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A Study on the Effect of Methanolic Extract of Plumeria alba on Acetaminophen-induced Kidney Damage

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ABSTRACT

Background: Incidence of acetaminophen-induced nephropathy is a growing concern, with limited treatments available. This study evaluated the effects of methanolic extract of *Plumeria alba* flower (MEPAF) in acetaminophen-induced nephrotoxicity in Wistar rats.

Materials and Methods: Twenty-five Wistar rats were divided into five groups (A - E) of five rats each. Group A (Control) received feed and water. Group B received 1800mg/kg/bwt of acetaminophen and Group C received 900mg/kg/bwt of MEPAF. Groups D-E rats received co-administration of 1800mg/kg/bwt of acetaminophen and 180mg/kg/bwt of MEPAF, 1700mg/kg/bwt of acetaminophen and 850mg/kg/bwt of MEPAF respectively. All administrations were orally and daily for 28 days. On the 29th day, the rats were sacrificed, blood samples collected for kidney function test (urea, uric acid and creatinine evaluations) and kidneys harvested for histopathological examination.

Results: Administration of 1800mg/kg/bwt of acetaminophen for 28 days induced a significant ($p<0.05$) increase in body and relative organ weights, serum urea, uric acid and creatinine along with histopathological changes (acute tubular necrosis, degeneration and haemorrhage). However, co-administration with *Plumeria alba* flower extract ameliorated these conditions.

Conclusion: *Plumeria* alba flower extract could potentially provide protection against acetaminophen-induced renal toxicity. The observed nephroprotection could be attributed to the inherent antioxidant properties of *Plumeria alba*.

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Introduction

Acetaminophen (paracetamol) is a commonly used over-the-counter analgesic and antipyretic medication known for its effectiveness and safety when taken within the recommended doses [1]. It is primarily administered orally in the form of tablets or liquid solutions. After ingestion, acetaminophen is rapidly absorbed from the gastrointestinal tract, reaching peak plasma concentrations within 30 minutes to 2 hours [2]. Due to its water solubility, the drug is readily distributed throughout the body, quickly crossing cell membranes, including the blood-brain barrier, allowing it to affect both the central nervous system and peripheral tissues [3]. Acetaminophen metabolism primarily occurs in the liver, involving two main pathways: glucuronidation and sulfation. In the glucuronidation pathway, acetaminophen is conjugated with glucuronic acid by the enzyme UDP-glucuronosyltransferase (UGT), forming a water-soluble and inactive metabolite known as acetaminophen glucuronide. This metabolite is then excreted in the urine [4].

Research has shown that acetaminophen (APAP) overdose can potentially cause hepatorenal damage in both experimental animals and humans, and in severe cases, it can lead to death [5,6]. Acute renal failure has been reported in approximately 1-2% of patients due to APAP overdose. The toxicity of acetaminophen in both hepatic and extrahepatic tissues is closely linked to its metabolism [7,8]. While acetaminophen is relatively safe when used at therapeutic doses, overdose or prolonged use can result in severe hepatotoxicity and nephrotoxicity, posing a significant public health concern [1,9].

Plants provide medicinal effects through their phytoconstituents found in different parts10. *Plumeria alba* Linn, also known as White Champa, has been used in the ancient medicine systems of several civilizations for its cardiotonic, purgative, diuretic, rheumatic, and hypotensive properties. Several studies have highlighted that various solvent extracts from different parts of *Plumeria alba*, such as flowers, leaves, and stems, possess high antioxidant and antimicrobial potential [11,12]. Literary investigations suggest that some leaf extracts of *Plumeria alba*

have antioxidant properties. However, some solvent extracts of *Plumeria alba* still need to be explored for their antioxidant potential on nephrotoxicity. Hence, the present study was designed to evaluate the effect of methanolic extract of *Plumeria alba* flower on acetaminophen-induced kidney damage.

Materials and Methods

Acetaminophen

Acetaminophen was procured from Ezeaku pharmaceutical store Nnewi, Anambra State.

