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ASSESSMENT OF ACUTE AND SUB-ACUTE TOXICITY STUDY OF *Garcina kola* HECKEL SEEDS IN WISTAR RAT

[1]Aremu Adeshina Salmat, [1]Muhammed Otuofu Amali, [1]Aliyu Abdulmalik and [*2]Aremu Abdulfatai

[1]Department of Pharmacology and Toxicology, Faculty of Pharmacy, University of Ilorin, Ilorin, Kwara State, Nigeria.
[2]Department of Veterinary Pharmacology and Toxicology, Faculty of Veterinary Medicine, University of Ilorin, Ilorin, Kwara State, Nigeria.

*Corresponding authors' email: aremu.a@unilorin.edu.ng

ABSTRACT

Garcina kola Heckel have been used in the treatment of many diseases such as diabetes mellitus, erectile dysfunction, chronic cough and liver disease. This study aimed at investigating acute and sub-acute toxic effects of *Garcina kola* Heckel seed on physiological, biochemical and histopathological parameters of Wistar rat. Acutely, nine rats (n=3) were used as; A (control); B (1000 mg/kg) and C (2000 mg/kg). Sub-acutely, twenty-five rats grouped; A-E (n=5). A (control), B (125 mg/kg); C (250 mg/kg); D (500 mg/kg) and E (1000 mg/kg). Rats were treated with the extract consecutively for 21 days. *Garcina kola* Heckel seed is safe acutely at tested dose (1000 and 2000 mg/kg) as no mortality/visible toxic reaction was observed. The extract showed non-significant weight gain (day 7) but reduced significantly across the 21 days with most significant reduction in 1000 mg/kg. Haematological result showed that PVC, RBC, haemoglobin and platelets had no significant ($P>0.05$) effect unlike white blood cell and its differentia (neutrophils, lymphocytes and monocytes) which decrease significantly ($P<0.05$). Creatinine increased significantly ($P<0.05$) all treated groups. Albumin, ALT, ALP decrease significantly. AST statistically not significant except group 2 while Total Bilirubin and Total protein decreased significantly compared to the control. Conclusively, *Garcina kola* Heckel seed is safe acutely at administered dosages. Weight was significantly reduced in the course of the treatment while altering the haematological and biochemical parameters. Histopathological result showed that no significant changes were observed using both assessments ensuring a further indication of the safety of the *G. kola* extract.

Keywords: *Garcina kola* Heckel seed, weight, Haematology, Serum chemistry

INTRODUCTION

Understanding regional and native applications of medicinal plants is the main goal of ethnopharmacology (Schultz and Garbe, 2023). Many of the drugs that are currently on the market have been made either directly or indirectly from plants, which have long been a great source of medicines (Ahad *et al.*, 2021). It is estimated that over 80% of modern medications and pharmaceuticals are herbal based products usually employed by world population (Saggar *et al.*, 2022). *Garcinia kola* Heckel, commonly known as bitter kola, is a perennial tree belonging to the family Clusiaceae and is widely distributed across West and Central Africa (Tauchen *et al.*, 2023). As a result of wide and therapeutic functions, *Garcinia kola* Heckel is a valuable ingredient in African ethnomedicine, making the plant a crucial component of folk medicine (Dogara *et al*., 2022). The seeds of *G. kola* are extensively consumed in Nigeria and many other African countries for cultural, nutritional, and medicinal purposes (Yogom *et al.*, 2020). Traditionally, bitter kola is chewed for its perceived stimulant effects and used in ethnomedicine for the management of ailments such as cough, liver disorders, infections, inflammation, and diabetes (Obeta *et al.*, 2023). Its widespread use is largely attributed to its rich phytochemical composition, including biflavonoids (notably kolaviron), tannins, saponins, alkaloids, and phenolic compounds, which have been associated with antioxidant, antimicrobial, anti-inflammatory, and hepatoprotective activities (Nwozo *et al.*, 2023).

