



Nephroprotective effect of *Anacardium occidentale* (cashew) apple juice on kidney of paracetamol-induced injury in Albino rats

Joseph Oyepata Simeon^{1*}, Sabastine Aliyu Zubairu², Joseph Opeyemi Tosin³

¹Department of Pharmacology, Faculty of Pharmaceutical Sciences, Federal University, Oye-Ekiti State, Nigeria

²Department of Pharmacology and Therapeutics, Faculty of Pharmacy, Gombe State University, Gombe State, Nigeria

³Department of Pharmacology, Faculty of Pharmacy, Lead City University, Ibadan, Oyo State, Nigeria

Abstract

Background and aims: Cashew is an evergreen tropical tree native to South America. It has spread to several locations around the globe, including Africa. The plant's various parts have been effective in treating a variety of diseases. This study aims to assess the nephroprotective effect of aqueous *Anacardium occidentale* cashew apple juice on the kidney of paracetamol (PCM)-induced injury in albino rats.

Methods: Wistar rats were used to conduct this study. Group 1 was given saline as usual. While groups 3, 4, and 5 were administered 1, 2, and 4 ml/kg of the aqueous extract, group 2 received normal saline. In groups 2-5, animals received oral PCM 2000 mg/kg body weight on the eighth day. All animals were weighed again and sacrificed under a light diethyl ether vapor 20 hours after the last dose administration.

Results: The extract significantly ($P < 0.05$) raised packed cell volume (PCV), white blood cell (WBC), red blood cell (RBC), hemoglobin (Hb), and platelet values compared to group 2. There was no significant difference ($P > 0.05$) in the weight-to-body size ratio of rats in none of the groups given extracts ($P < 0.05$) when compared to group 2. Creatinine and urea level were considerably lower in the groups who received extract. Additionally, histological research supports biochemical parameters.

Conclusion: The study shows that *A. occidentale* cashew apple may help manage renal disorders and protect the kidney against hazardous substances.

Keywords: *Anacardium occidentale*, Cashew apple, Kidney, Paracetamol, Rats, Toxicity

*Corresponding Author:

Joseph Oyepata Simeon,
Emails: oyepata.joseph@fuoye.edu.ng,
simeon4unme@yahoo.com

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Introduction

The cashew tree (*Anacardium occidentale*) is an evergreen tropical tree (1,2). The tree can reach a height of 14 m (46 ft), although dwarf varieties, which can only reach 6 m (20 ft), are more productive and yield more money. The cashew seed is frequently made into a snack nut called cashew nut and can be consumed on its own, cooked with other ingredients, or made into cashew cheese or cashew butter. The nut is popularly known as cashew (3-5). Tree nut proteins, which are frequently left behind or unaffected by cooking, cause cashew allergies. The kidney, or boxing-glove-shaped drupe, that appears towards the end of the cashew apple is the actual fruit of the cashew tree (6-9). The seed is protected by a double shell of anacardic acid, an allergenic phenolic resin. Chemically linked to the more well-known and toxic allergenic oil urushiol, found in allied poison ivy and lacquer tree species and a potent skin irritant, anacardic acid is a severe irritant (10,11). Paracetamol (PCM) has an acceptable safety profile when used at prescribed doses. However, it is now understood that PCM can damage the kidneys when administered at a much higher dose. In addition, oxidative stress can play a

significant role in causing nephrotoxicity (12).

Medicinal plants are thought to be a significant source of novel chemicals with potential therapeutic benefits (13-16). The cashew tree (*A. occidentale*) is an Anacardiaceae flowering plant genus. There are 600 species in the family, divided among 73 genera. Eight species of *Anacardium*, all endemic to tropical America, are present, with the cashew being by far the most economically significant. It is an Amazonian tree with multiple uses that can reach heights of 15 meters (17). It has a thick, twisted trunk and tangled branches frequently touching the ground. The cashew tree yields a variety of materials and goods. The leaves and bark have therapeutic uses. The cashew nut is popular worldwide and has a high market value as food. Even the oil in the nut's shell is used medicinally and has industrial benefits in the polymers and resin sectors due to its high phenol concentration (18). The pseudo-fruit, a sizeable amount of pulpy and luscious flesh, also goes by the name "cashew fruit" or "cashew apple" and has a delightful flavor. The Wayapi tribe of Guyana, the Tikinia in northwest Amazona, and Brazilian and Peruvian herbal

