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Research Article

Modulation of Cadmium Induced Haematological and Renal Damages by Ethanol Leaf Extract of *Pterocarpus mildbraedii* in Male Wistar Rats

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ABSTRACT

The leaf of *Pterocarpus mildbraedii* is a popular vegetable in Nigerian ethnomedicine, where it is applied in the management of various disorders. This study was carried out to investigate the ameliorative potential of ethanol leaf extract of *P. mildbreadii* on cadmium induced haematological and renal damages in male Wistar rats. The leaf extract and the toxicant were administered orally to four groups of rats at doses of 400 mg/kg and 10 mg/kg body weight respectively for 14 days. Indices of renal function (serum urea, creatinine, sodium and potassium) and haematological parameters were analyzed using standard methods. Cadmium caused a significant increase ($p < 0.05$) in the concentrations of urea, creatinine, sodium and potassium. It also caused a significant ($p < 0.05$) decrease in haematological parameters such as Hb, HCT, RBC, MCV, MCHC, lymphocytes and platelets while the levels of WBC, neutrophils and monocytes increased compared to control. Ethanol leaf extract of *P. mildbreadii* reversed the cadmium induced alterations in haematological and renal indices. Histological observation of the kidney tissue revealed abnormal histological architecture in animals intoxicated with cadmium. Animals treated with leaf extract of *P. mildbreadii* did not show any damage in histology of the kidney tissue. These results suggest the ameliorative potentials of leaf extract of *P. mildbreadii* on haematological and renal disorders in the rats.

Keywords: *Cadmium, haematology, renal damage, Pterocarpus mildbraedii leaves.*

INTRODUCTION

Cadmium is a noxious environmental pollutant with hazardous effects on plants, animals and man (Ozyigit and Genc, 2020; Shaari *et al.*, 2022). It is present in the earth's crust to the extent of 0.1-0.5 ppm, usually in association with the ores of copper, zinc and lead (ATSDR, 2012). It has been beneficially utilized in various industrial processes including the production of plastics, alloys, batteries, pigments and electroplating (Kumar *et al.*, 2021). Environmental accumulation of cadmium has been attributed to its multiple industrial applications (Renugadevi and Prabu, 2009) as well as its release from cigarette smoke, incineration of waste and combustion of fossil fuel (Nair *et al.*, 2013). Generally, inhalation and ingestion of contaminated water or foods represent the major routes of exposure in man (Albir, 2013).

Within the blood circulatory system, cadmium binds to erythrocyte membrane (Kanter *et al.*, 2005), albumin and glutathione (Orr and Bridges, 2017) prior to delivery in the liver where it upregulates the expression of metallothionein (Hambach *et al.*, 2013). Subsequently, cadmium binds to metallothionein to form cadmium-metallothionein complex which is released back into circulation and transported to the kidneys to undergo filtration, tubular reabsorption, degradation and deposition of the freed cadmium ions (Klaassen and Liu, 1997). Accumulation of cadmium in the kidney tubules instigates nephrotoxicity through a free radical mechanism (Nair *et al.*, 2013; Kumar *et al.*, 2019). Similarly, cadmium

induces oxidative damage to the red blood cells and depresses haematological indices such as haemoglobin concentration, packed cell volume and red blood cell count (Ashour, 2014; Hounkpatin *et al*., 2013; Olajide *et al*., 2020). Because cadmium toxicity is mediated by free radicals, it was proposed that natural and synthetic antioxidants would modulate the deleterious effects of this element in man (Kumar *et al*., 2019).

Pterocarpus mildbraedii is one of many plant species available in Nigeria whose leaves are used for nutritional and/or medicinal purposes (Hamza *et al*., 2018). In addition to being used as vegetable, the leaves of this plant are also applied traditionally in the treatment of ailments including pain, fever and microbial infections (Usunomena and Chinwe, 2016). The leaves are rich in protein, mineral elements and vitamins (Akinyeye *et al*., 2010). Alkaloids, flavonoids and tannins have been identified in these leaves (Uchegbu *et al*., 2015; Usunomena and Chinwe, 2016). The leaf extract of *Pterocarpus mildbraedii* has also been demonstrated to exhibit antioxidant (Usunomena and Chinwe, 2016), renoprotective (Urom and Usin, 2023) and haematoprotective properties (Victor and Nnonyelum, 2017). *Pterocarpus mildbraedii* has also been reported to ameliorate cadmium induced hepatotoxicity, oxidative stress and dyslipidaemia in albino rats (Akpanyung *et al*., 2022).