Despite most of these reported health uses, scientific attention has been directed toward the potential toxic effects of the plant, particularly with prolonged consumption or when use at high doses (Hudson *et al.*, 2018). As a natural product, bitter kola is often perceived as inherently safe; however, this assumption is increasingly being challenged by experimental and clinical evidence indicating that bioactive compounds capable of exerting therapeutic effects may also induce adverse toxic responses (Chintada, and Golla, 2025). Toxicity of *Garcinia kola* may arise from excessive intake, chronic exposure, interactions with conventional drugs, or variations in preparation and dosage, especially in the absence of standardized guidelines for its medicinal use (Sahil *et al.*, 2021). Several experimental studies have reported dose-dependent toxic effects of *G. kola* seed extracts on vital organs, including the liver, kidneys, and reproductive system (Emmanuel *et al.*, 2022). Hepatotoxicity has been linked to alterations in liver enzyme levels while nephrotoxic effects is usually characterized by impaired renal function markers and structural kidney damage as reported in several animal models studies (Abarikwu *et al.*, 2017). The stimulant properties of *Garcinia kola* are mostly attributed to its caffeine-like constituents which raised concerns regarding cardiovascular and neurological toxicity when consumed excessively (Reyes and Cornelis, 2018). Concerns have been raised regarding the reproductive toxicity of *G. kola*, especially in male subjects, with reports of impaired spermatogenesis, reduced sperm quality, and testicular structural alterations (Enaiho and Ekhoye, 2025). Based on the widespread consumption and medicinal application of *Garcinia kola*, there is need for critical evaluation of the toxicological properties of the plant, understanding the mechanisms, target organs, and dose thresholds associated with its toxicity will contribute to safer use, inform public health recommendations, and support the development of standardized herbal formulations. This study was conducted to investigate the acute and sub-acute toxicity of *Garcina kola* Heckel Seeds in Wistar Rat using physiological, haematological, biochemical and histopathological changes as indices of toxicity.

MATERIALS AND METHODS

Ethical Approval

The Ethical approval was obtained from the Faculty of Pharmaceutical Sciences through the Ethical Review committee of the University of Ilorin, Ilorin, Nigeria. This work approved and assigned approval number: FPS-ERC/ASN/2023/4.

Plant Collection, Identification and Preparation

Seeds of *Garcinia kola* Heckel was taxonomically identified and authenticated in the herbarium of the Department of plant Biology, University of Ilorin, Nigeria and the specimen was deposited with voucher no: **UILH/002/1217/2022**. It was then air dried at room temperature for 15 days. The air-dried content was then blended into powdery form.

Extraction and Separation of Seeds of *Garcinia kola* Heckel

Two kilograms of powdery Seeds of *Garcinia kola* Heckel was soaked in 5 liters of ethanol for 72 hours. Mixture was gently decanted and filtered using filtered paper. The filtrate was immediately evaporated at temp 40°C using a rotary evaporator with brand name Buchhi(R). The concentrate (wet residue) was dried and stored 4°C in the refrigerator.

Experimental Animals

Wistar albino rats weighing between 160-220 g, were used in this study. They were housed using international standard. Rats were maintained on a 12-hour light cycle, at controlled temperature (23±2°C) and humidity (50%). Animals were fed with standard laboratory feed and allowed to access feed and water *ad libitum*. The animals were treated humanely and with regard for alleviation of suffering and the study was approved by University of Ilorin Ethical Committee.

Constitution and Administration of Ethanolic Extract of *Garcinia Kola* Heckel

The stock concentration of both extracts was prepared by dissolving 5 g of the extract in 50 mL of Normal saline at concentration of 100 mg/ml. These preparations were orally administered.

Weight Estimation

The weights of the rats in all groups were monitored from the first day using an automated electronic scale. The rats were randomly divided into groups.

Acute Toxicity Study

The organization for economic co-operation and development (OECD) guidelines 425 was followed to determine the acute toxicity of the extracts in a stepwise procedure. The Albino rats were fasted overnight and weighed. The rats of single sex, weighing between 200- 220 g were put in two single groups consisting of three animals each. They were maintained under standard conditions (room temperature at 22 ± 3°C, 12 hr light/dark) and allowed free access to water along with standard pelleted diet for one week before the experiment. The group 1 & 2 of animals were subjected to acute toxicity study given the oral administration of *Garcinia kola* Heckel seed extract at a dose of 2000 mg/kg orally and observed at regular intervals of 30 minutes, 1, 2, 4, 8, 12 and 24 hours for skin/fur changes, mucus secretion, sleep, coma, lethargy, and mortality.