Plants Material and Preparation

The fresh *Plumeria alba* flowers used in this research were purchased at Onu -Ebonyi market in Izzi Local Government Area Ebonyi State, Nigeria. The flowers were air dried under shade and blended to a coarse powder form; 50g was soaked in 250mls of 98% methanol and allowed to stay for 48 hours with intermittent shaking after which it was sieved with porcelain cloth. Then, the Whatman No. 1 filter paper was used to filter the solutions. The extract was evaporated to solid form using a Rotary Evaporator and stored in a refrigerator for use [13].

Ethical Approval

Ethical clearance was obtained from the Ethical Committee of the Faculty of Basic Medical Sciences, College of Health Sciences, David Umahi Federal University of Health Sciences, Ebonyi State, Nigeria, before the commencement of the research.

Procurement and Housing of Experimental Animals

Twenty-five (25) healthy adults male Wistar rats weighing 120g-240g were procured from Animal Farm, Ebonyi State University, Ebonyi State and housed in the Animal house section of the Faculty of Basic Medical Sciences, College of Health Sciences, David Umahi Federal University of Health Sciences, Ebonyi State, and then kept for fourteen days for laboratory adaptation, while having free access to rat feed and water. The body weight of animals was obtained using a Sansa electronic weighing scale before and after laboratory adaptation and at weekly intervals throughout the experiment.

Experimental Design

The adult male Wistar rats weighing (120g - 240g) were randomly distributed into five groups (A, B, C, D, and E) of which 5 animals each. Group A (Control) received only distilled water and rat feed throughout the experiment. Group B received 1800mg/kg of only acetaminophen daily for four weeks; Group C received 900mg/kg of Methanolic extract of *Plumeria alba* flowers daily for four weeks; Group D received co-administration of 180mg/kg of methanolic Extract of *Plumeria alba* flower and 1800mg/kg of acetaminophen daily for four weeks, Group E received co-administration of 850mg/kg of methanolic extract of *Plumeria alba* flower and 1700mg/kg Acetaminophen daily for four weeks, All administration was done and once daily with the syringe and oral cannula between 10 to 11 am daily.

Collection of Tissue and Blood Samples

Twenty-four hours after the last administration on the 28th day, the animals from each group were weighed first using a weighing balance to get the animal's final weight before sacrifice. They were anaesthesized using chloroform. The blood samples (2mls) were collected through puncture of the orbital sinus from each animal, and the blood samples were allowed to stand for about 15 minutes to clot. Pasteur pipette was used to suck up the serum and placed into sterile sample test tubes for the conduct of kidney function test. The animals were afterwards humanely sacrificed by cervical dislocation, and their kidneys harvested and put in normal saline to maintain normal physiological conditions, after which they were weighed and fixed in 10% formalin for further histological processing.

Sample Analysis

Hematoxylin and Eosin staining method was used to produce the histological slides of the kidney specimens following to standard histological procedures. Light microscopy analysis was performed on the slides. Spectrophotometric analysis was used to quantify the levels of blood uric acid, urea and creatinine in the test specimens.

Data Analysis

Data was analyzed using the Statistical Package for Social Science (SPSS Version 23). The results were expressed as mean ± S.E.M. Data for Kidney Enzymes and Relative Organ Weight were analyzed using One-way ANOVA, followed by Post hoc LSD. Body weight was analyzed using a student-dependent T-test. Values were considered significant at $P \leq 0.05$.

Result

Effect of Methanolic Extract of Plumeria Alba Flower on body weight of experimental Animals

An increase in body weight was seen in group C, which received 900mg/kg methanolic extract of *Plumeria alba* flower only. However, the results showed no significant changes when the pre- administration body weight was compared to the post-administration body weight across all the groups, as shown in Table 1.

Table 1: Effect of Methanolic Extract of Plumeria Alba Flower on body weight of Experimental Animals

Groups	Body Weight (Mean ± Std. Error Mean)		P-Value
	Pre-administration	Post-administration	
A	160.2±14.82	180±2.89	0.299
B	183.8±8.81	183.8±8.81	0.059
C	176.2±11.53	203.33±5.24	0.162
D	181.2±6.48	174.67±7.51	0.113
E	165.2±9.87	190±18.34	0.331

Data was analyzed using paired sampled t-test, and values were considered significant at $p \leq 0.05$*

Effect of Methanolic Extract of Plumeria Alba Flower on relative organ weight (Kidney) of Experimental Animals

An increase in organ weight was seen in group B, which received 1800mg/kg acetaminophen compared to the control group. A decrease in organ relative weight was seen in group C, which received 900mg/kg methanolic extract of *Plumeria alba* flower compared to control group A. The result shows no statistically significant changes in organ weight across all groups compared to the control (Table 2).

