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HISTOLOGICAL EVALUATION OF RENAL DAMAGE IN DIABETIC WISTAR RATS TREATED WITH ETHANOL LEAF EXTRACT OF *Pterocarpus Mildbraedii* (WHITE PADOUK)

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ABSTRACT

Chronic hyperglycemia significantly contributes to diabetes-related kidney damage. Since the kidneys play a crucial role in drug metabolism and excretion, renal recovery in diabetic individuals may be impaired. This study evaluated the renal health of diabetic Wistar rats after oral administration of the ethanolic leaf extract of *Pterocarpus mildbraedii* (ELEPM).Thirty adult Wistar rats were divided into six groups (n = 5). Diabetes was induced in Groups II–VI using 120 mg/kg alloxan intraperitoneally. Group I served as the non-diabetic control; Group II was diabetic but untreated. Groups III, IV, and V received 100 mg/kg, 200 mg/kg, and 400 mg/kg of ELEPM, respectively, while Group VI received 2.5 mg/kg of metformin. Treatments lasted 21 days. Body weights were recorded at the beginning and end, after which animals were sacrificed and blood samples collected. Histological and biochemical analyses were conducted using standard methods. All groups except the untreated diabetic group showed weight gain. ELEPM at 400 mg/kg demonstrated the most pronounced antihyperglycemic effect among the extract doses, though still significantly ($p<0.05$) less effective than metformin. Serum urea and creatinine levels were significantly higher ($p<0.05$) in the untreated diabetic group compared to the ELEPM-treated groups. Histological assessment of rats given 400 mg/kg ELEPM revealed moderate renal regeneration with mild fatty changes and tubular distortion. Oral administration of ELEPM, particularly at 400 mg/kg, shows promise in mitigating hyperglycemia and renal damage in diabetic conditions, suggesting potential as a supportive therapy for diabetic nephropathy.

Keywords: *Pterocarpus mildbraedii*, Kidney, Diabetes, Metformin, Urea

INTRODUCTION

The human kidney plays a vital role in maintaining physiological homeostasis by eliminating metabolic waste products through urine (Mescher, 2016). Beyond waste excretion, it regulates several critical body functions, including acid-base balance, electrolyte concentrations, extracellular fluid volume, and blood pressure (Glodny *et al*., 2009). When kidney function deteriorates severely, the condition progresses to end-stage renal disease (ESRD), a major global health concern. Diabetic kidney disease (DKD) is the leading cause of ESRD, significantly contributing to its worldwide burden (Sukkar *et al*., 2020; Wen *et al*., 2022). It is estimated that approximately 30–40% of individuals with diabetes develop DKD, a troubling statistic given that global diabetes prevalence is projected to rise from 537 million to 783 million by 2025 (Parkov and Miyamoto, 2023).

Conventional treatments for ESRD resulting from diabetes, such as renin-angiotensin system blockers and sodium-glucose co-transporter 2 (SGLT-2) inhibitors, have proven effective in slowing disease progression but do not offer a cure (Ortiz *et al*., 2023). As a result, many diabetic patients eventually require dialysis or kidney transplantation. These interventions not only diminish patients' quality of life but also place considerable strain on healthcare systems. This underscores the pressing need to explore alternative, cost-effective, and accessible therapeutic options, particularly from natural sources. The World Health Organization (WHO, 2020) reports that a significant proportion of populations in developing countries depend on traditional herbal medicine, largely due to its affordability, availability, and relative safety (Smith, 2005).

One such promising natural remedy is *Pterocarpus mildbraedii*, a plant from the Leguminosae family native to several African countries. Its tender leaves are widely consumed in South-Eastern Nigeria for culinary purposes (Adegbite and Ezekwesili, 2017). Beyond its nutritional value, *P. mildbraedii* has demonstrated notable biological activities in various studies, including anti-inflammatory (Fajobi *et al*., 2020) and hepatoprotective properties (Akinwunmi *et al*., 2022). Phytochemical screening of the plant's leaves revealed a rich presence of bioactive compounds such as alkaloids, flavonoids, tannins, steroids, glycosides, terpenoids, phlobatannins, and saponins (Abare-Jen *et al*., 2020). Preliminary findings on its potential to mitigate drug-induced kidney damage suggest that *P. mildbraedii* may offer therapeutic benefits in managing diabetic kidney disease, thereby highlighting the relevance and importance of further research into its nephroprotective effects.

