Original Article

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Therapeutic Potential of Ethanolic Extract of Garcinia Kola in Managing Hyperglycemia and Hepatic Dysfunction in Diabetic Male Wistar Rats

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Abstract:

Objective: There has been an increase in age-standardized mortality rates from diabetes. This study aimed to evaluate the therapeutic potential of the ethanol extract of *Garcinia kola* in managing hyperglycemia and organ damage in streptozotocin-induced diabetic adult male albino rats.

Material and Methods: A total of 25 adult male Wistar rats (120–230 g) were used in this study, randomly assigned to five groups, comprising five rats each. Group A served as the normal control, while Group B was the diabetic control. Diabetes was induced in Groups B, C, D, and E using a single intraperitoneal injection of streptozotocin at 120 mg/kg body weight. Following induction, Groups C and D received oral doses of *G. kola* extract at 300 mg/kg and 500 mg/

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kg body weight, respectively, whereas Group E was treated with glibenclamide at 5 mg/kg body weight. All treatments were administered once daily for 14 consecutive days.

Results: The results demonstrated a statistically significant (p-value<0.05) reduction in glucose levels in the treated groups compared to the untreated diabetic control (Group B). Significant variations in body weight were also observed across the experimental groups. Groups C and D exhibited elevated serum liver enzymes and bilirubin levels relative to Group B. However, no statistically significant differences (p-value>0.05) were observed in kidney function parameters between Groups C and D.

Conclusion: This study confirmed the anti-diabetic efficacy of *G. kola* and also established that exposure to *G. kola* may cause liver dysfunction.

Keywords: alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, diabetes, *Garcinia kola*, streptozotocin, hyperglycemia

Introduction

Diabetes mellitus is a metabolic disease marked by increased blood glucose levels due to abnormalities in insulin secretion, insulin activity, or a combination of the two[1]. According to the 2025 International Diabetes Federation (IDF) Diabetes Atlas, an estimated 589 million adults (20–79 years) are currently living with diabetes, representing approximately 11.1% of the global adult population (1 in 9 adults)[2,3]. The WHO also highlights diabetes as one of the most pressing non-communicable diseases, affecting over 800 million people worldwide, particularly in low- and middle-income countries[4]. In sub-Saharan Africa, the burden is steadily rising, with Nigeria, Africa's most populous nation, ranked among the top 10 countries with the highest number of adults living with diabetes[5]. Insufficient insulin secretion and insulin resistance are the primary pathological characteristics of type 2 diabetes mellitus (T2DM)[5]. From 2000 to 2019, age-standardized mortality rates from diabetes rose by 3%. In lower-middle-income countries, diabetes-related deaths saw a 13% increase during the same period[6].

Renal complications from diabetes are a serious public health concern and may be linked to persistent liver disease associated with hepatorenal syndrome[7-8]. Individuals with diabetes mellitus face an elevated risk of developing kidney disorders, particularly after living with the condition for several years. Additionally, kidney impairment can occur alongside liver cirrhosis, presenting as either glomerular damage or hepatorenal syndrome[9]. Impaired liver function can intensify high blood sugar levels in diabetic patients and contribute to a faster progression of diabetes-related health issues. The high incidence of diabetes and its complications, which affect various organs, including the liver and kidneys, underscores the need for alternative and safer therapeutic options[10].

Many pharmaceutical treatments are available for managing diabetes, but their effectiveness may be limited by adverse effects, cost, and issues with patient adherence. This highlights the importance of alternative medicines, particularly those derived from natural sources with minimal side effects. Plants are among the most promising sources for discovering new antioxidant agents[11]. Due to their therapeutic properties, availability, and affordability, humans have been consuming plant seeds, roots, stems, flowers, and fruits for centuries to treat various ailments. *Garcinia kola* seeds are traditionally used for both recreational purposes and as a remedy for malaria.

