



Research Article

Hepatoprotective and Nephroprotective Effects of Aqueous
Extract Of *Garcinia kola* (Bitter Kola) in Indomethacin-Induced
Poisoning in Wistar Rats

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ABSTRACT

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Indomethacin, a non-steroidal anti-inflammatory drug, is known for its oxidative stress properties that cause significant organ damage, raising concerns about its use as a rodenticide and its potential risks to humans and animals. This study investigated the hepatoprotective and nephroprotective effects of aqueous *Garcinia kola* (Bitter kola) seed extract on indomethacin-induced liver and kidney damage in Wistar rats. The experiment involved 24 Wistar rats divided into six groups, including controls and groups treated with indomethacin and various doses of *Garcinia kola* extract (100 mg/kg, 200 mg/kg, and 300 mg/kg) or Atropine sulfate as a reference antidote. After 5 days of oral administration, blood samples were collected for liver and kidney function tests, alongside histopathological assessment. Indomethacin significantly elevated liver enzymes (AST, ALP) and kidney markers (serum creatinine, urea), indicating damage. However, rats treated with 300 mg/kg *Garcinia kola* extract showed normalized biochemical parameters (AST, ALP, total bilirubin, serum creatinine, urea, and total protein) comparable to the normal control group. Histological analysis confirmed the absence of liver or kidney damage in this group. These results suggest that *Garcinia kola* seed extract has potent hepatoprotective, nephroprotective, and antidotal effects, likely due to its bioactive compounds. The extract could potentially serve as an emergency intervention in cases of accidental poisoning pending medical treatment. Further research is recommended to explore the mechanisms involved and to conduct clinical trials to confirm its efficacy.

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INTRODUCTION

The liver and kidneys are essential organs responsible for filtration and detoxification, playing a crucial role in maintaining overall health (Daoudi *et al.*, 2021). However, these organs are highly susceptible to damage from toxic substances, including medications like non-steroidal anti-inflammatory drugs (NSAIDs) (Daoudi *et al.*, 2021). Indomethacin is a non-steroidal anti-inflammatory drug (NSAID) that was first introduced in 1963 and used in the treatment of severe osteoarthritis, rheumatoid arthritis, gouty arthritis or ankylosing spondylitis (Eljafari *et al.*, 2020; Gebril *et al.*, 2020). Despite its therapeutic benefits, prolonged use of indomethacin has been associated with severe hepatotoxicity and nephrotoxicity due to its ability to induce oxidative stress (Eljafari *et al.*, 2020; Gebril *et al.*, 2020; Gupta, 2018; Ogidi *et al.*, 2020; Tavakkoli *et al.*, 2017). It's also used as rodenticide by some people in Nigeria due to the drug's effect and dangerous effect on rats and mice (Ahmad *et al.*, 2021; Audet *et al.*, 2017; Gebril *et al.*, 2020). Although some protective agents like atropine have shown moderate efficacy in mitigating these effects, there remains a pressing need for more potent, naturally derived alternatives.

Garcinia kola (Bitter kola), a medicinal plant found predominantly in West Africa, has gained attention for its potential therapeutic benefits. The seeds of *Garcinia kola* are rich in bioactive compounds such as flavonoids, saponins, and phenols, which have demonstrated antioxidant, anti-inflammatory, and hepatoprotective properties in animal models (Omodamiro *et al.*, 2020; Rotimi *et al.*, 2022). Despite the promising findings in the existing literatures (Aj *et al.*, 2018; Apalowo *et al.*, 2019; Atanu & Okpe, 2021; Bartimaeus & Waribo, 2018; Igbinsosa *et al.*, 2022; Iyare & Omorodion, 2023; Okonkwo *et al.*, 2015; Waribo *et al.*, 2019) the extent of *Garcinia kola*'s protective effects against specific toxic insults such as those caused by indomethacin remains poorly understood. While some studies (Bennett & Saliu, 2022; Igbinsosa *et al.*, 2022; Ojatula & Ezenwa, 2023; Omodamiro *et al.*, 2020; S. & O. O., 2016; Salami *et al.*, 2023; Umoh *et al.*, 2020, 2020; Waribo *et al.*, 2019) have explored its general pharmacological effects, the detailed mechanisms of its hepatoprotective and nephroprotective potential particularly in the

context of indomethacin-induced damage have not been fully elucidated. This study addresses this critical gap by investigating the specific hepatoprotective, nephroprotective, and antidotal effects of *Garcinia kola* in an indomethacin-induced toxicity model in Wistar rats.