Sub-Acute Study (Dosing Protocol)

Twenty-five male rats were used for this study; five rats per group (n=5). Four of the groups were administered crude ethanol extract of *G. kola* Heckel seeds for twenty-one (21) days. One of the groups is the control and they were treated with 0.9% Normal saline, others with 125, 250, 500 and 1000 mg/kg. The administration was done orally using oral gavage daily for 21 days. Rats were thereafter sacrificed, and liver, kidney organ and blood samples were collected.

Blood Sample Collection and Animal Sacrifice

Two to three milliliters of blood sample was collected using standard procedure in heparin and plain sample bottles. The rats in all the groups were sacrificed humanely, liver and kidney organs were harvested for histopathological analysis.

Biochemical Analysis

The serum chemistry analyses were carried out using commercial test kits (Biorex®) and this includes total protein, alanine aminotransferase (ALT), aspartate aminotransferase (ASP), alkaline phosphatase (ALP), creatinine, albumin, and total bilirubin.

Histopathology

The histopathology was done on the liver and kidney for toxicity complication observed following standard method. Formalin-fixed slides of the liver and kidney were prepared and stained with haematoxylin & eosin (H&E) and Periodic acid & Schiff reagent (PAS). Stages of the technique include fixation, tissue processing, sectioning, staining, and photomicrography. Photomicrographs of the tissue sections were obtained at magnification × 400 using MD900 Am Scope digital camera and a microscope.

Statistical Analysis

The 2013 version of Microsoft Excel was used to enter quantitative data and calculate its means and standard error of the mean. The results were presented as means ± standard error of mean. Statistically significant differences were determined using one way analysis of variance (ANOVA) followed by Dunnett's post hoc test using Graph Pad Prism version 5. Differences were considered statistically significant at $p < 0.05$.

RESULTS AND DISCUSSION

Determination of the Acute Toxicity of the Ethanolic Seeds Extract of *Garcinia Kola* Heckel

At the dose of 2000 mg/kg administered to a group of three (3) animals no death or toxic effect of the drug was observed throughout the whole observation period that the experiment was carried out as shown in Table 1. This suggests that the dose of the plant extracts used was not acutely toxic.

Table1: Acute Toxicity Assay *G. Kola* Seeds

Group (n=3) Dose (mg/kg)	Dead Rats (n)	Toxic Signs	Toxic Signs
Distilled water	0	No toxic changes observed	Mortality—Nill Mortality—Nill Mucus secretion. Nil Sleep and coma. Nil Lethargy…. Nill

Group (n=3) Dose (mg/kg)	Dead Rats (n)	Toxic Signs	Toxic Signs
B (1000 mg/kg)	0	No toxic changes observed	Mortality—Nill Mortality—Nill Mucus secretion. Nil Sleep and coma. Nil Lethargy…. Nill
C (2000 mg/kg)	0	No toxic changes observed	Mortality—Nill Mortality—Nill Mucus secretion. Nil Sleep and coma. Nil Lethargy…. Nill

Determination of Sub-Acute Toxicity Studies and Weight Estimation on the Ethanolic Seed Extracts of *Garcinia Kola* Heckel

At a dose of 125 mg, 250 mg, and 500 mg of the ethanolic seed extracts of *Garcinia kola* Heckel the animals showed no signs of toxicity, and no death was recorded but at dose 1000 mg 80% death were recorded. The extract showed increased weight gain at week 2 but decreased non-significantly at week 3 in all the tested doses in the course of the study (Table 2).