Preliminary research indicates that these seeds may have neuroprotective, anti-inflammatory, and blood sugar-regulating effects[12–13]. *G. kola* has gained significant research interest in recent years, primarily due to its unique biflavonoid complex, kolaviron, which appears to be exclusive to *G. kola*. Evidence suggests that this constituent may act through multiple mechanisms relevant to the pathophysiology of diabetes. Research by Salau et al.[14] reported that *G. kola* produced its antidiabetic effect via the inhibition of α-glucosidase and α-amylase activities. Recently, it was reported that the reduced glucose concentration could be due to the activity of *G. kola* seed extract against inflammation and ROS of free radicals on the pancreatic beta cells[15–16]. Several researchers have identified *G. kola* as a potentially valuable compound for drug discovery[17–19]. While several studies have reported the antioxidant and antidiabetic properties of *Garcinia kola*[12–13], the evidence is inconsistent and often limited to single-outcome assessments. In particular, few studies have simultaneously examined its impact on hyperglycemia and its potential toxicity on vital organs under diabetic conditions. This leaves an important gap in understanding whether *Garcinia kola* can provide therapeutic benefit without compromising organ integrity. Therefore, the present study was designed to evaluate both the antihyperglycemic efficacy and the potential organ-specific toxicity of *Garcinia kola* in streptozotocin-induced diabetic male albino rats.

Material and Methods

Experimental animals

For this study, twenty-five 8-week-old male Albino rats weighing 120–230 g and fourteen 4-week-old Swiss Wistar mice of both sexes weighing 20–30 g were procured from the Department of Zoology and Environmental Biology, University of Nigeria, Nsukka. The animals were kept in a controlled environment (25±2 °C with a 12-hour light/dark cycle). They were provided with standard pellets (Grand Cereals Ltd, Enugu, Nigeria) twice a day and had unrestricted access to clean water. The study was conducted in accordance with the established guidelines for the care and use of laboratory animals.

Plant collection and identification

The seeds of *G. kola* used for this research were purchased from Orba Market in Nsukka, Enugu State, Nigeria. The seeds were identified and confirmed by Mr. Felix I. Nwafor from the Herbarium Unit, Department of Plant Science and Biotechnology, University of Nigeria, Nsukka, with the herbarium registration number UNH/04/0303C.

Preparation of seed extract

The seeds were dried at ambient temperature (29–35 °C) for three weeks and subsequently ground into a coarse powder using a Crestor high-speed milling machine (Strathclyde, Scotland). Extraction of *Garcinia kola* seeds using ethanol was carried out according to the method previously reported by Wang et al.[20]. Ethanol extraction was performed by macerating a measured quantity (550 g) of powdered *G. kola* seeds in 1.5 L of ethanol for three days. The resulting suspension was passed through a 0.15 µm mesh using Whatman No. 1 filter paper, and the filtrate was evaporated under reduced pressure using a rotary evaporator 40 °C (Model 349/2, Corning Ltd., England) to obtain the crude ethanol extract. The total yield (36.8 g) was stored in a refrigerator for further use.

Ethical approval

Ethical approval was granted by the Research and Ethics Committee, University of Nigeria.

Experimental design

Twenty-five male albino rats were randomly assigned to five groups of 5 animals each. Dose selections for *G. kola* and Glibenclamide were in accordance with a report by Chukwudi-Emelike et al.[21].

Group A: Normal control.

Group B: Positive control (induced with streptozotocin (120 mg/kg b.w) but untreated).

Group C: Induced with streptozotocin (120 mg/kg b.w) and treated with 300 mg/kg body weight of crude extract.

Group D: Induced with streptozotocin (120 mg/kg b.w) and treated with 500 mg/kg body weight of crude extract.

Group E: Induced with streptozotocin and treated with the standard drug (Glibenclamide, 120 mg/kg body weight), serving as the standard (negative) control.

Induction of Diabetes

An experimental diabetic model was developed in male albino rats by administering streptozotocin (120 mg/kg) intraperitoneally[22-23]. After 24 hours, the blood glucose level of each animal was measured, and only animals confirmed to be diabetic were selected for the study.

Treatment of Diabetes with plant extract

One gram of the crude ethanol extract of *G. kola* was dissolved in a mixture of Tween-80 and normal saline. The prepared solution was administered orally once per day throughout the treatment period.

Collection of blood sample and preparation of serum

Following the 14-day treatment period, chloroform was used to anesthetize the experimental rats, after which 7 mL of whole blood was collected from the medial canthus of the eye. The collected blood was transferred into a plain tube and allowed to clot for 30 minutes. The tube was then placed in a centrifuge (Gallenkamp, Germany) and spun at 1,000 rpm for 10 minutes to separate the serum from the blood. The extracted serum was pipetted into a clean, dry plain bottle using a Pasteur pipette and stored in a refrigerator (Haier Thermocool, England) for further analysis.

