of the general integrity of the cells was observed in the hepatic cells of group 2 experimental animals. This result implies a restoration of the distorted integrity of the hepatic and renal cells of the experimental animals on administration of the seed extract of *Ricinodendron heudelotii* and this is in agreement with the findings that the normal structure of kidney similar to control group without any tissue degeneration, inflammation, necrosis and tubular dilation was observed on administration of doses of *Nigella sativa*[20].

The results obtained from this study implies that the seed extract of *Ricinodendron heudelotii* has protective potency against acetaminophen-induced toxicity on the hepatic and nephrotic cells, however, its amelioration were seen to be concentration dependent.

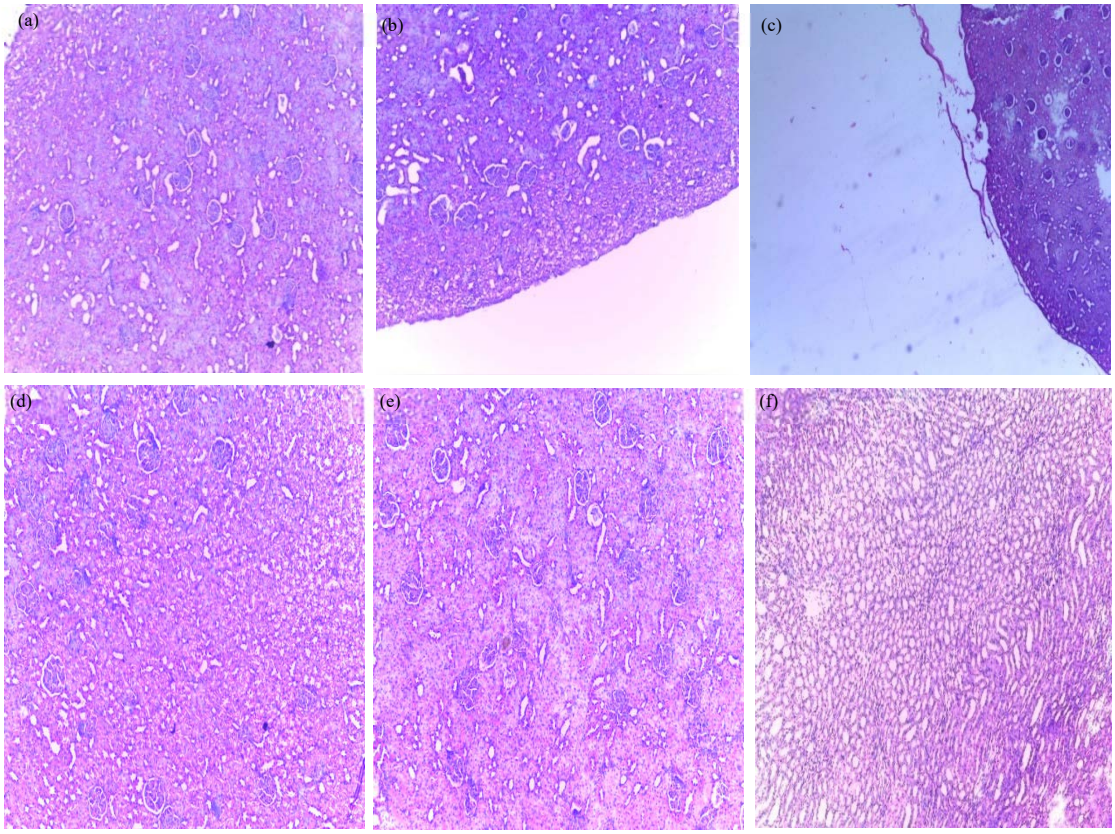

Fig. 2(a-f): Photomicrograph of nephrotic of experimental Wistar albino rats, (a) Renal tubules with no histological change (Group 1), (b) Degenerating changes in some renal tubules (Group 2), (c) Distorted cells and histologic changes (Group 3), (d) Histologic changes of the renal tubules (Group 4), (e) No obvious histological change (Group 5) and (f) No obvious histologic change (Group 6)

CONCLUSION

The use of an overdose of acetaminophen caused toxicity in the nephrotic and hepatic cells of Wistar albino rats, hence leading to the damage of the cells. The ethanol seed extract of *Ricinodendron heudelotii* had no toxic effect in the rats, but had an ameliorative/protective effect on the nephrotic and hepatic cells of the rats against the acetaminophen-induced toxicity; hence, the seed extract can be used therapeutically.

SIGNIFICANCE STATEMENT

This study discovered the ameliorative potency of the ethanol seed extract of *Ricinodendron heudelotii*, hence, its protective capability against acetaminophen-induced hepatic and nephrotoxicity. This study will enhance the use of the seed extract of *Ricinodendron heudelotii* for various other therapeutic uses.

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