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Effect of *Gongronema latifolium* and *Telfairia occidentalis* Leaf Fractions on Hepato-renal Function of Streptozotocin-induced Diabetic Wistar Rats

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Abstract

The effects of oral administration of methanol and ethyl acetate leaf fractions of *Gongronema latifolium* (GL) and *Telfairia occidentalis* (TO) on the liver and kidney functions of streptozotocin-induced diabetic Wistar rats were investigated. Fifty-four male rats were sorted into 9 groups of 6 animals each. Streptozotocin (60 mg/kg bw) was administered intra-peritoneally to induce diabetes in Groups II – IX. Groups I and II served as normal control (NC) and diabetic control (DC) respectively. Groups III, IV and V were treated with insulin (10 IU/kg), methanol and ethyl acetate fractions of GL respectively. Groups VI and VII were treated with methanol and ethyl acetate fractions of TO respectively while groups VIII and IX were treated with combined methanol and ethyl acetate fractions of GL and TO respectively. All fractions were administered at 500 mg/Kg bw for 28days. Biochemical parameters of liver and kidney and their respective histopathology were assessed. The result showed significant ($p<0.05$) increase in the AST, ALT, ALP activities, total bilirubin, urea, creatinine, sodium, potassium and chloride concentrations coupled with significant ($p<0.05$) decrease in the total protein and albumin concentrations in the DC group, when compared to the NC. However, the fraction treated groups showed significant ($p<0.05$) decreases in the AST, ALT, ALP activities and total bilirubin, urea, creatinine, sodium, potassium and chloride concentrations with significant ($p<0.05$) increase in the total protein and albumin concentrations when compared to the DC group. The histological features of the fraction treated groups was evident with improved cyto-architecture of liver and kidney tissues compared to the atrophying areas of degenerated cells and micro-vesicular steatosis seen in the DC group. This study therefore demonstrate the ameliorative potential of *Gongronema latifolium* and *Telfairia occidentalis* methanol and ethylacetate fractions against diabetic-induced hepato-renal toxicity in Wistar rats.

Keywords: Diabetes; Hepatotoxicity; Renal toxicity; *Gongronema latifolium; Telfairia occidentalis*

1. Introduction

Diabetes mellitus is a metabolic disorder associated with high blood glucose levels caused by decreased insulin secretion and or decreased sensitivity of body cells to the stimulatory impact of insulin [1, 2]. Chronic hyperglycemia can lead to damage and dysfunction in various internal organs including the liver and kidney. The prevalence of diabetes has continued to rise globally, attributed to various factors including lifestyle changes and an aging population [3, 4].

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According to a report by The International Diabetes Federation (IDF) [5], diabetes mellitus was said to be responsible for more than 6.7 million deaths. Furthermore, in 2030, it is believed that more than 643 million people will be down with diabetes mellitus, hence why most people and culture especially in rural areas are paying keen attention to medicinal plant. Medicinal plants have been used for ages in the treatment of different illnesses including the management of diabetes mellitus, especially in the rural areas where access to conventional medicine may be limited [6, 7]. Plants have been used across various cultures and traditions for ages due to their therapeutic properties, availability and affordability [8].

Studies has shown that diabetes mellitus is most often accompanied by chronic kidney and liver diseases, obesity, among others. The liver plays an essential role in glucose homeostasis by coordinating several glucose formation and utilization pathways at normal physiological levels, while the kidney serves as an excretory tissue that is involved primarily with regulating the blood pressure, water and electrolytes levels in the body [9]. Hence the aim of this study is to determine the effect of leaf fractions of *Gongronema latifolium* and *Telfairia occidentalis* on the liver and kidney enzyme activities and tissues in diabetic male Wistar rats.

Gongronema latifolium and *Telfairia occidentalis* have both been confirmed to be used both for nutritional and medicinal properties. They are both antidiabetic plants that have been used traditionally as polyherbal mixture for the management of the disease and its related hepatic and renal associated complications. Studies have also confirmed the individual pharmacological activity of these plants, hence the combined fraction study.

2. Materials and method

2.1. Collection and Identification of Plant Material

Fresh leaves of *Gongronema latifolium* and *Telfairia occidentalis* were purchased from Ikot Ambang market, Akwa Ibom State, Nigeria. The plants were identified and authenticated at the Department of Botany and Ecological Studies, Faculty of Biological Sciences, University of Uyo, Uyo, Nigeria. They were assigned voucher numbers UUPH9(a) for *Gongronema latifolium* and UUPH1(a) for *Telfairia occidentalis*, and deposited at the Department of Pharmacognosy and Natural Medicine, Faculty of Pharmacy Herbarium, University of Uyo, Nigeria.