medicine use cashew leaf and bark tea as a douche for vaginal discharge and treatment for frequent diarrhea (19-22). Among the ailments it is used to treat in Brazil are syphilis-related skin illnesses, eczema, psoriasis, scrofula, dyspepsia, genital problems, bronchitis, cough, intestinal colic, leishmaniasis, venereal disease, and impotence. Europeans used Brazil cashew fruit and juice to heal fever, freshen breath, and “conserve the stomach” in the sixteenth century. It is used as a diuretic, stimulant, and aphrodisiac in addition to treating syphilis (23). The cashew fruit is a delicious source of vitamins, minerals, and other nutrients. It contains up to five times as much vitamin C as oranges and mineral salts. Because of its high concentration of vitamin C and mineral salts, cashew fruit is used as a catalyst in treating early aging of the skin (24). Cashews contain anacardic acid, with the nutshells having the highest content (25). According to several clinical investigations, anacardic acid has been found in cashews (26-29), with the nutshells having the highest content. Tyrosinase activity slows down the aging process by darkening the skin, and some cancer cells are poisonous to anacardic acid (30-33). However, for dietary conditions, dietary anacardic acid has the potential to lower body fat accumulation. The interest in medicinal plants has grown over the past 20 years, and so has the number of studies into how they affect humans and animals biologically. Even though hazardous plants are common, up to 80% of people in impoverished nations use herbal therapy (34).

Brazil also utilizes the leaves and bark to treat ailments such as impotence, bronchitis, cough, intestinal colic, leishmaniasis, and skin conditions associated with syphilis, in addition to eczema, psoriasis, scrofula, dyspepsia, genital problems, and venereal infections. Additionally, a significant antioxidant capability was observed against hepatocarcinogenesis induced by aflatoxin B1 in Wistar rats (35). Cashew tree bark metabolites demonstrated an antipyretic effect for anacardic acid in preclinical studies (36). Using vegetable oil derived from cashew nuts, researchers performed mutagenic studies on *Salmonella* Typhimurium, demonstrating mutagenicity with or without the activation of the S9 fraction (37). It has been established that the tannic acid in cashews inhibits the *Salmonella* Typhimurium TA98 lineage's ability to mutate. The bark and leaves of the cashew tree possess tannins, a class of plant compounds with known biological action (38).

Numerous clinical studies have shown that tannins can treat some cancer cells and reduce the effects of aging on skin darkening by reducing tyrosinase activity (39-40). This study's objective is to assess the nephroprotective effect of *A. occidentale* cashew apple juice on the kidney of PCM-induced injury in albino rats.

Materials and Methods

Plants collection

The plant's native environment, the nearby Oye village in

Ekiti State, Nigeria, produced fresh *A. occidentale* fruit. The Department of Botany at Federal University in Ekiti State, Nigeria, confirmed the plant's provenance.

Extraction

The orange-reddish cashew apple plant material was gathered in the Oye Local Government of Nigeria's Ekiti State. Cashew apple fruits were cut and crushed in a laboratory setting. The juice was then extracted from the resulting mash after pressing. The resulting extract was kept and stored at freezing temperature until required.

Animals

Adult albino rats, both male and female, were bought from the FUYOYE animal house. The animals were acclimatized to the standard laboratory conditions with temperature ($25 \pm 2^\circ\text{C}$) and fed with standard animal pellet feed, ad libitum.

Animal treatment

Ahmad and Zeb model was used in this study (41). To this end, 36 rats in total were employed in this study. Group 1 was given saline as usual. While groups 3, 4, and 5 were administered 1, 2, and 4 mL/kg of the extract, group 2 received normal saline. In groups 2 through 5, animals received oral PCM 2000 mg/kg body weight on the eighth day. All animals were weighed again and sacrificed under a light diethyl ether vapor twenty hours after the last dose.