Table 2: Weight of Experimental Animals Observed Weekly

	Duration (weeks)		
Treatment Groups	**1 RWC (%)**	**2 RWC (%)**	**3 RWC (%)**
Normal saline	100.8±0.4	107.1±1.1	109.8±2.6
125 mg/kg *Gk*	101.5±0.5	106.4±1.2	99.40±2.9
250 mg/kg *Gk*	100.3±0.7	106.3±1.8	102.1±3.5
500 mg/kg *Gk*	101.0±0.3	105.9±2.7	95.58±8.6
1000 mg/kg *Gk*	100.9±0.3	100.3±0.2	93.7±0.2

Data was expressed as Relative Weight Change (RWC) in mean±SEM, using column Statistic analysis. n=5. Gk: *Garcinia kola* Heckel;

Haematology

The haematology result showed that the PVC, RBC, haemoglobin (Hb) and platelets (PL) were statistically unchanged compared to untreated control. WBC and its differential count like Neutrophils, Lymphocytes and Monocytes significantly ($p<0.05$) decreased across treated groups compared to untreated control. Platelet counts of treated rats decreased non-significantly ($p>0.05$) compared to untreated control rats (Table 3).

Table 3: Haematology of Wistar Rats Administered Ethanolic Seed Extracts of *Garcinia Kola* Heckel

Grps/index	Untreated Control	125 $mgkg^{-1}$	250 $mgkg^{-1}$	500 $mgkg^{-1}$	1000 $mgkg^{-1}$
PCV (%)	36.13±0.71	37.64±3.11	35.00±1.83	37.00±3.76	34.00±1.83
RBC×10^6/ µL	7.11±0.42	7.48±0.72	7.00±0.22	7.33±0.64	6.84±0.32
HB (g/dl)	12.10±0.73	12.75±1.27	11.83±0.61	12.43±1.46	11.70±0.81
MCV (fl)	60.65±1.50	60.15±0.50	60.0±0.72	71.0±1.31	70.0±0.00
MCH (pg)	17.31±0.11	17.07±0.25	17.19±0.09	17.30±0.49	17.51±0.08
MCHC (g/dl)	40.00±0.81	40.20±0.36	40.33±0.21	40.32±0.84	40.80±0.46
WBC×10^3/µl	8.80±2.68	3.73±0.21[a]	5.03±0.78[a]	5.05±3.10[a]	4.86±2.43[a]
Lymph×10^3/µl	4.77±1.03	2.22±0.11[a]	3.04±0.55[a]	3.25±0.97[a]	2.84±1.22[a]
Mono×10^3/µl	0.08±0.01	0.03±0.02	0.05±0.03	0.02±0.01	0.05±0.07
Platelet×10^5/dl	20.20±0.68	19.80±6.81	17.38±9.22	18.75±5.44	22.90±0.77

ata rep. as Mean ±SD: n=5

[a] Significant [a]$p\leq0.05$

Biochemical Analysis

Creatinine increased significantly ($P<0.05$) all treated groups compared to the control. Albumin significant ($P<0.05$) decrease except 2 and 5 that increased significantly when compared. ALT, ALP decreased significantly ($P<0.05$) in all treatment except in group 2 & 4 that increased ($P<0.05$) when compared to the control. AST values in all treated groups were statistically not significant except group 2 when compared with control group, Total Bilirubin values indicate a significant ($P<0.05$) decrease values while Total Protein showed in Group 3 decreased significant compared to group 2, 3 & 5 that increased significantly when compared to the control (Table 4)

Table 4: Biochemical Analysis of Albino Rats Treated with the Extracts

Dose of *Garcinia kola* (GK)	***Creatinine* (µmol/L)**	***Albumin* (g/dL)**	***ALP* (U/L)**	***ALT* (U/L)**	***ASP* (U/L)**	***Total Bilirubin* (µmol/L)**	***Total protein* (g/dL)**
Normal saline	86.9 ± 1.5	2.5 ± 0.1	46.9 ±1.0	47.6 ±1.2	42.0 ±0.8	31.1 ± 0.9	9.4 ± 0.2
125 mg/kg	99.3 ± 0.3	1.7 ± 0.1	53.5 ±1.1	38.9 ± 0.8	35.8 ±1.6	30.5 ± 0.3	8.1 ± 0.3
250 mg/kg	79.8 ± 0.4	2.1 ± 0.2	48.6 ±0.9	39.0 ±1.2	37.8 ±1.6	45.8 ±0.5	8.4 ± 0.3
500 mg/kg	79.3 ± 1.7	2.2 ± 0.1	51.2 ±0.6	41.3 ± 0.8	37.2 ±1.4	41.4 ± 0.6	7.8 ± 0.3
1000 mg/kg	71.4 ± 5.5	1.0 ± 0.3	48.5 ±1.3	25.7 ± 0.3	44.8 ±1.8	49.4 ±0.5	6.7 ± 0.5