2.2. Preparation of Leaf Extract

The leaves of both plants were washed, drained, air-dried and ground into a coarse powder. The powders of *G. latifolium* and *T. occidentalis* (600g) each were macerated in 10L of 70 % ethanol for 72 hours with intermittent stirring. Thereafter, the mixtures were filtered with cheese materials and Whatman No 1 filter papers to obtain filtrates for each plant sample. The filtrates were concentrated in a Water Bath at 40 ºC yielding the crude extracts of *Gongronema latifolium* and *Telfairia occidentalis*.

2.3. Partitioning of Extract into Fractions

Crude extracts of *Gongronema latifolium* and *Telfairia occidentalis* were subsequently dissolved in methanol and absorbed onto 100g of silica gel (mesh 60-120) and allowed to dry. The dried samples were loaded onto a Buckner funnel pre-packed with silica gel G and the set up connected to a vacuum pump. The sample was partitioned successively and exhaustively with ethyl acetate and methanol using the vacuum liquid chromatography (VLC) technique to obtain their respective fractions. The fractions were then concentrated at 40 ºC to dryness using rotary evaporator. The dried fractions were preserved in a refrigerator at 4 ºC until subsequently used for the study.

2.4. Experimental Animals and Design

Fifty four (54) healthy male Wistar rats, were obtained from the Animal house of the Department of Pharmacology and Toxicology, Faculty of Pharmacy, University of Uyo, Uyo, Nigeria. They animals were acclimatized for two weeks in well ventilated cages, with free access to water and rat feed (Vital feeds, Nigeria Limited) ad libitum. The protocol for the experiment was approved by the University of Uyo Research and Ethical Committee, University of Uyo, Nigeria. The animals were randomly selected into nine (9) groups of six (6) animals each and treated twice daily for 28 days, as shown in Table 1.

Table 1 Experimental Design

Groups	Induction	Treatment	Dosage
Group 1	Non- induced	Distilled water	1 ml
Group 2	Diabetic	Distilled water	1 ml
Group 3	Diabetic	Insulin	10 IU/kg
Group 4	Diabetic	GL (methanol) fraction	500 mg/kg
Group 5	Diabetic	GL (ethylacetate) fraction	500 mg/kg
Group 6	Diabetic	TO (methanol) fraction	500 mg/kg
Group 7	Diabetic	TO (ethylacetate) fraction	500 mg/kg
Group 8	Diabetic	GL + TO (methanol) fraction	250 mg/kg + 250 mg/kg
Group 9	Diabetic	GL + TO (ethylacetate) fraction	250 mg/kg + 250 mg/kg

2.5. Induction of Diabetes

Streptozotocin (STZ) was purchased from Sigma Chemical Co., St Louis, MO, USA. Diabetes mellitus was induced by intra-peritoneal administration of 60 mg/kg bw of STZ after the animals were fasted overnight. Seventy-two hours after the administration of streptozotocin, blood glucose levels were measured to confirm the development of diabetes, using the Glucose test indicator strips (One-Touch Horizon Glucometer). Animals with higher or equal to 200 mg/dl after 3 days of induction were considered diabetic and used for the studies.

2.6. Treatment and Animal Sacrifice and Preparation of Sera for Analysis

The different fractions of *Gongronema latifolium* and *Telfairia occidentalis* were administered daily through an oral cannula for 28 days. Insulin was administered through intra-peritoneal injection. At the end of the treatment period, the rats were fasted overnight and euthanized by injecting with ketamine, blood sample was collected via cardiac puncture using sterile needles into sterile plain sample bottles. Serum samples were obtained from clotted blood into sterile plain tubes after centrifugation at 3500 rpm for 10 minutes using a bench top centrifuge and serum collected and stored for subsequent biochemical analysis. The liver and kidney of the experimental animals were removed and fixed in 10 % buffered formalin in preparation for tissue processing.

2.7. Biochemical Analysis

The concentration of Alanine Transaminase (ALT), Aspartate Transaminase (AST) and Alkaline phosphatase (ALP) were assayed following the protocol as described by Wroblewski and LaDue, [10], Reitman and Frankel [11] and Bowers et al. [12] respectively. While the activities of total protein, total bilirubin, albumin, creatinine, urea and electrolytes was determined by the method as described by Henry [13], Jacobs [14] and Tietz [15].