Hematological study

Blood was collected from each rat and put into EDTA-coated sample bottles after they were killed under diethyl ether anesthesia. The 21-gauge (21 G) needles attached to a 5 mL syringe were used to draw the blood samples. Hematological measurements include total and differential white blood cell count, full blood count (FBC), hemoglobin (Hb), packed cell volume (PCV), platelet concentration (PLC), and hemoglobin (Hb). These parameters were examined using the automated hematology system.

Chemical pathology analysis

Blood was drawn into a clear bottle, allowed to coagulate, and then centrifuged at 300 rpm for 10 minutes. The collected serum was used to estimate the levels of urea, creatinine, Na^+ and K^+ .

Histological study

A portion of each kidney was surgically removed, weighed, and fixed in 10% formaldehyde for histology processing.

Statistical analysis

The data were expressed as the mean and standard error of the mean (SEM). The results were statistically analyzed using one-way analysis of variance (ANOVA) before Dunnett's test for multiple comparisons between the control and treated groups. A *P* value under 0.05 was

considered to be statistically significant.

Results

Effect of *Anacardium occidentale* fruit juice on haematological parameters of PCM-induced toxicity

Anacardium occidentale cashew apple significantly ($P < 0.05$) caused an increase in PCV, Hb, RBC, WBC, and platelet count compared to group 2. There was a reduction in the PCV, Hb, RBC, WBC, and platelets in the PCM group (Table 1).

Effect of *Anacardium occidentale* fruit juice on body weight ratio of PCM-induced toxicity

There was an increase in the body weight ratio of the group that received only PCM. Compared to the PCM group, there was no significant difference in the weight-to-body size ratio of rats in all groups that received extract ($P < 0.05$) (Table 2).

Effect of *Anacardium occidentale* fruit juice on kidney parameters of PCM-induced toxicity

Compared to the standard group, there was a significant increase ($P < 0.05$) in the group that received PCM only. Creatinine and urea level were significantly lower ($P < 0.05$) in the groups who received extract when compared to the PCM group (Table 3).

Effect of extract on the histology of kidney of rats

Rat kidneys treated with distilled water in histological sections revealed normal glomeruli and tubules. However, sections of the kidneys from rats given just PCM (2000 mg/kg) treatment revealed abnormal glomeruli and microvesicles in the tubular lining cells. Rats that were given doses of PCM and *A. occidentale* extract of 2 and 4 mL showed normal glomeruli in their kidney sections, and the tubules were bordered with anucleate epithelial cells with enhanced eosinophilia that sloughed into the tubule lumen (Figure 1).

Discussion

The renal system has two bean-shaped organs called kidneys (42,43). They help the body in excreting waste through urine. Before returning blood to the heart, they aid in filtering it. The kidneys regulate the body's fluid equilibrium among its many essential tasks. Herbal plants have been used for many years for therapeutic and health purposes. Local consumption of medicinal plants without a graduated dose or anticipated use time is common (44), which may have unintended consequences for the tissue,

organ, or bodily system (45). Using cashews for ailments such as diabetes, high cholesterol, heart disease, stomach and intestinal (gastrointestinal) diseases, skin illnesses, and other afflictions is not sufficiently supported by reliable scientific research (46).

In this study, PCM caused an increase in urea and creatinine levels, which was significantly reduced in the groups receiving *A. occidentale* fruit juice. Healthy kidneys filter the blood to remove creatinine. The body excretes creatinine as waste in the urine. A high amount of creatinine is a sign of kidney trouble. Although urea is sometimes seen as a metabolic waste product, it serves two essential physiological purposes: ammonia purification and water preservation (47), suggesting that the fruit juice of the plant may help treat or prevent diseases brought on by toxins linked to PCM or PCM itself. Creatinine is a chemical by-product of how one's muscles produce energy (48).