Biochemical analyses

Liver function tests

Aspartate aminotransferase (AST) assay

Aspartate aminotransferase (AST) activity was determined following the procedure outlined by Mañourová et al[19]. A 0.1 mL serum sample or distilled water (blank) was added to labeled tubes, followed by 0.5 mL of Reagent 1 (phosphate buffer, L-aspartate, β-oxoglutarate). After thorough mixing, the tubes were incubated at 37 °C for 30 minutes. Subsequently, 0.5 mL of Reagent 2 (2,4-dinitrophenylhydrazine) was added and incubated at 25°C for 20 minutes. Finally, 5.0 mL of 0.4 N sodium hydroxide was added, mixed, and the absorbance was read at 546 nm after 5 minutes.

Alanine aminotransferase (ALT) activity

ALT activity was measured following the method described by Reitman and Frankel[24]. A 0.1 mL volume of serum was transferred into the test tube designated for the sample, while 0.1 mL of distilled water was added to the blank tube. Thereafter, 500 µL of ALT substrate buffer (Reagent One, R1), containing phosphate buffer, L-alanine, and α-oxoglutarate, was added to both tubes. The contents were mixed thoroughly and incubated in a water bath at 37 °C and pH 7.4 for 30 minutes. After incubation, 0.5 mL of Reagent Two (R2), which contains 2,4-dinitrophenylhydrazine, was added to each tube. The mixtures were gently mixed and allowed to stand at room temperature (25 °C) for exactly 20 minutes. Finally, 0.5 mL of sodium hydroxide solution was introduced into both the blank and sample tubes, followed by thorough mixing. Absorbance was then recorded at 546 nm exactly 5 minutes after the addition of sodium hydroxide.

Alkaline phosphatase (ALP) activity

ALP activity was determined using the method described by Babson et al.[25], as specified in the Randox diagnostic kit protocol. Three tubes were prepared and

labeled as test, standard, and blank. A volume of 50 µL of serum, standard solution, and distilled water was dispensed into the respective tubes. Subsequently, 50 µL (0.05 mL) of ALP substrate was added to each tube. The contents were gently mixed and incubated at 37 °C for precisely 10 minutes. After incubation, 2.5 mL of the ALP color developer was added to each tube at timed intervals and thoroughly mixed. The absorbance of the resulting solutions was then read at a wavelength of 630 nm.

Kidney function tests

Determination of serum creatinine

Serum creatinine concentration was measured following the procedure described by Burtis and Ashwood[26], as specified in the Randox kit (UK). Three tubes were labeled as test, standard, and blank. Into each respective tube, 50 µL of serum, standard solution, and distilled water were added. Subsequently, 500 µL of the working reagent was dispensed into all tubes and mixed thoroughly. The absorbance of each mixture was then recorded at a wavelength of 510 nm.

Determination of Urea

Three test tubes were designated as serum, standard, and blank. Subsequently, 10 µL of serum, standard solution, and distilled water were added to their respective tubes. To each, 100 µL of sodium nitroprusside and urease reagent (R1) was introduced, followed by thorough mixing and incubation at 37 °C for 10 minutes. After incubation, 2.5 mL each of reagent R2 and reagent R3 were sequentially added, mixed immediately, and incubated again at 37 °C for 15 minutes. Absorbance readings were taken at 546 nm.

Determination of total bilirubin

Total bilirubin concentration was measured in the presence of caffeine, which facilitated the release of albumin-bound bilirubin through its reaction with diazotized sulfanilic acid[27]. Two cuvettes were prepared and labeled as "sample blank" and "sample." Into each cuvette, 0.20 mL of Reagent 1 (sulfanilic acid and hydrochloric acid) was added, followed by 0.05 mL of Reagent 2 (sodium nitrite) and 1 mL of Reagent 3 (caffeine and sodium benzoate). Subsequently, 0.2 mL of serum was introduced into both cuvettes. The mixtures were thoroughly mixed and allowed to stand for 10 minutes at 25 °C. After incubation, 1 mL of Reagent 4 (tartrate and sodium hydroxide) was added to each cuvette, mixed again, and left to stand for an additional 30 minutes at 25 °C. The absorbance of the sample was then recorded against the blank at a wavelength of 578 nm.