In line with ongoing efforts to further explore the pharmacological benefits of *Pterocarpus mildbraedii* leaves, this study assessed the ameliorative potential of ethanol leaf extract against Cadmium induced haemato-renal toxicity in male Wistar rats.

MATERIALS AND METHODS

Pterocarpus mildbraedii leaves

Fresh leaves of *Pterocarpus mildbreadii* were sourced from a vegetable market in Onna local government area, Akwa Ibom, Nigeria. The leaves were authenticated by a taxonomist in the Department of botany and ecological studies, university of Uyo. A voucher number UUPH 34 was assigned to the leaf sample and deposited in the university herbarium.

Extraction of *Pterocarpus mildbraedii* leaves

Ethanol extract of *Pterocarpus mildbreadii* leaves was prepared based on the previously established protocol (Akpanyung *et al.,* 2020). The crude extract was preserved in a freezer at -4^{0}C.

Experimental animals

Twenty-four (24) male Wistar rats weighing 180-200 g, were used in this study. They were obtained from the animal house of the faculty of basic medical sciences, university of Uyo, where the study was carried out. The animals were housed in standard aluminum cages and maintained in compliance with the guidelines for the care and use of laboratory animals (NRC, 2011). The animals were allowed free access to commercially formulated pelletized diet (Grand Cereals Ltd, Jos, Nigeria) and water. The rats were allowed to acclimatize to the laboratory environment for a period of 14 days before commencement of the study.

Chemicals

Cadmium chloride used in the study was of analytical grade obtained from BDH Ltd, Poole, England. Other reagents used in this study were also of analytical grade.

Preparation of the cadmium chloride

Cadmium chloride (20 mg) was dissolved in 10 mL of distilled water to give a stock solution of 2 mg/mL. The stock was prepared daily and appropriate dosage was administered to each animal from the stock solution.

Experimental design

The twenty-four rats were randomly separated into four groups (1 - 4) with 6 animals in each group. They were treated according to the under listed protocol:

Group 1: was the normal control, given feed and water for 14 days

Group 2: received 10 mg/kg bw cadmium chloride daily for 14 days.

Group 3: was treated with 400 mg/kg bw of extract daily for 14 days.

Group 4: was co-administered 10 mg/kg bw of cadmium chloride and 400 mg/kg bw of extract for 14 days.

The extract of *Pterocarpus mildbreadii* and cadmium chloride were administered orally with the help of an oral cannula.

Animal sacrifice and collection of blood samples

After the last day of treatment, the rats were fasted overnight and euthanized under chloroform anaesthesia. Blood samples were collected by cardiac puncture. A portion (2 ml) of the blood sample from each animal was put into EDTA bottles and used for haematological analysis. Another portion (3 ml) of the blood sample was transferred into plain sample bottles and allowed to clot (60 minutes). Serum was obtained by centrifugation at 3000 rpm for 15 minutes. The serum was separated into plain bottles and preserved at -4^{0}C for further use to assay for kidney function parameters. The kidneys were also harvested and preserved in 10% phosphate buffered formalin for histological studies.

Determination haematological indices and parameters of kidney function

Automated analyzer (Sysmex KX-21N, Japan) was used for the determination of complete blood count based on the manufacturer's guidelines. Serum urea, creatinine, sodium, potassium, chloride and bicarbonate ions were assayed

with reagent kits supplied by Fortress Diagnostics, Antrim, UK.

Histological studies

The fixed kidney samples were sectioned and microscopically examined after staining with haematoxylin and eosin in accordance with the procedure of Bancroft and Gamble (2018). Photomicrographs were prepared using the light microscope (Leica DM750 with ICC50W Camera).