Data was expressed as mean±SEM, n=5, using Column Statistic. Gk: *Garcinia kola* Heckel, Alanine aminotransferase (ALT), and Alkaline phosphatase (ALP), Aspartate aminotransferase (ASP)

Histopathology

Histological result of the effect of ethanolic extract of *G. kola* Heckel seeds on albino rats' liver and kidney are shown in Plate 1 - 2. Plate 1: Hematoxylin and eosin (H&E) stain of the kidney x 400, the photomicrograph of the rat kidney administered with different doses of the ethanol extract of *Garcinia kola* Heckel, the glomerulus, bowman space and distal convoluted tubules of the control groups compared with the treated groups 125 mg and 250 mg shows no observable/visible lesion but at 500 mg and 1000 mg there is toxicity of the glomerulus and bowman spaces which become shrinking as compare with the control and the lower doses. Plate 3: Hematoxylin and eosin (H&E) stain of the Liver x 400, the photomicrograph of the rat liver given ethanol extract of *Garcinia kola* Heckel, the sheet of hepatocytes, central vein and sinusoids space are fenestrated as the dose of the treated groups 125 mg, 250 mg, 500 mg and 1000 mg increasing compared with the control groups. Plate 2: (PAS) Periodic acids-Schiff staining of the rat kidney x 400, the PAS stain of photomicrograph of the rat kidney given ethanol extract of *Garcinia kola* Heckel, the glomerulus, bowman space and distal convoluted tubules of the control groups compared with the treated groups 125 mg and 250 mg shows no observable/visible lesion but at 500 mg and 1000 mg there is toxicity of the glomerulus and bowman space which become shrinking as compare with the control and the lower doses Plate 4: (PAS) Periodic acids-Schiff staining of the Liver x400, the PAS stain of photomicrograph of the Liver rat given ethanol extract of *Garcinia kola* Heckel, the central vein is visible, the sheets of the hepatocytes are good, the central vein are good in shape and the sinusoids of the control groups compared with the treated groups 125mg, 250mg, 500mg and 1000mg shows no observable/visible lesion.