MATERIALS AND METHODS

Sample Collection and Identification

Fresh *Garcinia kola* seeds were purchased from Bakin dogo Central Market, Kaduna, and authenticated at the herbarium unit of the Department of Biological Sciences, Nigerian Defence Academy, Kaduna (Voucher No. NDA/BioH/2023/54).

Plant Preparation and Extraction

The Fresh *Garcinia kola* seeds were rinsed with clean water, peeled, and sliced into small pieces. They were then air-dried in the shade and ground into powder using an electric blender. A total of 367.23g of powdered seeds was soaked in 1.7 liters of distilled water, stirred and left for 48 hours. The resulting mixture was filtered through Whatman filter paper, and the filtrate was evaporated using a water bath at 40°C, yielding 9.6g of dried extract, which was stored at room temperature.

Phytochemical screening of aqueous extract of *Garcinia kola* (Bitter kola) seeds

Phytochemical screening was carried out using the standard procedure for the identification of phytochemical constituents as described by Shaikh & Patil, (2020); Abdelfatah *et al.* (2021); Pant *et al.* (2017) and Mamta *et al.* (2023). The extract solution was prepared by dissolving 10g of extract in distilled water to make up a 100 ml solution. The extract solution was then used for phytochemical screening. Tests were done for confirmation of alkaloids, flavonoids, tannins, saponins, cardiac glycosides, phenols and steroids

Experimental Animals

Twenty-four (24) adult Wistar rats of both sexes, weighing between 120–180g, were used in this study. The rats were obtained from the Department of Veterinary Medicine, Ahmadu Bello University, Zaria, Nigeria. They were housed in well-ventilated laboratory cages under controlled conditions of 12-hour light and dark cycles at room temperature. Rats were provided standard commercial feed (Vital Feeds Nigeria Ltd.) and clean water *ad libitum*. Before the commencement of the experiment, the animals were allowed to

acclimatize for two weeks to reduce stress-induced variability in the experimental outcomes. The study adhered strictly to institutional guidelines for the care and use of laboratory animals, and all experimental procedures were approved by the ethical committee of the Nigerian Institute for Trypanosomiasis Research (NITR), Kaduna, Nigeria, in compliance with international ethical standards.

Indomethacin Preparation and Administration

Indomethacin was obtained from Andy Pharmaceutical Store in Kaduna, Kaduna State. The capsule were broken, 50mg of indomethacin powder was dissolved in 2ml of distilled water and then administered it orally using oral gavage needle to induce poison in Wistar rats (Ogidi *et al.*, 2020; Sarhat *et al.*, 2019).

Experimental Design

The rats were randomly divided into six groups (n=4 per group) and treated as follows:

- Group I (Normal control): Received feed and water ad libitum.
- Group II (Negative control): Induced with indomethacin (50mg/kg) orally.
- Group III (Positive control): Indomethacin (50mg/kg) + atropine sulphate (0.1ml/IM).
- Group IV: Indomethacin (50mg/kg) + 100mg/kg *Garcinia kola* extract.
- Group V: Indomethacin (50mg/kg) + 200mg/kg *Garcinia kola* extract.
- Group VI: Indomethacin (50mg/kg) + 300mg/kg *Garcinia kola* extract.