The presence of cytochrome P-450 mixed-function oxidase isoenzymes in the kidney has been linked to the pathophysiology of renal toxicity in acetaminophen overdose despite the finding of additional mechanisms, such as the role of prostaglandin synthetase and N-deacetylase enzymes (49,50). Contrarily, even though its conjugates have been related to the production of nephrotoxic chemicals, glutathione is considered a crucial element in detoxifying acetaminophen and its metabolites. The hepatorenal syndrome, which can exacerbate fulminant hepatic failure, can be distinguished from acetaminophen-induced renal failure (51). Renal failure caused by acetaminophen typically appears after hepatotoxicity. It is uncertain what function N-acetylcysteine therapy should serve in the context of acetaminophen-induced renal failure.

Anacardium occidentale raised the values of RBC, PCV, WBC, and monocytes which were significantly reduced in the group that received PCM only. Hemoglobin's value

Table 2. Effect of *Anacardium occidentale* fruit juice on body weight ratio of paracetamol-induced toxicity

Group	Body weight ratio
N/S	0.79 ± 0.32
PCM 2000 mg/kg	0.85 ± 0.32
PCM+10 mL OA	0.84 ± 0.38
PCM+20 mL AO	0.83 ± 0.54
PCM+40 mL AO	0.83 ± 0.11

NS, Normal saline; PCM, Paracetamol; OA, *Anacardium occidentale*.

Table 1. Effect of *Anacardium occidentale* fruit juice on haematological parameters of PCM-induced toxicity

Group	RBC (X 10 ¹² /l)	PCV (%)	Hb (g/dL)	WBC (X 10 ⁹ /l)	Platelet count	Monocytes (%)
Normal saline	7.4 ± 1.21*	44.00 ± 1.47*	13.56 ± 0.87*	5.4 ± 1.83*	350 ± 3.43*	4.13 ± 1.83*
PCM 2000 mg/kg	5.80 ± 0.97	17.92 ± 2.27	10.24 ± 0.64	2.82 ± 1.10	309 ± 4.79	2.9 ± 1.63
PCM+1 mL OA	4.11 ± 0.76	34.67 ± 1.28*	10.73 ± 0.34	5.29 ± 1.43*	345 ± 3.92*	4.01 ± 1.71*
PCM+2 mL AO	5.36 ± 0.76*	37.7 ± 2.12*	10.8 ± 0.34	5.24 ± 1.33*	380 ± 3.15*	5.6 ± 1.25*
PCM+4 mL AO	6.05 ± 0.43*	4.22 ± 1.8*	10.23 ± 0.34	6.52 ± 1.40*	403 ± 3.81*	5.7 ± 1.19*

*Means significant at $P < 0.05$.

DW, distilled water; WBC, white blood cells; RBC, red blood cells; HGB, Hemoglobin; PCM, Paracetamol; OA, *Anacardium occidentale*.