Effect of Methanolic Extract of Plumeria Alba Flower on relative organ weight (Kidney) of Experimental Animals

An increase in organ weight was seen in group B, which received 1800mg/kg acetaminophen compared to the control group. A decrease in organ relative weight was seen in group C, which received 900mg/kg methanolic extract of Plumeria alba flower compared to control group A. The result shows no statistically significant changes in organ weight across all groups compared to the control (Table 2).

Table 2: Effect of Methanolic Extract of Plumeria Alba Flower on Relative Organ Weight (Kidney) of Experimental Animals

Groups	Mean	P value
Control (Group A)	1.47±0.00	
Group B	1.62±0.01	0.165
Group C	1.36±0.00	0.285
Group D	1.53±0.01	0.067
Group E	1.47±0.00	1
Total	1.41±0.00	

Data was analyzed using One-way ANOVA and values were considered significant at $p < 0.05$*

Effect of Methanolic Extract of Plumeria Alba Flower and Acetaminophen on Kidney Function of Animals

Our findings demonstrate a significant increase in creatinine levels in groups B and D, which were administered 1800mg/kg of acetaminophen only and a combination of 1800mg/kg of acetaminophen and 180mg/kg of Plumeria alba flower extract, compared to the control ($p<0.05$). In contrast, a significant decrease was observed in group C, which received 900mg/kg of Plumeria alba flower, and group E, which received a combination of 1700mg/kg of acetaminophen and 850mg/kg of Plumeria alba flower extract.

There was a significant increase in urea concentration in Groups B and D compared to the control. Groups C and E showed a significant decrease compared to the control. A significant increase in the concentration of uric acid in Groups B and D compared to the control group was observed. Groups C and E significantly decreased (Table 3).

Table 3: Effect of Methanolic Extract of Plumeria Alba Flower and Acetaminophen on Kidney Function of Animals.

		Mean ± Std. Error	P Value
Creatinine(mg/dl)	Control (Group A)	0.28±0.03	
	Group B	0.51±0.03	0.007
	Group C	0.18±0.03	0.002
	Group D	0.38±0.00	0.028
	Group E	0.23±0.02	0.000
Urea(mg/dl)	Control (Group A)	41.2±1.29	
	Group B	53.6±4.41	0.054
	Group C	28.67±1.76	0.004
	Group D	50.4±1.80	0.014
	Group E	36.53±2.54	0.177
Uric acid(mg/dl)	Control (Group A)	12.03±0.04	
	Group B	14.30±0.70	0.033
	Group C	9.55±0.25	0.000
	Group D	13.36±0.29	0.007
	Group E	11.74±0.23	0.005

Effect of Methanolic Extract of Plumeria Alba Flower and Acetaminophen on Kidney Histoarchitecture of Animals

Photomicrograph group A, B, C, D and E depict histopathological changes in kidneys for normal, acetaminophen-induced nephrotoxic rat, *Plumeria alba* administered rat, and acetaminophen- induced nephrotoxic rat co-treated with 180, 850 mg/kg of *Plumeria alba*, respectively. Photomicrograph B shows daily oral dose administration of acetaminophen-induced severe renal tissue degeneration, intra-renal haemorrhage, tubular necrosis, infiltration of inflammatory cells, and fatty glomeruli. These changes were ameliorated in rats co-treated with graded oral doses of *Plumeria alba*, with the most profound amelioration seen in the group treated with the highest dose of *Plumeria alba.*