All treatments were administered orally for five days. At the end of the treatment period, the rats were sacrificed under light anesthesia (chloroform inhalation), and blood samples were collected via cardiac puncture for biochemical analysis. Liver and kidney tissues were harvested for histopathological evaluation.

Biochemical Analysis

The rats were euthanized (lightly anaesthetized by chloroform inhalation), and then blood samples were taken by cardiac puncture using sterile needle and syringe. Each sample was kept in non-heparinized tubes. Biochemical examination was done for liver and kidney function tests (LFT and KFT) (Hasan *et al.*, 2018).

Histopathological Assessments

Liver and kidney tissues were fixed in 10% formalin and processed for histopathological

examination. The tissues were sectioned, stained with hematoxylin and eosin, and observed under a light microscope for structural abnormalities such as hepatic necrosis, vascular congestion, tubular necrosis, and inflammatory cell infiltration.

Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) software version 24. All results were expressed as Mean \pm Standard Deviation (SD). A one-way analysis of variance (ANOVA) was employed to assess differences between the experimental groups. Post-hoc multiple comparison tests, specifically Tukey's Honest Significant Difference (HSD) test, were used to identify significant differences between groups. The choice of ANOVA was based on the need to compare means across multiple groups, while Tukey's HSD was selected for its reliability in controlling the family-wise error rate in multiple comparisons. Statistical significance was set at $P < 0.05$. This threshold was chosen to ensure the results are robust and to reduce the likelihood of type I errors.

RESULTS

Phytochemical Composition of *Garcinia kola* Seed Extract

The qualitative phytochemical analysis of the aqueous extract of *Garcinia kola* seeds revealed the presence of several bioactive compounds known for their medicinal properties (Table 1). The extract tested positive for alkaloids, flavonoids, saponins, tannins, cardiac glycosides, and phenols, while steroids were absent. These phytochemicals are associated with antioxidant, anti-inflammatory, and hepatoprotective activities, which may contribute to the extract's protective effects observed in this study.

Biochemical Parameters of Liver Function

Indomethacin significantly disrupted liver function, as indicated by elevated levels of serum liver enzymes and total bilirubin in the negative control group compared to the normal control (Table 2). Specifically, ALT increased from 256.00 ± 1.00 IU/L in the normal control to 420.33 ± 0.58 IU/L in the negative control ($P < 0.05$). AST and ALP levels similarly increased, along with total bilirubin, reflecting hepatic damage. Treatment with *Garcinia kola* extract led to a dose-dependent amelioration of these effects. The group receiving 300 mg/kg of the extract showed liver enzyme levels that were not significantly different from the

normal control (ALT: 257.33 ± 0.58 IU/L; AST: 87.67 ± 0.58 IU/L; ALP: 490.67 ± 0.58 IU/L; total bilirubin: 0.10 ± 0.01 mg/dL; $P > 0.05$). This suggests that *Garcinia kola* effectively counteracted indomethacin-induced hepatotoxicity at this dose.

Biochemical Parameters of Kidney Function

Indomethacin also caused significant nephrotoxicity, as evidenced by elevated serum creatinine, urea, and total protein levels in the negative control group (Table 3). Serum

creatinine increased from 0.52 ± 0.01 mg/dL in the normal control to 0.83 ± 0.01 mg/dL in the negative control ($P < 0.05$). Similarly, serum urea and total protein levels were significantly higher. Treatment with *Garcinia kola* extract at 300 mg/kg effectively normalized these parameters. The serum creatinine (0.53 ± 0.02 mg/dL), urea (120.20 ± 5.90 mg/dL), and total protein levels (6.04 ± 0.78 g/dL) in this group were comparable to the normal control, indicating nephroprotective effects

Table 1: Qualitative phytochemical analysis of aqueous extract of *Garcinia kola* seeds

Phytochemicals	Aqueous Extract of <i>Garcinia kola</i>
Alkaloids	+
Flavonoids	+
Saponins	+
Tannins	+
Cardiac Glycosides	+
Phenols	+
Steroids	-