Statistical analysis

Results are presented as mean ± standard error of mean (SEM). Statistical analysis was conducted using statistical package for social sciences (SPSS, Version 25). Analysis of data was carried out using the one-way ANOVA and least significant difference (LSD) post hoc multiple comparison test. Statistical significance was considered at $p < 0.05$.

RESULTS

Effect of the extract on some parameters of kidney function.

The concentrations of some of the parameters of kidney function in Wistar rats intoxicated with cadmium chloride and treated with *Pterocarpus mildbreadii* is presented in Table 1. It was observed that animals treated with $CdCl_2$ exhibited a significant increase ($p < 0.05$) in serum levels of urea, creatinine, sodium and potassium when compared to the control group. Animals treated with extract of *Pterocarpus mildbreadii* showed a decrease towards normal in the serum concentrations of urea, creatinine, sodium and potassium when compared to Group 2.

Effects of ethanol leaf extract of *Pterocarpus mildbraedii* on haematological indices.

The effect of ethanol leaf extract of *Pterocarpus mildbraedii* on some haematological indices in male Wistar rats is shown in Table 2. Treatment with cadmium chloride resulted in a significant decrease ($p < 0.05$) in the concentrations of Hb, HCT, RBC, MCV, MCHC, Lymphocytes and platelets while the levels of WBC, neutrophils and monocytes increased compared to control. The leaf extract of *Pterocarpus mildbreadii* alone or concomitantly with cadmium chloride significantly ($p < 0.05$) improved some of these parameters.

Histopathology of the kidney tissue

The photomicrographs obtained from histological evaluation of the kidney tissues of the experimental animals are presented in Figure 1. Normal histological features of the kidney tissue were observed in the control animals (KI). Photomicrograph K2 showed histological features of kidney of rat treated with $CdCl_2$ (Group II) showing degenerating renal parenchymal (#) consisting of fibrin network with trapped inflammatory infiltrates (arrow) and degenerating renal tubules (*). Photomicrograph K3 revealed normal histological features of kidney of rat treated with the leaf extract of *Pterocarpus mildbreadii* (Group III). K4 showed the histology of kidney of rat treated concomitantly with cadmium chloride and *Pterocarpus mildbreadii.* Indicating no damage in the renal tissue.

Table 1. Some Parameters of Kidney Function in Wistar Rats Treated with Cadmium Chloride and *Pterocarpus Mildbreadii* Leaf Extract.

Groups	Urea (mg/dL)	Creatinine (mg/dL)	Potassium (mmol/L)	Sodium (mmol/L)
Group 1 (Control)	11.62 ± 0.71	0.52 ± 0.06	5.01 ± 0.52	148.32 ± 1.80
Group 2 ($CdCl_2$)	17.27 ± 1.00[a]	0.96 ± 0.05[a]	11.13± 0.44[a]	151.55 ± 1.30
Group 3 (PM)	13.21 ± 0.74[b]	0.48 ± 0.06[b]	6.24 ± 0.30[b]	144.11 ± 1.15[b]
Group 4 (PM and $CdCl_2$)	12.15 ± 0.88[b]	0.61 ± 0.01[b]	6.32 ± 0.44[b]	146.16 ± 1.69[b]

Values presented as mean ± SEM. The mean was considered statistically significant at $p < 0.05$ with "a" when compared to Group 1; "b" when compared to Group 2. Where, $CdCl_2$ = Cadmium Chloride (10 mg/kg); PM = *Pterocarpus mildbreadii* (400 mg/kg)

Table 2. The Effect of Ethanol Leaf Extract of *Pterocarpus milbreadii* on Some Haematological Parameters in Male Rats Treated with Cadmium Chloride