MATERIALS AND METHODS

Animal

A total of twenty-five (25) adult male Wistar rats, each weighing between 130 and 170 grams, were used in this study. The rats were obtained from an animal farm in Nnewi and housed under standard laboratory conditions. They were allowed to acclimate for two weeks prior to the start of the experiment. Throughout the study, the rats were housed in well-ventilated cages with appropriate bedding and had unrestricted access to food and water.

Collection and Preparation of Plant Extract

Fresh leaves of *Pterocarpus mildbraedii* were carefully harvested from a natural vegetation site in Uli, located within

the Ihiala Local Government Area of Anambra State, Nigeria. Upon collection, the leaves were thoroughly rinsed with clean water to remove dust and debris, then air-dried under shade to preserve their phytochemical integrity. Once fully dried, the leaves were finely ground using a traditional local grinder to obtain a uniform powder. A total of 500 grams of the powdered leaf material was macerated in 2000 mL of 98% ethanol (JHD, England) for 48 hours to facilitate the extraction of bioactive compounds. The resulting mixture was initially filtered using a clean porcelain cloth to remove coarse particles, followed by a secondary filtration with Whatman No. 1 filter paper to ensure clarity and purity of the extract. The filtered solution was then concentrated under reduced pressure using a rotary evaporator (Model TT-52, Techmel & Techmel, USA) to remove excess solvent. Further drying was carried out in a thermostat-controlled oven (Model DHG-9023A, PEC Medicals) until a semi-solid, gel-like extract was obtained. The final ethanol leaf extract of *Pterocarpus mildbraedii* (ELEPM) was stored at 4°C in a refrigerator until required for experimental use.

Diabetes Mellitus Induction

A stock solution of Alloxan monohydrate was prepared by dissolving 1 gram of the compound in 10 mL of distilled water, yielding a concentration of 100 mg/mL. Experimental induction of diabetes mellitus (hyperglycemia) was carried out by administering a single intraperitoneal injection of the Alloxan solution at a dose of 120 mg/kg body weight. Prior to induction, the animals were fasted for 12 hours to stabilize baseline blood glucose levels. Following Alloxan administration, fasting blood glucose levels were monitored using a glucometer. Rats exhibiting fasting blood glucose concentrations exceeding 120 mg/dL on three consecutive days were considered diabetic and subsequently selected for inclusion in the study, in accordance with the criteria described by Mostafavinia *et al*. (2016).

Animal Grouping

Thirty Twenty five adult Wistar rats were divided into five groups of five each. Groups II-V were induced with Type-1 diabetes, and the following medication was delivered. Group I: (Normal Control) Take 2 mL of distilled water orally.
Group II: Diabetic untreated rats
Group III: Received 100 mg/kg bw of *e*thanol leaf extract of *Pterocarpus mildbraedii* orally
Group IV: Received 200 mg/kg bw of *e*thanol leaf extract of *Pterocarpus mildbraedii* orally
Group V: Administered 400 mg/kg bw of *Pterocarpus mildbraedii* orally
Group VI: Administered 2.5 mg/kg bw of metformin orally

Measurement of Body Weight

The body weight of each rat in the experimental groups was determined with a Camry Emperos weighing scale. Weights were recorded using their corresponding group and label identifiers. Measurements were taken both before and after the experiment.

Sample Preparation

To perform kidney function testing, 2 mL of blood was placed in an EDTA tube and centrifuged at 4,000 rpm for 15 minutes. The resulting plasma was stored for biochemical analysis.

Serum Urea Determination

Ten (10) µL of sample was introduced into a tube containing 1000 µL of the working reagent. The contents of the tube were thoroughly mixed, incubated for 5 minutes at 37ºC (Kaplan and Teng, 1982). Blood urea concentration was determined with the aid of the formular below:

$$Urea\ conc\ \left(\frac{mg}{dl}\right) = \frac{A\ Sample}{\frac{Acal}{STD}} \times conc. \frac{cal}{STD\left(\frac{mg}{dl}\right)}$$

Serum Creatinine

Exactly 0.1 mL of sample was added to a tube containing 1.0 mL of reagent, and the contents were carefully mixed. After 30 seconds, the initial absorbances of the sample and standard were examined and the formula below was utilized to determine the serum creatine level (Bartels and Bohmer, 1972).