Determination of serum albumin

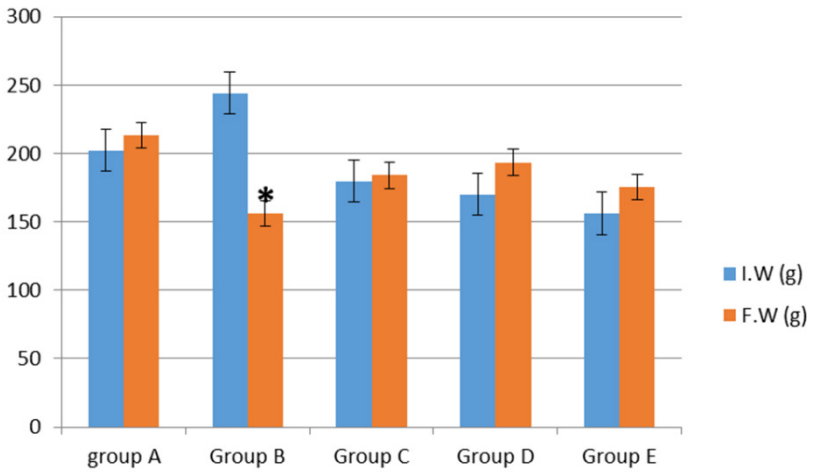
Serum albumin concentration was determined according to the method of Burtis and Ashwood[26], using the Randox kit (UK). Gain calibration was performed in cuvette mode with freshly prepared double-distilled water (ddH_2O). The ALB parameter was selected on the Run Test interface, and a water blank was run prior to sample analysis.

Statistical analysis

Data analysis was performed using Statistical Package for Social Sciences (SPSS) version 20. One-way analysis of variance (ANOVA) was used to determine significance. Results were expressed as mean ±standard error of the mean (SEM). Statistical significance was set at $p\text{-value}<0.05$.

Results

As shown in Figure 1, a statistically significant decrease ($p\text{-value}<0.05$) in the final weight was observed in the positive control group (Group B) when compared to the initial weight. However, no significant differences ($p\text{-value}>0.05$) were detected between the initial and final weights in the other experimental groups.



*statistically significant, I.W=initial weight, F.W=final weight, n=25, p-value≤0.05

Figure 1 Effect of *G. Kola* extract on mean value of initial and final body weight

In Figure 2, following streptozotocin induction at Week 0, all experimental groups demonstrated a marked increase in blood glucose levels by Week 1, except for the normal control group (Group 0), which maintained stable glucose concentrations throughout the study period. Group E exhibited the highest peak glucose level (~420 mg/dL) at Week 1, followed closely by Group B (~400 mg/dL), while Groups C and D showed moderate elevations (~330 mg/dL and ~240 mg/dL, respectively). Group A recorded the lowest increase (~130 mg/dL), indicating a comparatively milder hyperglycemic response. By Week 2, a gradual reduction in blood glucose levels was observed in Groups E, C, and D, suggesting the onset of glycemic control, whereas Group B maintained persistently elevated glucose concentrations with minimal change. Group A also exhibited a slight decline in glucose levels. At Week 3, the downward trend continued across Groups A, C, D, and E, with Group A reaching glucose levels similar to Groups C and D (~110–140 mg/dL). In contrast, Group B remained significantly hyperglycemic (~400 mg/dL) through Week 3.

In Figure 3, the serum liver enzymes generally showed increased levels of AST, ALT, and ALP compared to the control group. Serum bilirubin, albumin, and gamma-glutamyl transferase (GGT) also exhibited an elevation relative to the control group. Notably, Group C, which was treated with 300 mg/kg of the crude extract, displayed the most statistically significant increases in ALT, AST, ALP, GGT, albumin, and bilirubin (p-value<0.05) compared to the other groups.

For ALT, the findings demonstrated that Groups B and D had ALT levels approximately 5.95% higher than the reference Group A, while Group E had ALT levels approximately 4.19% lower than Group A. Group C demonstrated the most significant increase in ALT levels, showing a 34.10% increase compared to Group A. ALT levels are known to exhibit diurnal variation. Within hepatocytes, ALT catalyzes the formation of glutamate and pyruvate, both of which are essential intermediates for ATP synthesis[28].