Groups	HB (g/dL)	HCT (%)	RBC ($x10^{12}$/L)	MCV (fL)	MCH (pg)	MCHC (g/dl)	WBC ($x10^9$/L)	NEUT (10^3/µL)	LYM (10^3/µL)	MONO (10^3/µL)	PLATELET ($x10^9$/L)
Group 1 (Control)	14.70 ± 0.58	48.68 ± 1.64	7.58 ± 0.31	64.21 ± 0.62	19.37 ± 0.17	31.00 ± 0.26	9.32 ± 0.97	6.98 ± 0.66	85.48 ± 0.83	7.54 ± 0.29	1132.50 ± 30.29
Group 2 ($CdCl_2$)	10.62 ± 1.55^{acd}	37.13 ± 0.97^{acd}	6.15 ± 0.25^{a}	60.37 ± 1.65^{ac}	17.20 ± 0.65	28.60 ± 1.62^{acd}	13.46 ± 0.81^{a}	13.50 ± 0.71^{a}	71.66 ± 1.49^{a}	14.44 ± 0.72^{a}	961.40 ± 14.25^{a}
Group 3 (PM)	15.15 ± 0.57^{b}	44.48 ± 1.77^{ab}	7.03 ± 0.26	63.22 ± 0.79^{b}	21.55 ± 0.31^{abd}	34.06 ± 0.44^{abd}	13.30 ± 0.91^{a}	7.50 ± 0.66^{b}	81.30 ± 1.01^{ab}	10.78 ± 0.69^{ab}	1220.17 ± 17.96^{ab}
Group 4 (PM and $CdCl_2$)	14.04 ± 0.64^{b}	44.36 ± 1.65^{ab}	7.09 ± 0.26	62.56 ± 0.71	19.80 ± 0.32^{b}	31.65 ± 0.24^{abc}	13.60 ± 0.62^{a}	7.50 ± 0.70^{b}	83.58 ± 0.98^{b}	11.76 ± 0.74	1074.20 ± 14.40^{bc}

Values presented as mean ± SEM. The mean was considered statistically significant at $p < 0.05$ with "a" when compared to Group 1; "b" when compared to Group 2; "c" when compared to Group 3; "d" when compared to Group 4. Where CdCl2 = Cadmium chloride (10 mg/kg); PM = *Pterocarpus mildbraedii* (400 mg/kg).

DISCUSSION

In the present study, the beneficial effects of ethanol leaf extract of *Pterocarpus mildbraedii* against cadmium induced haemato-renal toxicity was investigated in male Wistar rats. Cadmium has been reported to be harmful to the haematopoietic system (Sugiharto *et al.*, 2020). Cadmium induced renal toxicity has also been documented (Saturag, 2018). These are in contradistinction, to the haematological (Omololu *et al.*, 2023) and nephroprotective (Urom and Usin, 2023) properties of *Pterocarpus mildbraedii* leaves. These observations provided impetus for the current investigation.

Heavy metal induced alteration in the haemogram is one of the most prominent sign of toxicity (Vinodini *et al.*, 2019). In the present study, cadmium chloride caused a significant reduction in the concentration of haemoglobin, RBC, PCV, MCV and MCHC. This is diagnostic of microcytic hypochromic anemia (Yuan *et al.*, 2014) and is in line with the findings of other authors (Sugiharto *et al.*, 2020; Olajide *et al.*, 2020; Wakeel *et al.*, 2020; Rani and Kumar, 2021). Factors germane to the induction of anemia include interference of this metal with the synthesis of erythropoietin (Mishra and Tandon, 2012) as well as accelerated erythrocyte destruction due to altered membrane permeability, increased mechanical fragility and/or malfunction in the metabolism of iron (Yuan *et al.*, 2014). It has also been noted that the preferential accumulation of cadmium in the liver, kidney and the spleen suppresses the activity of these haematopoietic organs (Gill and Epple., 1993). Interestingly, the ethanol extract of *Pterocarpus mildbraedii* reversed the deleterious effects of cadmium when administered individually and concomitantly with cadmium. This indicates that the extract contains bioactive compounds that enhance erythropoiesis. The bioactive constituents in the leaves of Pterocarpus include alkaloids, flavonoids and tannins (Usunomena and Chinwe, 2016). Flavonoids and tannins have been reported to exert a positive influence on haematopoiesis (Muriithi *et al.*, 2015).