$$Creatinine\ conc.\left(\frac{mg}{dl}\right) = (\Delta A\ sample)/\Delta Asample \times standard\ conc.(mg/dl)$$

Histological Preparation and Analysis of Testes

The kidneys were fixed in 10% neutral buffered formalin for 48 hours before undergoing routine histological processing. This comprised dehydrating in a series of ethanol solutions, clarifying with xylene, and embedding in paraffin wax. A rotary microtome was used to cut 5 µm sections from paraffin-embedded tissues. The sections were placed on glass slides and stained with hematoxylin and eosin (H&E) to assess overall histoarchitecture. Microscopic images were acquired with a Motic digital camera, following the procedure described by Lotfi *et al*. (2013).

Statistical Analysis

Data generated were expressed as Mean ± Standard Deviation using SPSS (Ver. 23). The data were examined using one-way ANOVA. Mean differences were compared using the Tukey test. P-values of less than 0.05 were considered statistically significant.

RESULTS AND DISCUSSION

The body weight of diabetic rats administered ethanol leaf extract of *P. mildbreadii* is shown in Table 1, indicating a significant ($p<0.05$) weight increase in groups administered *P. mildbreadii* extract. A similar observation was made in the normal control group as well as the group administered the standard drug (metformin).

Table 1: Body Weight of Diabetic Wistar Rats Administered Ethanol Leaf Extract of *P. mildraedii*

Group	Treatment	Initial weight (g)	Final weight (g)	Weight change	p-value
Group I	2 mL of distilled H_2O	134.80±3.90	161.60±4.86	26.80±2.03	0.012
Group II	120 mg/kg Alloxan	151.80±4.07	131.80±3.14	20.00±1.43	0.041
Group III	Alloxan+100 mg/kg ELPM	153.00±4.16	133.60±4.16	19.40±3.20	0.040
Group IV	Alloxan+200 mg/kg ELPM	124.00±5.70	140.80±5.25	16.80±2.45	0.006
Group V	Alloxan+400 mg/kg ELPM	129.00±3.80	143.60±4.29	14.60±3.56	0.008
Group VI	2.5 mg/kg metformin	130.40±3.80	148.80±3.86	18.40±2.67	0.029

Results are expressed as Mean ± Standard deviation. *P-value* < 0.005 is significant

Blood glucose levels in diabetic rats treated with ethanol leaf extract of *P. mildbraedii* are presented in Table 2. In the diabetic untreated group, blood glucose levels measured on Days 0, 7, and 14 were not significantly different ($p > 0.05$) from the level recorded at Week 21. However, in rats treated with 100 mg/kg of ELEPM, a reduction in blood glucose was observed on Day 0, which was not significantly different ($p > 0.05$) from the values on Days 7 and 14, but was significantly lower ($p < 0.05$) than the level recorded on Day 21. Similar trends were observed in the groups administered 200 and 400 mg/kg of ELEPM.

Table 2: Blood Glucose Levels of Diabetic Wistar Rats Administered Ethanol Leaf Extract of *P. mildbreadii*

Group	Treatment	Day 0 (mg/dL)	Day 7(mg/dL)	Day 14(mg/dL)	Day 21(mg/dL)
Group I	2 mL of distilled H_2O	79.50 ± 1.94^{a}	79.00 ± 4.26^{a}	77.50 ± 4.35^{a}	81.00 ± 2.34^{a}
Group II	120 mg/kg Alloxan	368.25 ± 3.30^{f}	365.72 ± 3.20^{f}	395.00 ± 4.35^{f}	422.50 ± 3.45^{e}
Group III	Alloxan+100 mg/kg ELPM	350.00 ± 3.88^{e}	186.50 ± 4.44^{e}	133.75 ± 4.27^{e}	100.08 ± 1.84^{d}
Group IV	Alloxan+200 mg/kg ELPM	340.00 ± 3.94^{d}	178.50 ± 4.32^{d}	125.00 ± 4.27^{d}	97.00 ± 4.22^{c}
Group V	Alloxan+400 mg/kg ELPM	336.23 ± 2.98^{c}	95.50 ± 4.66^{c}	96.00 ± 2.94^{c}	86.25 ± 3.54^{b}
Group VI	2.5 mg/kg metformin	320.32 ± 4.93^{b}	94.00 ± 2.91^{b}	94.00 ± 2.73^{b}	80.21 ± 2.10^{a}

Results are expressed as Mean ± Standard deviation. *P-value* < 0.005 is significant

Table 3 shows the urea and creatinine concentrations in diabetic Wistar rats administered ELEPM, indicating that urea and creatinine concentrations were not significantly different ($p>0.05$) across all treatments.