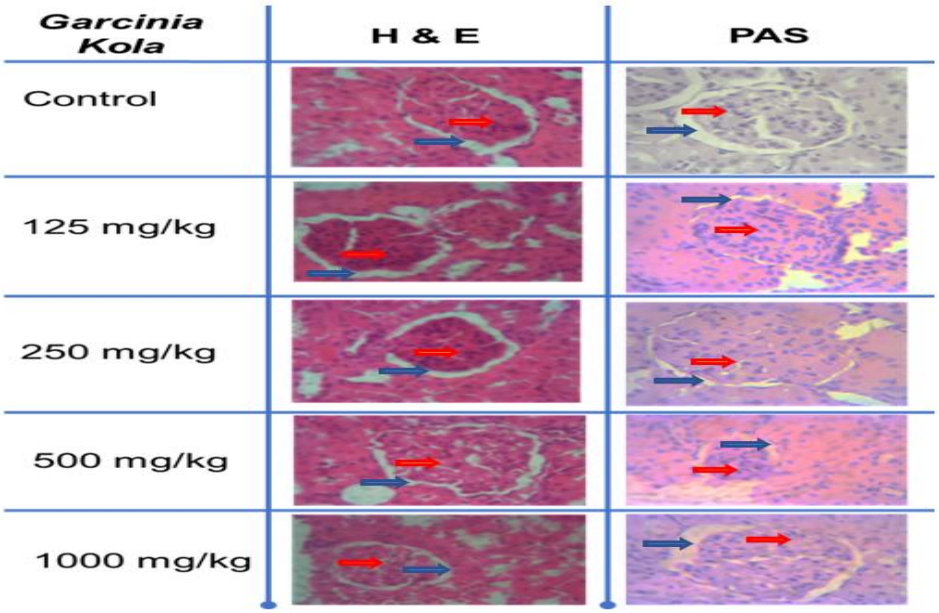

Figure 1: H&E (Hematoxylin and Eosin) and PAS (Periodic acids-Schiff) Stain of the Rat Kidney x400, Administered with Ethanolic Extract of *Garcinia kola* Heckel, the Glomerulus, Bowman Space and Distal Convoluted Tubules of the Control Groups Compared with the Treated Groups shows no Observable/Visible Lesion at 125 and 250 mg/kg doses but they become Smaller as the dose Increases NB. Red Arrow Denote Glomerulus and Blue Denote Bowman Space.

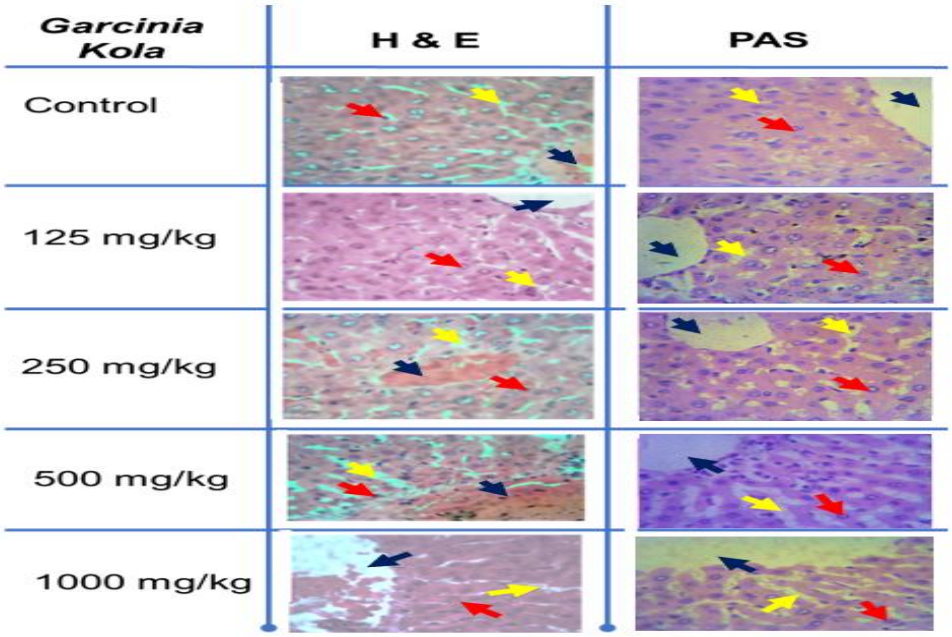

Figure 2: H&E (Hematoxylin and eosin) and PAS (Periodic Acids-Schiff) Stain of the Photomicrograph of the Rat Liver x400, H&E Administered Different doses of Ethanolic Extract of *Garcinia kola* Heckel, the Sheet of Hepatocytes Decreasing and Sinusoids Becoming Smaller as the dose of the Treated Groups Increasing Compared with the Control Groups. Plate 4: (PAS) shows no Observable/Visible Lesion as Compared with the Control Group

NB. Black arrow denote central vein, Yellow denote sinusoids space and Red denote hepatocyte

Discussion

Plants provide a source of inspiration for novel drugs discovery and this function is as a result of abundant quantities of phytochemicals, some of which are known to be toxic to vital organs and tissues (Porras *et al.,* 2021). In the acute study, the result showed that *Garcinia kola* seed possess a considerable margin of safety due to absence of any mortality and observable toxic effect at highest administered dosage (2000 mg/kg) throughout the study period. This result agrees with Tordzagla *et al.,* (2025) who reported that *G. kola* was non-toxic when administered to check their acute toxicity and the LD50.

Haematology is usually evaluated in toxicity assessments of food substances and medicinal plant (Jităreanu *et al.,* 2022). The blood picture of the current study showed that PVC, RBC, haemoglobin, MCV, MCH, MCHC and platelet counts showed non-significant changes, except WBC and its differential count (lymphocytes, monocytes and neutrophils) which decreased significantly across treatment groups. General haematology result of this toxicity study showed that crude extract of *Garcinia kola* Heckel seeds exhibited significant improvement on most haematological parameters. This result agrees with Aremu *et al.,* (2022) stating that most medicinal plants improve haematological indices. WBC on the other decreased significantly across the treated rats and this can lead to decreased immunity. This observation agrees with Aremu *et al.,* (2022) that pointed out that crude extract caused significant alteration in white blood cells.