2.8. Histological evaluation

The liver and kidney was excised and washed in phosphate-buffered saline, and fixed with 10% formalin overnight. Evaluation of liver and kidney histological architecture was done by staining with hematoxylin and eosin and the mounted slides were then examined under a light microscope. This was done according to methods as described by Okpoghono et al. (2018).

2.9. Data analysis

The data were analyzed using SPSS version 25.0. The data were subjected to descriptive analysis, analysis of variance (ANOVA) and least significant difference (LSD) post hoc multiple comparison. Significant differences between groups were considered at P-values less than 0.05 ($P<0.05$). Results are expressed as mean ± standard error of mean (SEM).

3. Result

3.1. Effect of *Gongronema latifolium*, *Telfairia occidentalis* and its combined fractions on Liver enzymes of Diabetic and Non-diabetic Rats

The effects of *Gongronema latifolium*, *Telfairia occidentalis* and combined fractions on liver enzymes in STZ-induced diabetic Wistar rats are shown in figure 1. There were significant ($p<0.05$) increase in the AST, ALT, ALP activities and total bilirubin concentration coupled with significant ($p<0.05$) decrease in the total protein and albumin concentrations in the diabetic control group, when compared to the normal control group. However upon treatment with the reference drug insulin and the fractions of *G. latifolium* and *T. occidentalis*, there were significant ($P<0.05$) decreases in the serum AST, ALT, ALP activities and total bilirubin concentration. There were also significant ($p<0.05$) increases in the total protein and albumin concentrations of the treatment groups, when compared to the diabetic control group. The observed significant ($P<0.05$) decrease in serum AST, ALT, ALP and total bilirubin activities was highest in combined methanol fraction of *G. latifolium* and *T. occidentalis* while methanol fraction of *G. latifolium* showed the highest significant ($P<0.05$) increase for total protein and albumin.

3.2. Effect of *Gongronema latifolium, Telfairia occidentalis* and its combined fractions on renal parameters of Diabetic and Non-diabetic Rats

The effects of *Gongronema latifolium, Telfairia occidentalis* and combined fractions on renal parameters in Wistar rats are shown in figure 2. There were significant ($p<0.05$) increase in the urea, creatinine, sodium, potassium, chloride and bicarbonate activities in the diabetic control group, when compared to the normal control group. However, upon treatment, there were significant ($p<0.05$) decreases in the urea, creatinine, sodium, potassium and chloride concentrations in all the fraction treated groups, and an insignificant ($p>0.05$) decrease in bicarbonate activity when compared to the diabetic control group. The observed significant ($p<0.05$) decreases in the fraction treated groups was highest in combined methanol fraction of *G. latifolium* and *T. occidentalis* for creatinine and potassium ions, while combined ethyl acetate fraction of *G. latifolium* and *T. occidentalis* showed the highest significant ($p<0.05$) decrease in sodium and chloride ions, while methanol fraction of *G. latifolium* showed the highest significant ($P<0.05$) increase for total protein and albumin.

3.3. Effect of *Gongronema latifolium, Telfairia occidentalis* and its combined fraction on histopathology of liver tissue of diabetic Wistar rats

The photomicrographs of the liver tissues are presented in figure 3. Normal histological features such as hepatic central vein, hepatic artery, hepatic duct, hepatocytes with normal nucleus were observed in the photomicrographs of the liver tissues of normal control group in this study. The exception was seen in the photomicrograph of the diabetic control group, which demonstrated an atrophying hepato-architecture with areas of degenerated hepatic cells (yellow arrow) increased degenerating and vacuolated hepatocytes (red arrow) and widespread micro-vesicular steatosis (black arrow), within the hepatic lobules. However, there was significant observed ameliorating effect in the liver tissues following the administration of insulin, *Gongronema latifolium* and *Telfairia occidentalis* fractions, singly and in combination in the liver tissue of diabetic Wistar rats compared to the diabetic control group.