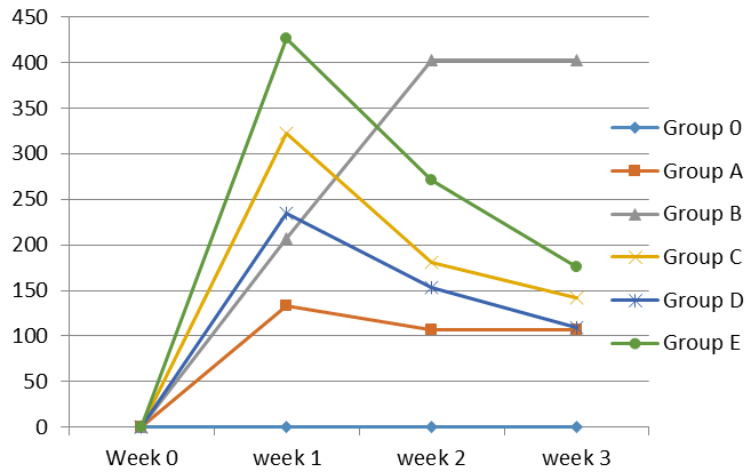
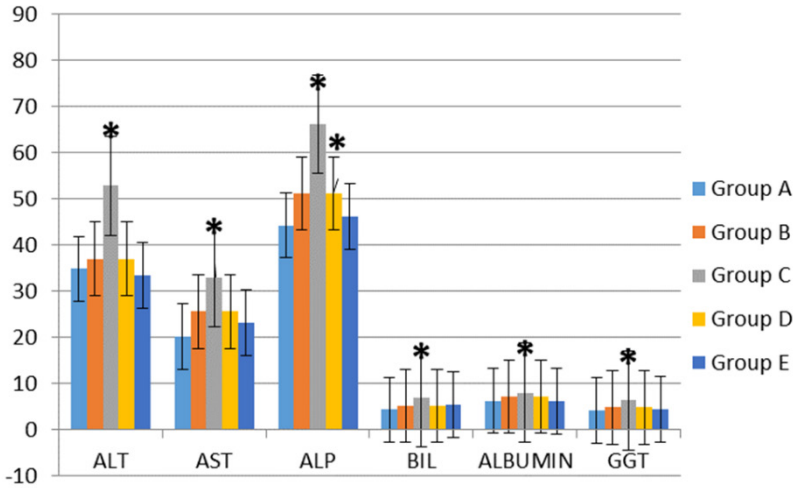


Figure 2 Effect of *G. kola* extract on mean blood glucose level, n=25, p-value≤0.05



*statistically significant, ALT=alanine aminotransferase, AST=aspartate aminotransferase, ALP=alkaline phosphatase, BIL=bilirubin, GGT=gamma-glutamyl transferase, n=25, p-value≤0.05

Figure 3 Effect of *G. kola* on mean liver enzymes

The variation in AST levels was assessed relative to the normal control group. All groups (A, B, D, and E) exhibited positive percentage changes, indicating elevated AST concentrations. Group C, however, showed a notably greater increase (38.79%), suggesting a pronounced alteration in AST levels compared to the normal group, which might not be easily detected through standard diagnostic methods. Like ALT, AST is an essential enzyme involved in amino acid metabolism[29].

In the assessment of ALP activity, Group C demonstrated a statistically significant difference (p-value<0.05) relative to the normal, positive, and negative

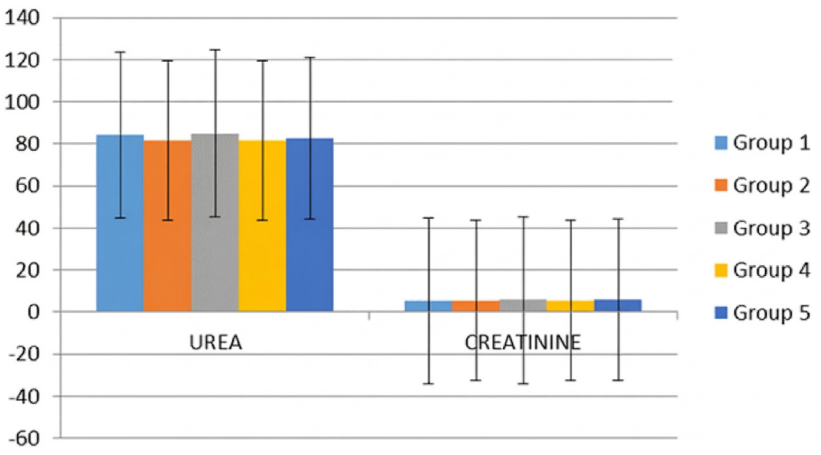


Figure 4 Effect of *G. kola* extract on kidney function (n=25)

control groups. Similarly, Group D exhibited a significant variation compared with the normal and positive control groups.