Key: + = Present, - = Absent

Table 2: Effect of aqueous extract of *Garcinia kola* (Bitter kola) on serum liver enzymes (ALT, AST, ALP and total bilirubin) with indomethacin-induced hepatotoxicity in Wistar rats

Groups	ALT (IU/L)	AST (IU/L)	ALP (IU/L)	Total bilirubin (mg/dl)
N	256.000 ± 1.000^a	85.667 ± 0.577^a	487.000 ± 1.000^a	0.103 ± 0.006^a
NC	420.333 ± 0.577^b	167.667 ± 0.577^b	660.000 ± 0.000^b	0.310 ± 0.010^b
PC (Atropine 0.1ml)	260.333 ± 0.577^c	87.000 ± 1.000^a	489.667 ± 0.577^c	0.123 ± 0.006^c
BK (100mg)	263.000 ± 1.000^d	103.000 ± 1.000^d	496.000 ± 1.000^d	0.213 ± 0.006^d
BK (200mg)	330.667 ± 0.577^e	89.333 ± 0.577^e	560.000 ± 1.000^e	0.130 ± 0.006^e
BK (300mg)	257.333 ± 0.577^a	87.667 ± 0.577^f	490.667 ± 0.577^f	0.103 ± 0.006^a

Values are expressed in mean \pm SD. $n = 3$, $p < 0.05$, SD: standard deviation, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, ALP: Alkaline phosphatase, N: Normal control, NC: Negative control, PC: Positive control (Atropine sulphate), BK: Bitter kola, Values with different superscript on the same column are significantly different from the N group at $p < 0.05$.

Table 3: Effect of aqueous extract of *Garcinia kola* (Bitter kola) on serum urea, serum creatinine, and total protein levels with indomethacin-induced nephrotoxicity in Wistar rats

Groups	Serum creatinine (mg/dl)	Serum urea (mg/dl)	Total protein (g/dl)
N	0.5237±0.0100 ^a	115.7955±0.1000 ^a	5.5800±0.0100 ^a
NC	0.8317±0.0100 ^b	181.4569±0.0058 ^b	10.7330±0.0100 ^b
PC (Atropine 0.1ml)	0.6308±0.0058 ^c	128.7115±0.1000 ^a	7.4400±0.0173 ^c
BK (100mg)	0.6930±0.0058 ^d	139.8347±0.0100 ^d	7.7400±0.0100 ^d
BK (200mg)	0.6355±0.0000 ^e	134.4769±0.0577 ^e	6.6100±0.5716 ^e
BK (300mg)	0.5341±0.0170 ^a	120.2024±5.9009 ^a	6.0422±0.7775 ^a

Values are expressed in mean ± SD. n= 3, p < 0.05, SD: standard deviation, N: Normal control, NC: Negative control, PC: Positive control (Atropine sulphate), BK: Bitter kola, Values with different superscript on the same column are significantly different from the N group at p<0.05.

Histopathological Observations

Histopathological examination supported the biochemical findings. Liver sections from the negative control group showed vascular congestion and slight hepatic necrosis, indicating hepatocellular injury (Figure 1b). In contrast, liver tissues from the *Garcinia kola*-treated groups, particularly at 300 mg/kg, exhibited normal histological architecture similar to the normal control group (Figure 1f).

Similarly, kidney sections from the negative control group demonstrated moderate hyperplasia of inflammatory cells and tubular necrosis (Figure 2b), signs of nephrotoxicity. The kidneys of rats treated with 300 mg/kg *Garcinia kola* extract displayed normal histological features with no signs of damage (Figure 2f).