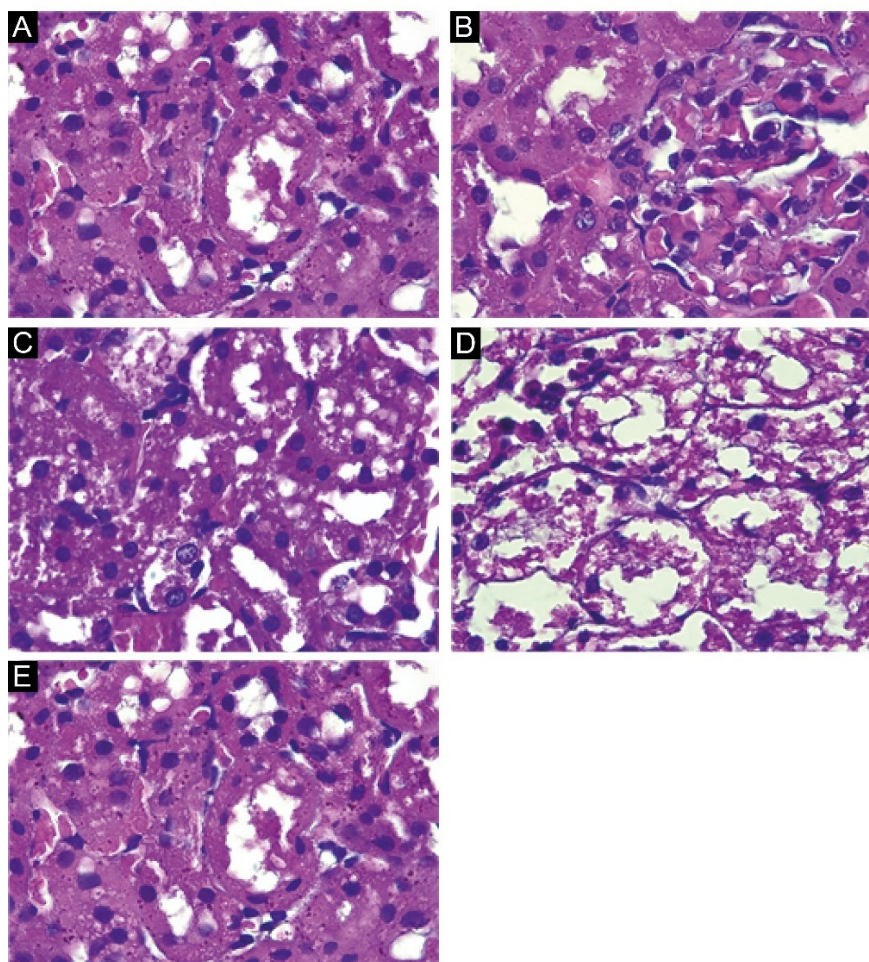


Figure 1. Histological views of kidneys of rats treated with normal saline 10 mL/kg (A), PCM 2000 mg/kg (B), PCM 2000 mg/kg and AO 10 mL bw (C), and PM 2000 mg/kg and AO 20 (D), PM 2000 mg/kg and AO 40 (E), at magnification A ($\times 100$) and B ($\times 400$) stained with H&E technique.

Table 3. Effect of *Anacardium occidentale* fruit juice on kidney parameters of paracetamol-induced toxicity

Group	UREA (mg/dL)	Creatinine (umol/L)	K ⁺ (mmol/L)	Na ⁺ (mmol/L)
Normal saline	46.22 \pm 2.15	48.24 \pm 3.11	9.30 \pm 0.92	122.00 \pm 2.38
PCM 2000 mg/kg	54.89 \pm 2.22	178.34 \pm 2.80	15.30 \pm 0.52	182.27 \pm 2.38
PCM 2000 + 10 mL OA	46.23 \pm 3.77	51.11 \pm 4.5*	11.43 \pm 0.56	145.00 \pm 2.11*
PCM 2000 + 20 mL AO	46.67 \pm 2.43*	38.15 \pm 2.93*	11.10 \pm 0.51	143.99 \pm 2.51*
PCM 2000 + 40 mL AO	45.27 \pm 2.99	36.72 \pm 4.89*	11.27 \pm 0.18	143.25 \pm 2.51*

*Significant at $P < 0.05$.

DW, distilled water; K potassium ion; Na, sodium ion; PCM, Paracetamol; OA=*Anacardium occidentale*

remained unchanged. Hematological markers can be utilized to assess plant extracts' risk to living organisms (52-55). When analyzing circulatory erythrocytes, diagnosing anemia, and determining whether the bone marrow can produce red blood cells as it does in mammals, red blood cells and the factors that affect them are crucial signs (56). The result from this study indicates that *A. occidentale* cashew apple can improve hematological indices and help protect the body against agents that destroy blood cells, which may be due to the presence of phytochemical constituent in *A. occidentale* cashew apple with antioxidant properties.