When a vital organ such as the liver or kidney is damaged by chemical agents, loss of organ function may be determined by certain biochemical markers such as serum alanine phosphatase (ALP), alanine amino transferase (ALT) and aspartate amino transferase (AST) (Tamber *et al.,* 2023). When liver cells are destroyed by chemical agent, AST and ALT are often released into the blood stream in conformity with the extent of the damage (Sroor *et al*., 2022). The non-elevation of these biochemical markers following treatment is a further pointer to their potential safety when administered individually. Studies have also previously indicated that ethanolic extract of *G. kola* Heckel seeds showed no significant difference in the values of AST, ALT, ALP, TB and Total Protein within the administered concentrations and reported a role for *G. kola* Heckel seeds as hepatoprotective agent against some toxic substances **(**Ojatula and Ezenwa, (2023), Nwachukwu *et al.,* 2022). The elevated levels of creatinine is a pointer that creatinine in all treated group compared with the control group indicate a statistically significant increase at the various doses. Histopathological assessment of the effect of *G. kola* Heckel seeds extract in the liver and kidney of the treated rats revealed generally that there is no significant changes in the liver which is an indicative of a normal reactive change in the liver cell. Further results of both the H & E and PAS photomicrographic stains of the kidney and liver did not show any histological changes which agrees with the previous reports that there were no histopathological effects on the liver and kidney except at the higher doses, showing the hepatic safety in healthy consumption of *Garcinia kola* Heckel seeds at a lower dose (Galam, *et al.,* 2013, Malann, 2018).

CONCLUSION

Conclusively, this study showed that *G. kola* Heckel seeds is safe at acute administered dosages because there is no mortality. Assessment of the hepatotoxic effects of the Ethanolic extract of *G. kola* Heckel seeds on some biochemical parameters like ALP, ALT, AST, Total protein (TP), Total Bilirubin (TB), Creatinine, and Albumin (ALB) indicated the potentially safety of the extract. Histopathological showed no significant histological changes using both assessment methods ensuring a further indication of the safety of the *G. kola* extract.