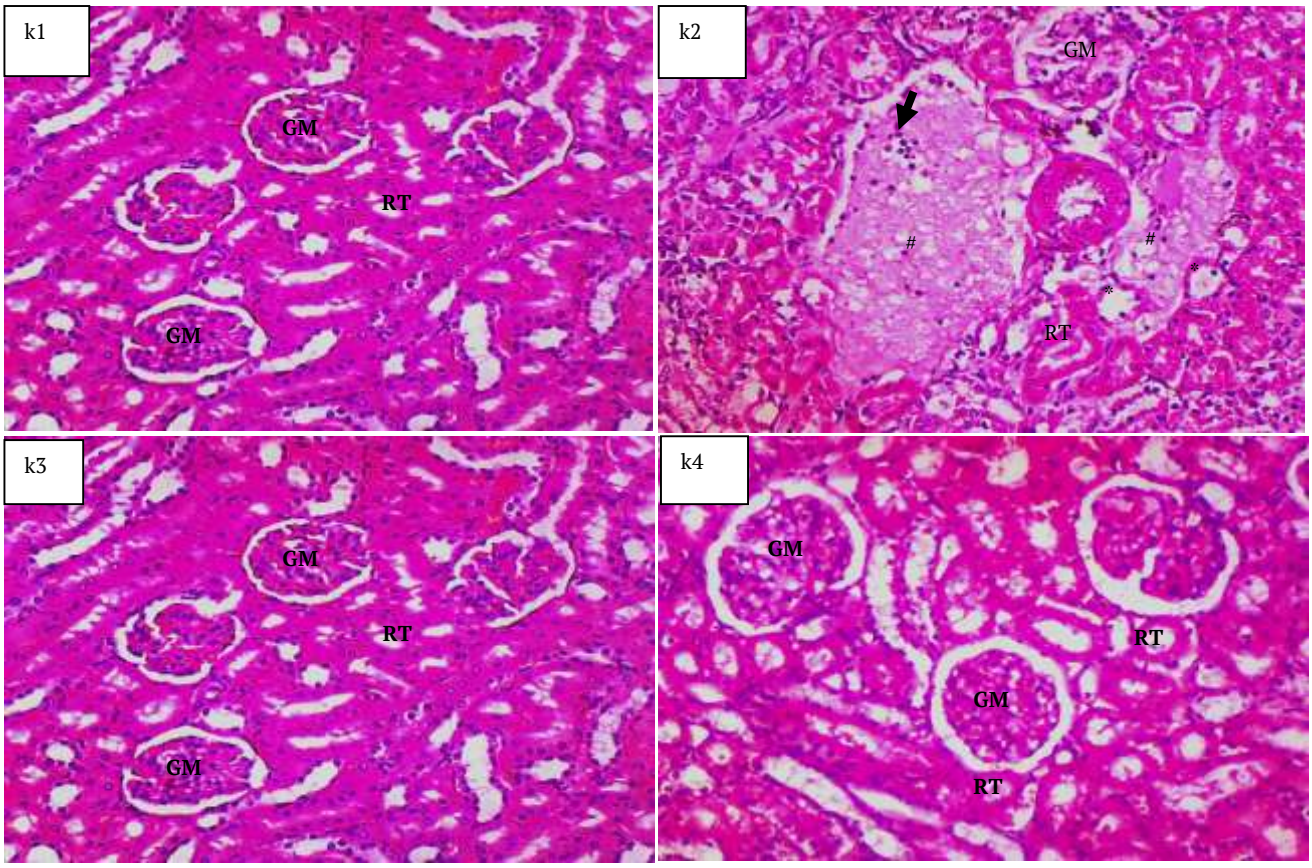

Figure 1. Photomicrograph of the Kidney of Control (k1) with Normal Glomeruli (GM) and Renal Tubule (RT) showing no Evidence of Pathologic Lesion.

The cytoarchitecture of the kidney of cadmium chloride intoxicated group (k2) was evidenced with degenerating renal parenchymal (#) consisting of fibrin network with trapped inflammatory infiltrates (arrow), and degenerating renal tubules (*); The administration of *Pterocarpus milbreadii* had no deleterious effect on the cytoachitecture of the kidney as normal glomeruli (GM) and renal tubule (RT) was observed (k3); The administration of cadmium chloride concomitantly with *Pterocarpus mildbreadii* leaf extract showed no evidence of pathologic lesion in the kidney tissues as presented in k4.