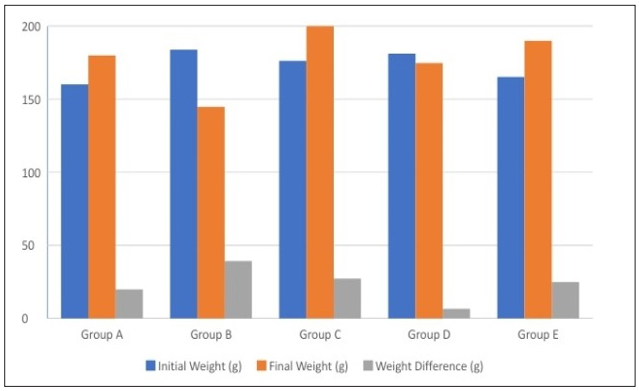


Figure 1: Effect of Methanolic Extract of Plumeria Alba Flower on body weight of Experimental Animals

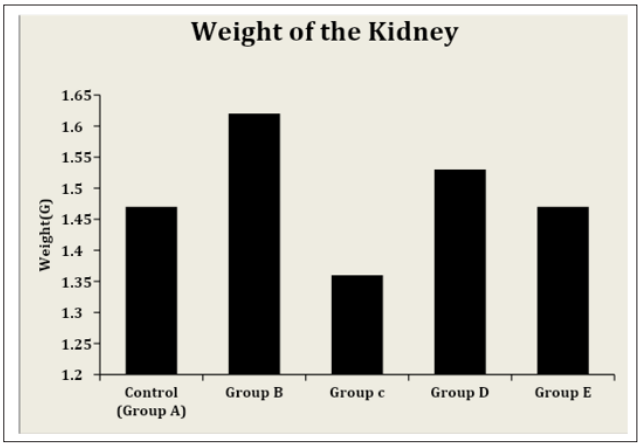


Figure 2: Effect of Methanolic Extract of Plumeria Alba Flower on Relative Organ Weight (Kidney) of Experimental Animals.

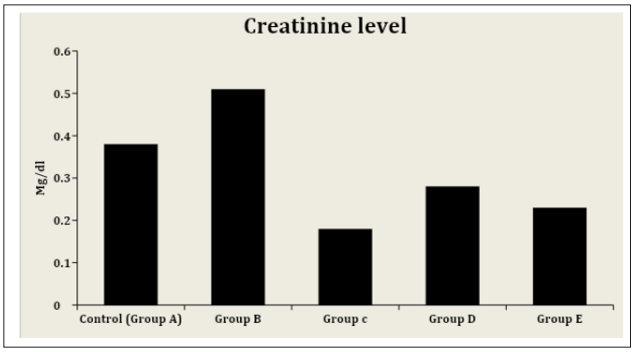


Figure 3a: Effect of the extract and acetaminophen on the Creatinine level of experimental animals.

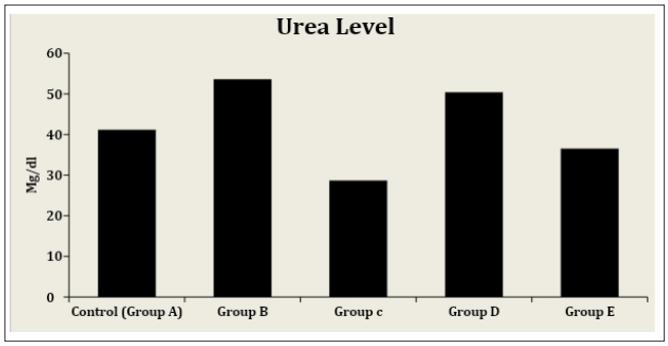


Figure 3b: Effect of the Extract and Acetaminophen on the Urea Level of Experimental Animals.