Table 3: Urea and Creatinine Concentration in Diabetic Wistar Rats Administered *P. mildbreadii*

Group	Treatment	Urea (mmol/L)	Creatinine (µmol/L)
Group I	2 mL of distilled H_2O	34.23 ± 3.42^{a}	2.25 ± 0.01^{a}
Group II	120 mg/kg Alloxan	40.98 ± 2.89^{b}	5.36 ± 0.08^{b}
Group III	Alloxan+100 mg/kg ELPM	37.02 ± 4.81^{ab}	2.47 ± 0.12^{a}
Group IV	Alloxan+200 mg/kg ELPM	36.82 ± 5.01^{a}	2.30 ± 0.18^{a}
Group V	Alloxan+400 mg/kg ELPM	36.93 ± 3.39^{a}	2.35 ± 0.90^{a}
Group VI	2.5 mg/kg metformin	37.02 ± 4.65^{ab}	2.40 ± 1.20^{a}

Results are expressed as Mean ± Standard deviation. *P-value* < 0.005 is significant

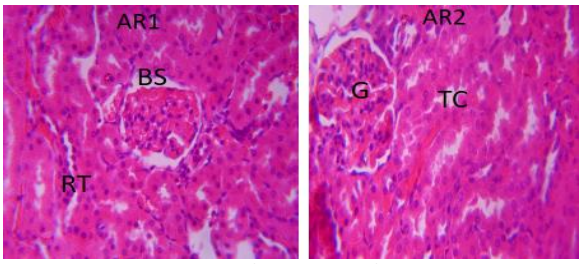


Plate I: Photomicrograph of the kidney from the control group (Ar1r2) showing normal renal architecture, including well-defined glomeruli (G), Bowman's space (BS), renal tubules (RT), and tubular cells (TC) at ×400 magnification (H&E)

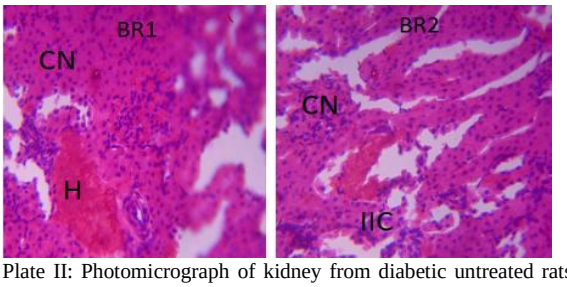


Plate II: Photomicrograph of kidney from diabetic untreated rats showing marked degeneration with coagulative necrosis (CN) of glomeruli and tubules, focal hemorrhage (H), and inflammatory cell infiltration (IIC)

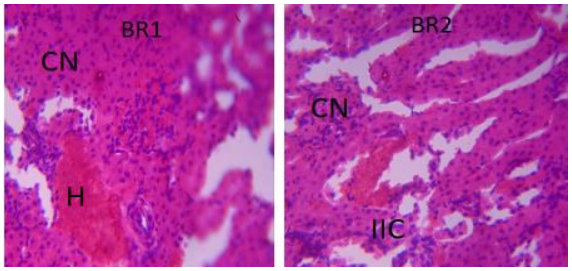


Plate III: photomicrograph of kidney of diabetic rats administered 100 mg/kg *ELEMP*. Dr1r2 shows mild regeneration of the glomeruli (NG) and non-distinct appearance of the tubular cells and mild inflammatory cell ×400 (H&E)

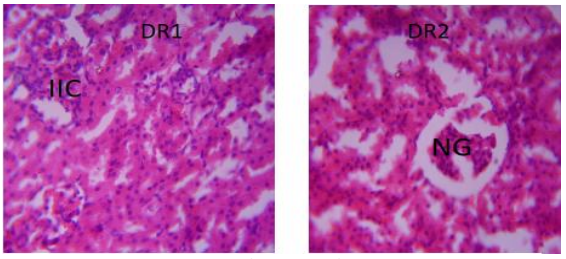
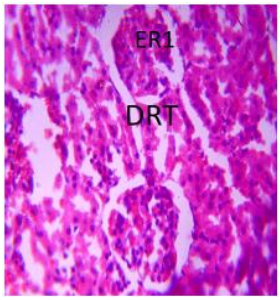