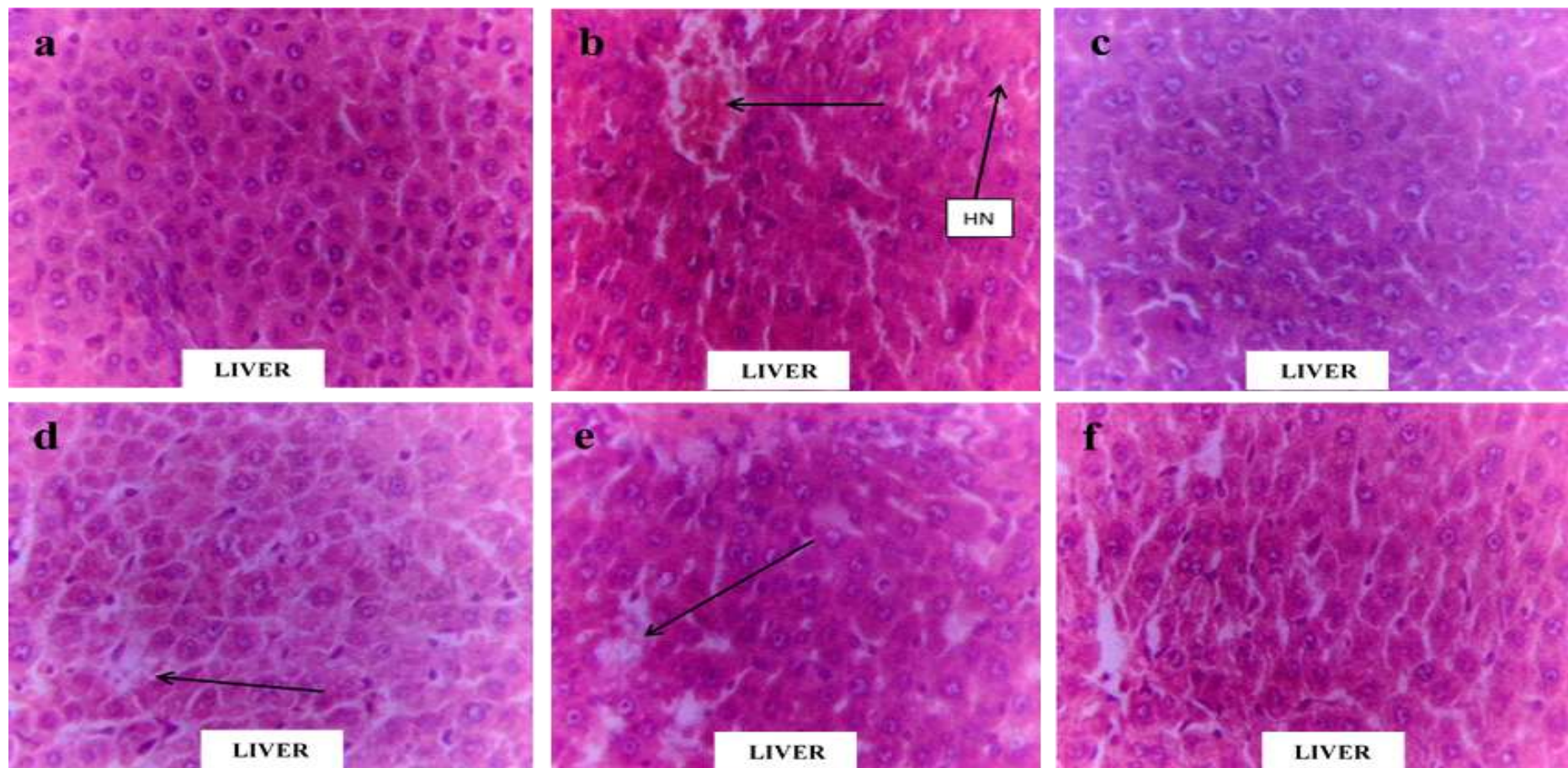


Figure 1: Histopathological images of liver tissue (H & E x400), (a) Normal control: Liver tissue showing normal architecture. (b) Negative control: shows vascular congestion (accumulation of blood within the liver's blood vessels) and slight hepatic necrosis (death of liver cells) in the liver tissue. (c) Positive control (Atropine sulphate): show normal hepatocytes. (d) BK 100mg: shows slight hepatic necrosis (death of liver cells) in liver tissue. (e) BK 200 mg, which shows moderate hepatic necrosis (death of liver cells) in liver. (f) BK 300 mg shows normal features in liver tissue.