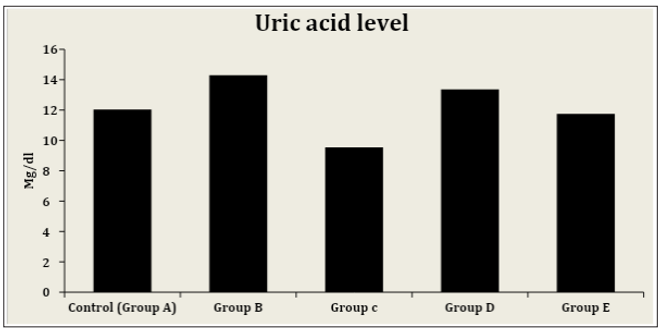
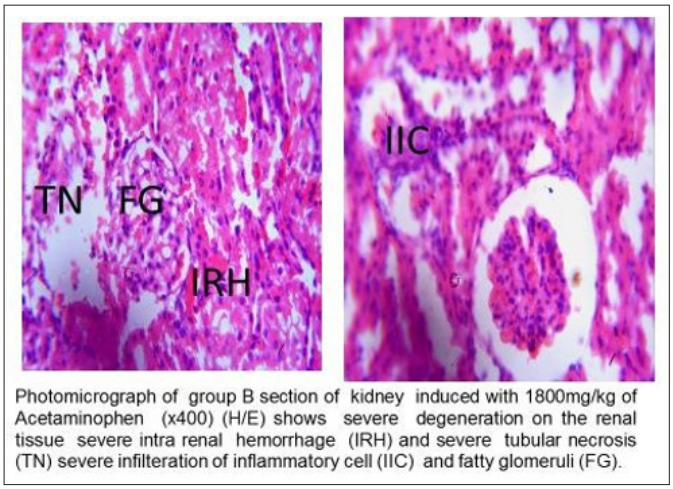
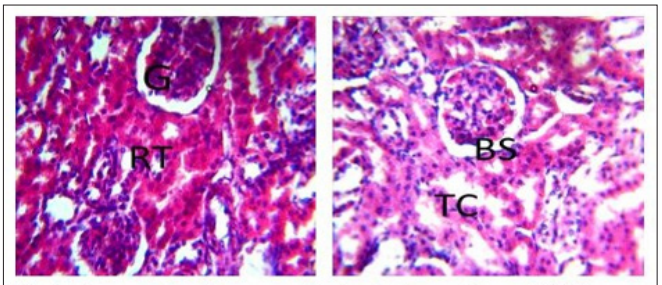


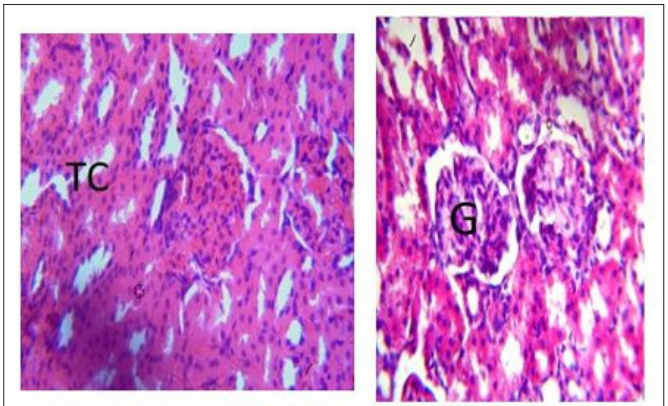
Figure 3c: Effect of the extract and Acetaminophen on the Uric Acid Level of Experimental Animals.



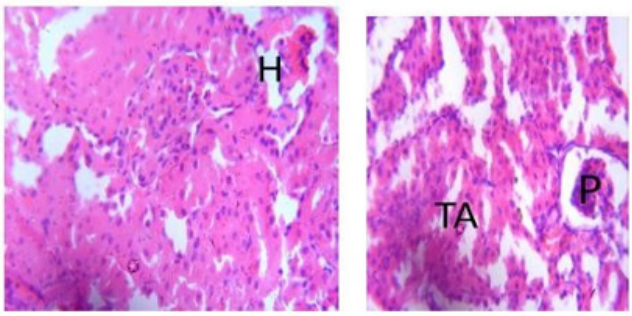
Photomicrograph of group B section of kidney induced with 1800mg/kg of Acetaminophen (x400) (H/E) shows severe degeneration on the renal tissue severe intra renal hemorrhage (IRH) and severe tubular necrosis (TN) severe infilteration of inflammatory cell (IIC) and fatty glomeruli (FG).