Discussion

This study investigated the therapeutic potential of *G. kola* in managing hyperglycemia and organ damage in diabetic male Wistar rats. Significant changes in body weight were observed across the experimental groups, with only Group B (diabetic control) showing a statistically significant reduction by the end of the study. This weight loss aligns with typical streptozotocin-induced diabetes outcomes[30], characterized by impaired glucose utilization, muscle wasting, and dehydration. In contrast, Groups C and D, treated with different doses of *G. kola* extract, maintained stable body weights comparable to the standard drug and normal control groups, suggesting a protective effect against diabetes-induced weight loss.

Regarding blood glucose levels, Groups C, D, and E demonstrated varying degrees of glycemic control, whereas Group B maintained elevated glucose levels. The antidiabetic effect of *G. kola* may be attributed to its biflavonoid content, known to inhibit α-glucosidase and α-amylase activities[31].

Alkaline phosphatase (ALP) is an enzyme predominantly located in the hepatobiliary system, bone, and placenta, with smaller concentrations found in intestinal tissues. It plays a key role in various dephosphorylation processes[32]. The increase in ALP levels suggests a cholestatic pattern, which may indicate liver disease[32]. This implies that the extract potentially caused bile duct obstruction, leading to elevated ALP levels[32].

This elevated level of transaminases has serious health implications. Such elevations are commonly found in cases of liver damage[32]. The observed increase in both AST and ALT levels suggests liver involvement, a typical response seen in cases of hepatotoxicity induced by toxic substances. Bilirubin activity results revealed a statistically significant difference (p-value<0.05) in Group C compared to the normal, positive, and negative control groups, as well as a significant difference in Group D relative to the normal group. The elevated bilirubin levels in these groups point to liver damage and potential bile obstruction caused by the *G. kola* extract[33]. Elevated bilirubin levels are commonly

associated with acute hepatitis A and B in adults, often leading to jaundice (particularly with hepatitis A), and are accompanied by increased ALP levels[34].

Regarding albumin activity, statistically significant differences (p-value<0.05) were observed between Groups B, C, and D compared to both the normal and positive control groups. Furthermore, a significant difference was noted between Group C and Group E (positive control) in comparison to the negative control group. Albumin accounts for 50% to 60% of the total protein in serum, making it one of the main protein components in the blood. Albumin, primarily synthesized in the liver, is commonly regarded as a marker of hepatic synthetic function[35]. Various factors can influence albumin levels, including protein deficiency, nephrotic syndrome, fluid retention, systemic inflammation (since albumin is a negative acute-phase reactant), and protein-losing enteropathy[29]. In addition to its numerous functions, albumin plays a critical role in maintaining serum oncotic pressure and facilitates the transport of both endogenous compounds (such as bilirubin) and exogenous substances (including medications)[35].

For GGT activity, a statistically significant difference (p-value<0.05) was observed in Group C compared to both the normal and the positive and negative control groups. GGT is an enzyme present in various organs, including the pancreas, seminal vesicles, kidneys, biliary tract, and liver. Its elevation is often regarded as indicative of hepatobiliary disorders, especially when associated with increases in other liver function biomarkers. GGT levels are commonly elevated in biliary diseases and can also rise in response to medications that induce cytochrome enzymes and excessive alcohol consumption.

Serum bilirubin, AST, ALP, and GGT are routinely evaluated as predictors of choledocholithiasis. Ahn et al.[34] identified GGT as the most reliable marker for common bile duct stones, reporting a sensitivity of 80.6% and specificity of 75%. In contrast, another investigation found that raised ALP levels constituted the strongest predictor of CBD calculi[27]. In the present study, however, treatment with the *G. kola* extract did not elicit any significant alterations in serum creatinine or urea concentrations (p-value>0.05), indicating an absence of nephrotoxic effects. This highlights the potential therapeutic benefit of *G. kola* in protecting against renal toxicity in diabetes. Conversely, the elevated levels of liver enzymes indicate that *G. kola* could have detrimental effects on the liver in diabetic individuals.

Conclusion

Exposure of the extract to experimental rats caused liver dysfunction without any significant effect on the kidneys. Although *Garcinia kola* has been widely reported to possess antioxidant, anti-inflammatory, and antidiabetic properties, concerns remain regarding its potential hepatotoxicity, indicating the need for careful dose selection.

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Conflict of interest

The authors report no potential conflicts of interest regarding the publication of this work.

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