3.4. Effect of *Gongronema latifolium, Telfairia occidentalis* and its combined fraction on histopathology of kidney tissue of diabetic Wistar rats

The photomicrographs showing the histopathology of kidney tissues of Wistar rats following the administration of *Gongronema latifolium*, *Telfairia occidentalis* fractions, singly and in combination are presented in figure 4. Normal histological features of the kidney including renal tubules, bowman's capsule and glomerulus were revealed in the normal control group, while the diabetic control group showed an atrophying renal micro-architecture, degenerating tubules with vacuolated ductal cells (red arrow), areas of hemorrhagic blood vessels (black arrow) and increase inter-connective tissue fibrosis (green arrows) within the renal cortical matrix. However, there was significant observed ameliorating effect on the kidney cells following the administration of *Gongronema latifolium*, *Telfairia occidentalis* fractions, singly and in combination in the kidney tissue compared to the diabetic control group. This restorative activity of the fractions singly and combination was statistically similar to the normal control group

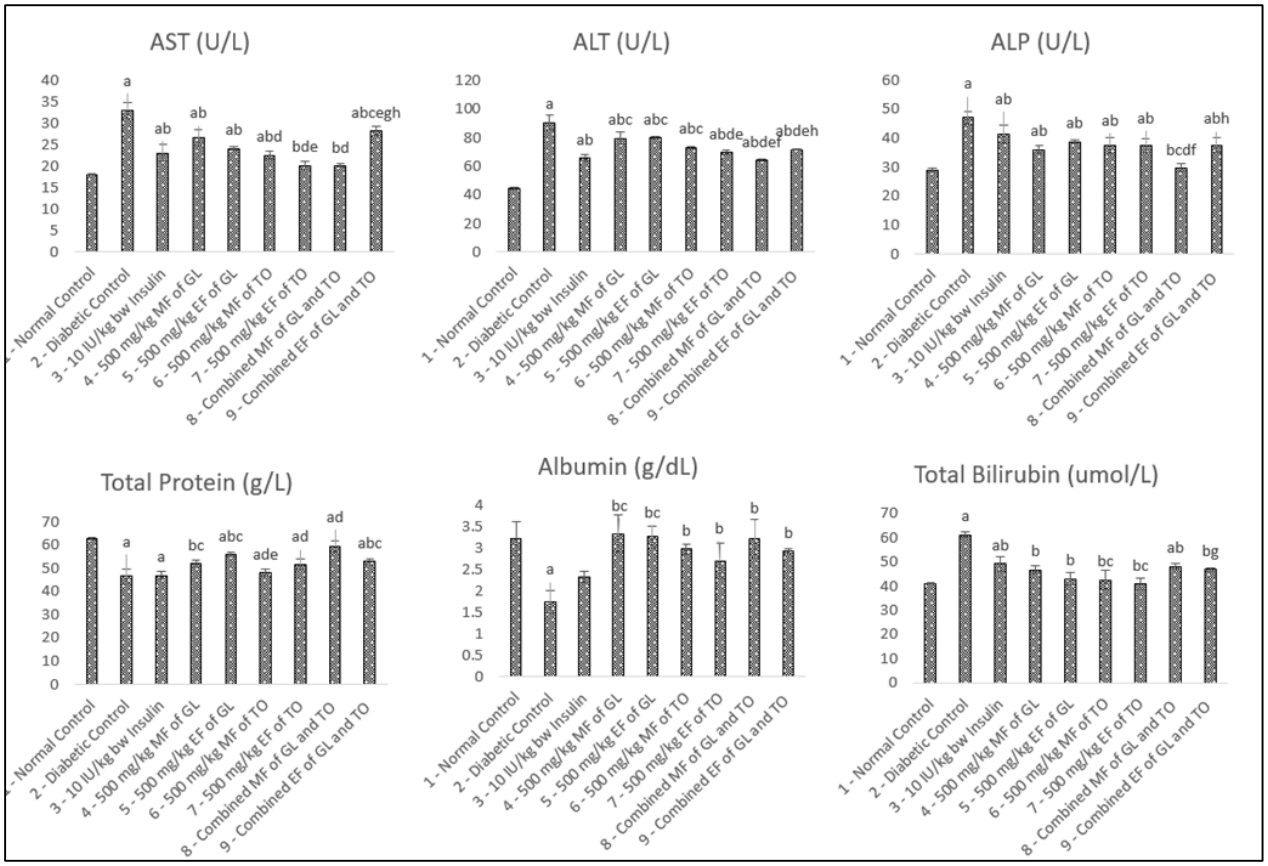

Figure 1 Liver function parameters in STZ-Induced Diabetic Wistar rat administered *Gongronema latifolium, Telfairia occidentalis* fractions. Data presented as Mean ± Standard Error of Mean (bars ± error bars). The means of different groups were compared and considered significantly different at ($p < 0.05$). The significant difference is defined thus; a = significantly different when compared to Group 1; b = significantly different when compared to Group 2; c = significantly different when compared to Group 3; d = significantly different when compared to Group 4; e = significantly different when compared to Group 5; f = significantly different when compared to Group 6; g = significantly different when compared to Group 7; h = significantly different when compared to Group 8. GL = *Gongronema latifolium*; TO = *Telfairia occidentalis*; MF = Methanol Fraction; EF = Ethylacetate Fraction