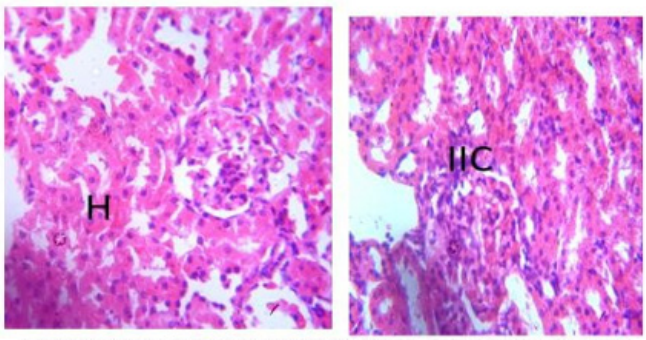
Photomicrograph of group A (control) section of kidney (X400)(H/E) shows normal renal architecture with glomeruli (G) , bowman space (BS), renal tubules (RT) and active tubular cell (TC)



Photomicrograph of group C section of kidney administered with 900mg/kg of *Plumeria alba* flower extract only (x400) (H/E) shows renal tissue with active tubular cells (TC) and glomeruli (G).



Photomicrograph of group D section of kidney with co-administration of 1800mg/kg of Acetaminophen and 180mg/kg of *Plumeria alba*flower extract (x400) (H/E) shows mild regeneration with moderate tubular atrophy (TA) ,pyknotic (P) and hemorrhagic (H) glomeruli.



Photomicrograph of group E section of kidney with co-administration of 1700mg/kg of Acetaminophen and 850mg/kg of *Plumeria alba* flower extract (x400) (H/E) shows moderate regeneration mild infilteration of inflammatory cell (IIC) arround the glomeruli and mild areas of hemorrhage(H)

Discussion

As depicted in Figure 1 and Table 1, oral administration of acetaminophen resulted in significant ($p>0.05$) progressive weight gain in group B rats compared to group A rats. This weight gain was further increased by co-administration of Plumeria alba in a dose-dependent manner, with the most significant ($p>0.05$) weight gain observed in group E. The weight gain observed in group B could be attributed to the administration route of APAP. This finding aligns with the results reported by Lakshmi et al. in a similar study [14]. Additionally, relative organ weight gain in the kidneys was observed in group B but was absent in group C, which received only 900mg/kg of Plumeria alba. The weight gain recorded for groups B and D could be linked to the weight gain effect of oral acetaminophen administration. This hypothesis warrants further validation.

In this study, renal injuries induced by acetaminophen been caused by the repeated oral administration of 1800 mg/kg of acetaminophen for 28 days. The mechanisms of acetaminophen toxicity are well-documented [6-9]. When large doses of the drug are ingested, there is an excessive formation of a highly reactive intermediate metabolite, N-acetyl-para-benzoquinone-imine (NAPQI). In the absence of glutathione, NAPQI arylates proteins (selenium-binding protein and glutamine synthetase) in the proximal tubule of the kidneys, initiating cell death [15]. Acetaminophen nephrotoxicity is marked by a significant increase in serum urea, uric acid, and creatinine, as well as severe degeneration of renal tissue, renal haemorrhage, and severe tubular necrosis. This study showed that acetaminophen significantly ($p<0.05$) elevated serum markers of renal function in group B rats. These elevations were significantly ($p>0.05$) attenuated by co-treatment with Plumeria alba in a dose-dependent manner, with the most significant ($p<0.005$) ameliorating effect observed at 850 mg/kg/day of Plumeria alba.

The histological findings supported the elevations observed in the serum renal function parameters, showing extensive renal tissue degeneration characterized by severe tubular necrosis, infiltration of inflammatory cells, and marked fatty glomeruli (Photomicrograph group B) in group B rats. These histological changes were improved by the oral administration of Plumeria alba extract, with the most significant amelioration observed in group E rats (Photomicrograph group E). As a rich plant, Plumeria alba flower extract may have inhibited the chain reactions of acetaminophen-generated free radicals or scavenged the reactive oxygen species before they reached their renal targets. Animal studies have demonstrated that Plumeria alba is a potent antioxidant, mediating its effect by scavenging reactive oxygen species (ROS) [16,17]. Therefore, the results of this study suggest that the ameliorating effects of Plumeria alba are likely due to the inhibition of free radical generation or its free radical scavenging activity.

Conclusion

The result of this present study showed that the methanolic extract of Plumeria alba flower exhibits protective property against acetaminophen induced renal damage in adult male Wistar rat. In the near future, Plumeria alba may be found useful as prophylactic agent against drug- induced nephrotoxicity.

Conflict of interest: None
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Consent for publication: Not applicable

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