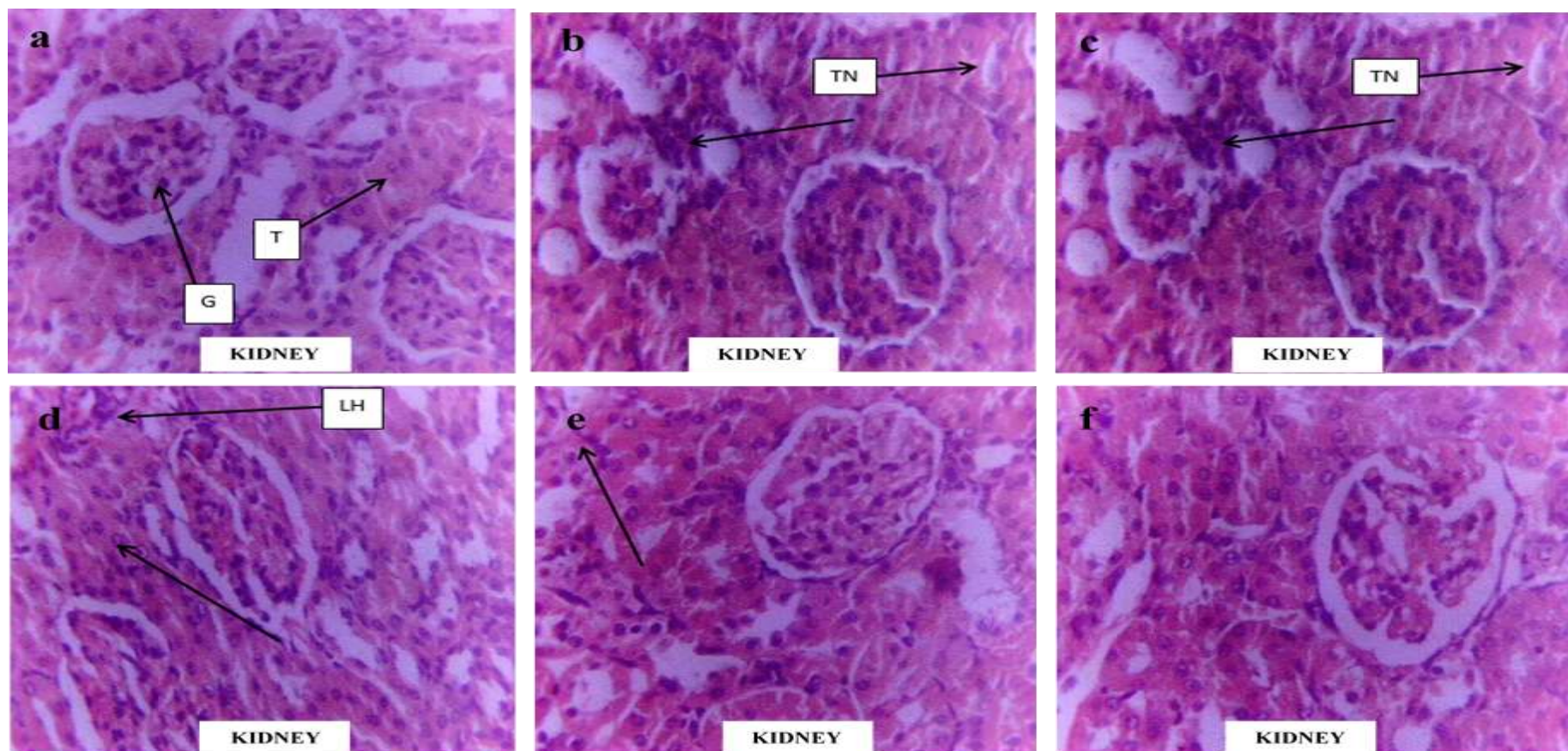


Figure 2: Histopathological images of kidney tissue (H & E x400), (a) Normal control: Liver tissue showing normal architecture. (b) Negative control: shows moderate hyperplasia inflammatory cells and tubular necrosis (damage or destruction of the tubular structures within the kidneys) in the kidney tissue. (c) Positive control (Atropine sulphate): shows slight hyperplasia inflammatory cells and tubular adhesion (a condition where irregular or excessive adhesions form between tubular structures within the kidney) in kidney tissue. (d) BK 100mg: shows moderate tubular distortion (structural abnormalities or changes in the tubular components of the kidney) with slight hyperplasia inflammatory cell in kidney tissue. (e) BK 200 mg: shows slight tubular necrosis (damage or destruction of the tubular structures within the kidneys) in kidney tissue. (f) BK 300 mg: shows normal features in kidney tissue with no damage.

DICUSSIONS

This study provides important new insights into the hepatoprotective, nephroprotective and partial antidotal effects of *Garcinia kola* extract, specifically in the context of indomethacin-induced toxicity. While the medicinal potential of *Garcinia kola* has been suggested in previous research, this study represents a significant advancement in understanding its specific protective mechanisms against drug-induced liver and kidney damage.

One of the key novel findings is the demonstration that *Garcinia kola* can mitigate both hepatotoxicity and nephrotoxicity induced by indomethacin, a widely used NSAID known for its harmful side effects on these organs. Although previous studies have shown *Garcinia kola* to possess general antioxidant and anti-inflammatory properties (Tauchen *et al.*, 2023; Umoh *et al.*, 2020), the extent to which it can protect against specific biochemical and histopathological damage induced by pharmaceutical agents like indomethacin was not fully explored until now.