The possibility of utilizing the leaves of *Pterocarpus mildbraedii* in the management of anaemia was earlier proposed by Victor and Nnonyelum (2017).

The white blood cells (leucocytes) are regulators of the immune system in animals. Hence, the observed increase in white blood cell count in this study could be regarded as a normal protective response of the immune system against invasion by foreign substances (Adebayo *et al.*, 2010). Neutrophilia, lymphopenia and monocytosis appear to be characteristic of cadmium induced toxicity which has also been reported elsewhere (El-Boshy *et al.*, 2015; Chatterjee *et al.*, 2016). Essentially, the tendency of the ethanol leaf extract of *Pterocarpus mildbraedii* to reverse cadmium induced alteration in the leukogram indicates its immunomodulatory potentials (Adegbite *et al.*, 2015; Otuechere and Farombi, 2020). The thrombocytes (platelets) are majorly involved in the process of blood coagulation. The significant decrease in platelet count induced by cadmium chloride would imply that the metal is inhibitory to thrombopoietin while the extract enhanced platelet count as a consequence of its positive impact on this hormone (Li *et al.*, 1999).

Elevation in the serum concentrations of urea and creatinine as a consequence of intoxication with cadmium chloride, as observed in this study, indicate renal impairment (Burtis *et al.*, 2012). This is in line with the report of other authors (Ashour, 2014; Emmanuel *et al.*, 2017; Dwivedi, 2021). There are indications that cadmium induced renotoxicity is mediated by free radicals (Genchi *et al.*, 2020; Mafulul *et al.*, 2020; Yan and Allen, 2021). Hence, the ability of ethanol leaf extract of *Pterocarpus mildbraedii* to normalize the raised concentrations of urea and creatinine could be attributed to its antioxidant properties as earlier postulated (Usunomena and Chinwe, 2016; Fajobi *et al.*, 2020; Urom and Usin, 2023). The kidneys also play a crucial role in regulating serum electrolyte balance (Ajani *et al.*, 2011). Therefore, fluctuations in serum electrolyte concentrations serve as markers of renal dysfunction

(Malgwi *et al*., 2014). In the present study, administration of cadmium chloride induced a significant increase in the serum concentrations of sodium and potassium ions which could be attributed to renal dysfunction (Onu *et al*., 2013). The leaf extract of *Pterocarpus mildbraedii* conferred renoprotection by restoring the levels of sodium and potassium ions to normal. Similar observation was made elsewhere (Ezekwesili *et al*., 2016).

The cadmium induced alterations in some histological features of the kidney tissue observed in this study are in agreement with the report of other authors (Dkil *et al*., 2020; Ilesanmi and Adeogun, 2022). Expectedly, ethanol leaf extract of *Pterocarpus mildbraedii* restored normal histological architecture to the kidneys as earlier observed by Urom and Usin (2023). In reference to the fact that cadmium induced renal damage proceeds by the free radical mechanism, it is considered safe to attribute the ameliorative impact of the extract to its antioxidant potentials as previously reported (Akpanyung *et al*., 2022).

CONCLUSION

The present study has adduced evidence that the administration of ethanol leaf extract of *Pterocarpus mildbraedii* ameliorated haematological parameters and renal indices in animals intoxicated with cadmium. Therefore, the leaf extract could be refined and applied in the management of haematological and renal disorders.

AUTHORS' CONTRIBUTIONS

EOA and UEB conceptualize the study; EOA, DEE and UEB carried out the methodology; validation was done by EOA and BOO; formal analysis was carried out by UEB; investigation was done by EOA and BOO; AEO, DEE, UEB and BOO provided the resources; data curation was done by EOA and UEB; writing of original draft preparation was done by DEE.; UEB, BOO and EOA. Participated in writing - review and editing; supervision was done by EOA.; project administration was carried out by UEB. All authors have read and agreed to the published version of the manuscript.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this paper.

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