Plate IV: Photomicrograph of kidney of diabetic rats administered 200 mg/kg *ELEMP*. Dr1r2 kidney shows mild degeneration, necrotic glomeruli (NG), and indistinct tubular cells .Mild infiltration of inflammatory cells (IIC) is also observed. ×400 (H&E)



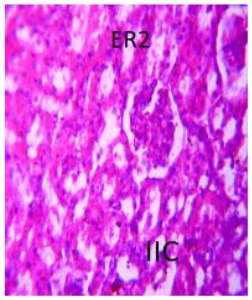
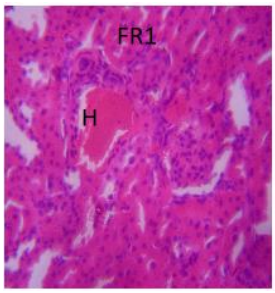


Plate V: Photomicrograph of kidney of diabetic rats administered 400 mg/kg *ELEMP*. Er1r2 shows moderate regeneration with mild fatty change (FC) and mild distortion of the renal tubules (DRT)



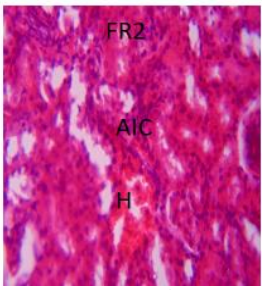


Plate VI: Photomicrograph of Photomicrograph of kidney of diabetic rats administered 2.5 mg/kg metformin. Er1r2 shows moderate regeneration with mild fatty change (FC) and mild distortion of the renal tubules (DRT). Fr1r2 section of the kidney induced with alloxan and high dose of extract showing mild regeneration with moderate aggregate of inflammatory cell (AIC) around the hemorrhagic (H) area

Discussion

People with diabetes often either do not produce enough insulin or their bodies do not respond to it effectively. This impairment hinders glucose from entering cells, resulting in elevated blood sugar levels while depriving the body's tissues of energy. Consequently, the body begins to utilize stored fat and muscle for energy, leading to rapid and unintended weight loss a condition referred to as diabetic weight loss. Both type 1 and type 2 diabetes can lead to this, alongside other clinical symptoms. Furthermore, as excess glucose is eliminated through urine, additional calories are lost, further contributing to weight loss (Chem, 2022).

The reduction in body weight observed in diabetic Wistar rats may be attributed to impaired cellular glucose uptake, prompting a metabolic shift toward the utilization of fat and muscle as alternative energy sources (Chem, 2022). However, this trend was reversed in groups treated with ethanol leaf extract of *Pterocarpus mildbraedii* (ELEMP). This observation aligns with the findings of Adegbite and Ezekwesili (2017), who demonstrated that both aqueous and ethanol leaf extracts of *P. mildbraedii* significantly reduced cholesterol levels in treated rats.

The decrease in blood glucose levels following administration of *P. mildbraedii* extract may be attributed to its phytochemical constituents with antihyperglycemic properties. This is consistent with the findings of Mishra *et al*. (2013), who reported that the heartwood of *Pterocarpus marsupium* possesses significant antihyperglycemic activity.

Additionally, the reduction in serum urea and creatinine levels following ELEMP administration suggests a protective effect against diabetes-induced kidney damage, likely due to the therapeutic properties of the extract's phyto-compounds. This supports the findings of Adegbite and Ezekwesili (2017; Nweke *et al*., 2018), who again noted a significant reduction in serum cholesterol levels in extract-treated rats.

Histological analysis further revealed improved kidney architecture in rats treated with 400 mg/kg of ELEMP, suggesting a regenerative or protective effect of certain bioactive compounds within the extract. These results are in line with the study by Urom and Usin (2023), and Nweke *et al.* 2019) which also reported histological improvement in diabetic models treated with plant-based extracts

CONCLUSION

This study demonstrates that *Pterocarpus mildbraedii* exhibits promising renoprotective properties in the context of diabetes-induced renal dysfunction. Its therapeutic potential appears to be mediated, at least in part, by its blood glucose-lowering effects. These findings support the potential use of *P. mildbraedii* as a complementary agent in managing diabetic nephropathy.

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