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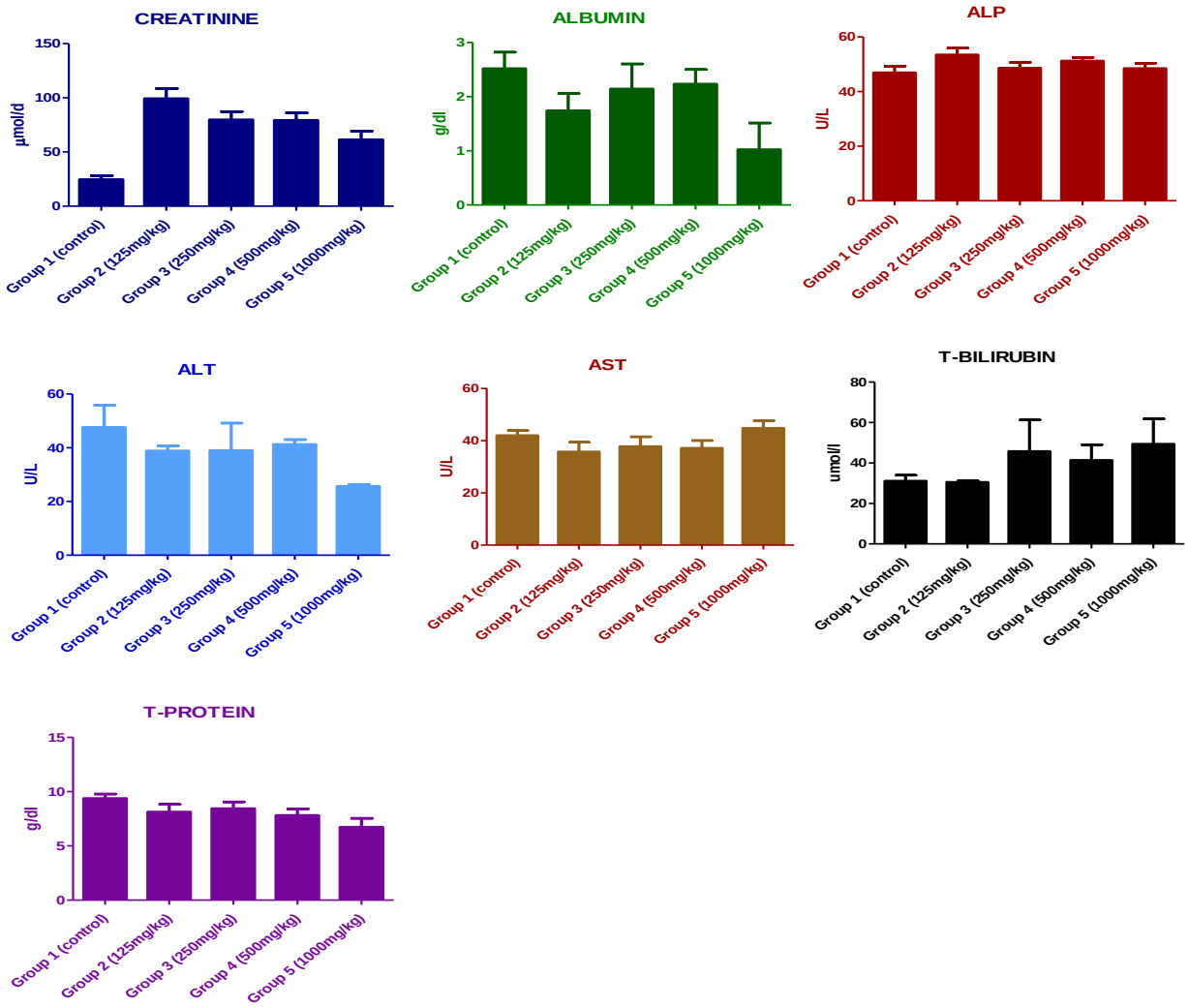
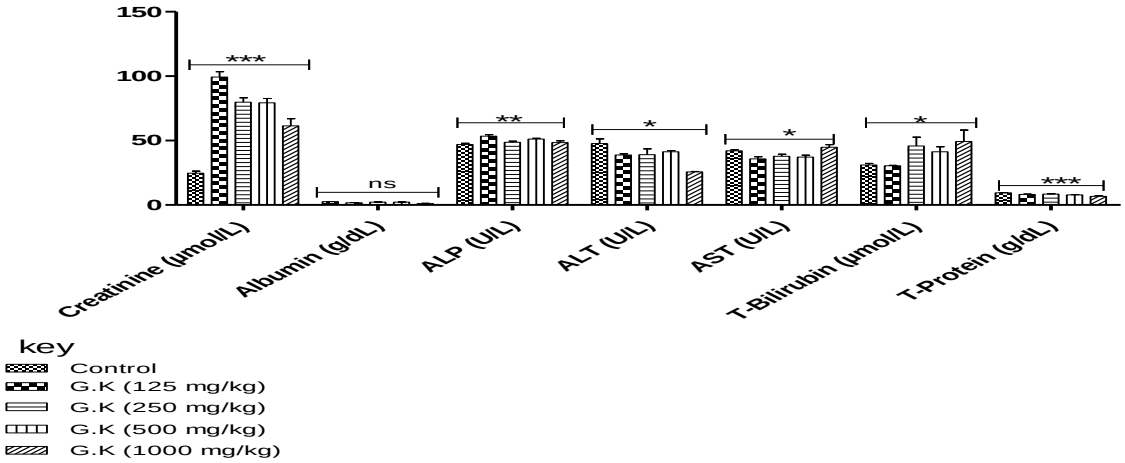
APPENDIX



Appendix 1: Error bar of Biochemical Analysis of Albino Rats Treated with the Extracts



Appendix 2: Biochemical Analysis with Significant Values at $p<0.05$