The reduction of liver enzymes (ALT, AST, ALP) and total bilirubin in the *Garcinia kola*-treated groups aligns with previous findings by Atanu & Okpe, (2021) and Rotimi *et al.* (2022), both of whom observed similar hepatoprotective effects of *Garcinia kola* in models of oxidative stress. Our results further extend these findings by demonstrating dose-dependent effects, where the highest dose (300 mg/kg) restored liver function markers to near-normal levels. This contrasts slightly with Igbiosa *et al.* (2022), who noted diminishing returns at higher doses in alcohol-induced liver damage, suggesting that efficacy may depend on the toxic agent involved. Regarding nephroprotection, our results agree with Atanu and Okpe (2021), who reported that *Garcinia kola* reduced aluminium-induced nephrotoxic markers in rats. However, our study provides stronger evidence of renal protection with

near-normal serum creatinine and urea levels at the highest dose. This suggests that *Garcinia kola*'s efficacy may vary depending on the severity of nephrotoxicity or the agent involved.

The dose-dependent effects observed in this study highlight the potential for *Garcinia kola* as a therapeutic intervention for drug-induced organ damage.

CONCLUSIONS AND RECOMMENDATIONS

This study demonstrates that *Garcinia kola* extract, particularly at a dose of 300 mg/kg, offers significant hepatoprotective and nephroprotective effects against indomethacin-induced toxicity in Wistar rats. The ability of *Garcinia kola* to restore key liver and kidney function markers and prevent histopathological damage suggests its potential as a natural therapeutic agent for mitigating drug-induced organ damage. These findings not only reinforce the antioxidant and anti-inflammatory properties of *Garcinia kola* but also provide new insights into its dose-dependent efficacy. Future research should focus on elucidating the specific molecular mechanisms responsible for these protective effects and investigating long-term outcomes in chronic toxicity models. Clinical trials are also necessary to confirm the efficacy and safety of *Garcinia kola* in humans, which could lead to its incorporation as an adjunct therapy in preventing or treating drug-induced liver and kidney damage.

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CONFLICT OF INTEREST

The authors confirm that there is no conflict of interest.

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