PCM overdose is frequently linked to various metabolic

issues, including blood electrolytes, urea, and creatinine abnormalities. Thomas et al reported that rats given a nephrotoxic dose of PCM underwent alterations in several markers (blood urea nitrogen and serum creatinine levels) (57). These alterations were brought on by suppressing the mitochondrial pathway during acetaminophen-induced cell death. In the current investigation, the serum levels of urea and creatinine in the PCM toxic group (group 2) rats were considerably higher than those in the healthy control group. These results are consistent with those of Simeon et al., who found that rats given PCM at a dose of 1 g/kg body weight had greater blood levels of urea and creatinine (58). Oyepata et al found a strong correlation

between nephrotoxicity and oxidative stress, which helped to explain the rise in urea and creatinine levels (59,60). The filtration surface area and filtration coefficient are altered by the increased production of H₂O₂ and O₂, which has the potential to impair glomerular filtration and result in a buildup of urea and creatinine in the blood (61). The PCM control group (group 1) showed considerably greater potassium and salt concentrations than the standard group compared to the regular group (group 2). This effect was noticeably boosted in the groups that received *A. occidentale*. This result aligns with the observations made by Kalantar-Zadeh et al (62), who found that PCM-treated rats had higher potassium (K⁺) and sodium (Na⁺) levels. The serum creatinine levels are an effective indicator of renal function. The extract of *A. occidentale*, tested in this study as a potential repair agent against toxicity, was brought on by PCM. It reveals that apple juice of *A. occidentale* may have the ability to improve kidney function parameters of PCM-induced toxicity or other related toxins. This effect may be due to the presence of beneficial phytochemical constituents. According to phytochemical analysis, the dried fruit of *A. occidentale* contains alkaloids, tannins, anthraquinones, glycosides, and phenols in both the ethanol and the aqueous extracts (63,64). These molecules have been shown to exhibit antioxidant activities in different studies (64,65). The prevalence of secondary metabolites in medicinal plants and their pharmacological properties have been studied over different plants (66). In general, plants produce a lot of secondary metabolites that constitute a significant source of microbicides, antioxidants, pesticides, and many pharmaceutical drugs (67-69). Hematological and biochemical markers were also consistent with histological examinations.

Conclusion

The findings of this study suggest that *Anacardium occidentale* cashew apple may be advantageous in preventing the kidney from damage by PCM or some hazardous toxins.

Authors' Contribution

Conceptualization: Joseph Oyepata Simeon, Sabastine Aliyu Zubairu, Joseph Opeyemi Tosin.

Data curation: Joseph Oyepata Simeon, Sabastine Aliyu Zubairu, Joseph Opeyemi Tosin.

Formal analysis: Joseph Oyepata Simeon, Sabastine Aliyu Zubairu, Joseph Opeyemi Tosin.

Funding Acquisition: Joseph Oyepata Simeon, Sabastine Aliyu Zubairu, Joseph Opeyemi Tosin.

Investigation: Joseph Oyepata Simeon, Sabastine Aliyu Zubairu, Joseph Opeyemi Tosin.

Methodology: Joseph Oyepata Simeon, Sabastine Aliyu Zubairu, Joseph Opeyemi Tosin.

Project Administration: Joseph Oyepata Simeon, Sabastine Aliyu Zubairu, Joseph Opeyemi Tosin.

Resources: Joseph Oyepata Simeon, Sabastine Aliyu Zubairu, Joseph Opeyemi Tosin.

Supervision: Joseph Oyepata Simeon, Sabastine Aliyu Zubairu, Joseph Opeyemi Tosin.

Validation: Joseph Oyepata Simeon, Sabastine Aliyu Zubairu, Joseph Opeyemi Tosin.

Visualization: Joseph Oyepata Simeon, Sabastine Aliyu Zubairu, Joseph Opeyemi Tosin.

Writing-original draft: Joseph Oyepata Simeon, Sabastine Aliyu Zubairu, Joseph Opeyemi Tosin.

Writing-review & editing: Joseph Oyepata Simeon, Sabastine Aliyu Zubairu, Joseph Opeyemi Tosin.

Competing Interests

The authors declare that there is no conflict of interest.

Ethical Approval

The protocol was approved by the Institutional Animal Ethics Committee (IAEC) constituted for the purpose of animal Federal University in Oye-Ekiti, Ekiti State, Nigeria.

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