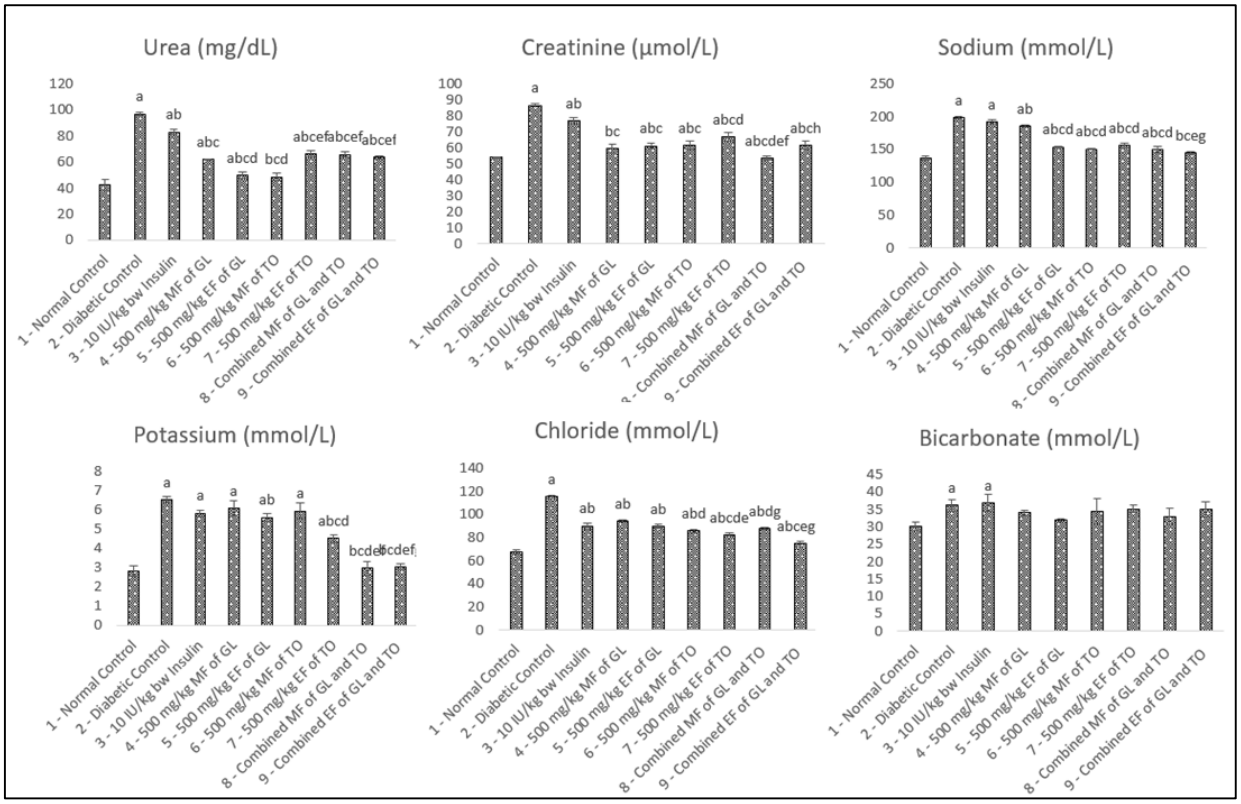

Figure 2 Kidney function parameters in STZ-Induced Diabetic Wistar rat administered *Gongronema latifolium, Telfairia occidentalis* fractions. Data presented as Mean ± Standard Error of Mean (bars ± error bars). The means of different groups were compared and considered significantly different at ($p < 0.05$). The significant difference is defined thus; a = significantly different when compared to Group 1; b = significantly different when compared to Group 2; c = significantly different when compared to Group 3; d = significantly different when compared to Group 4; e = significantly different when compared to Group 5; f = significantly different when compared to Group 6; g = significantly different when compared to Group 7; h = significantly different when compared to Group 8. GL = *Gongronema latifolium*; TO = *Telfairia occidentalis*; MF = Methanol Fraction; EF = Ethylacetate Fraction

3.5. Effect of *Gongronema latifolium, Telfairia occidentalis* and its combined fraction on Histopathology of Liver Tissue of Diabetic and Non-diabetic Rats

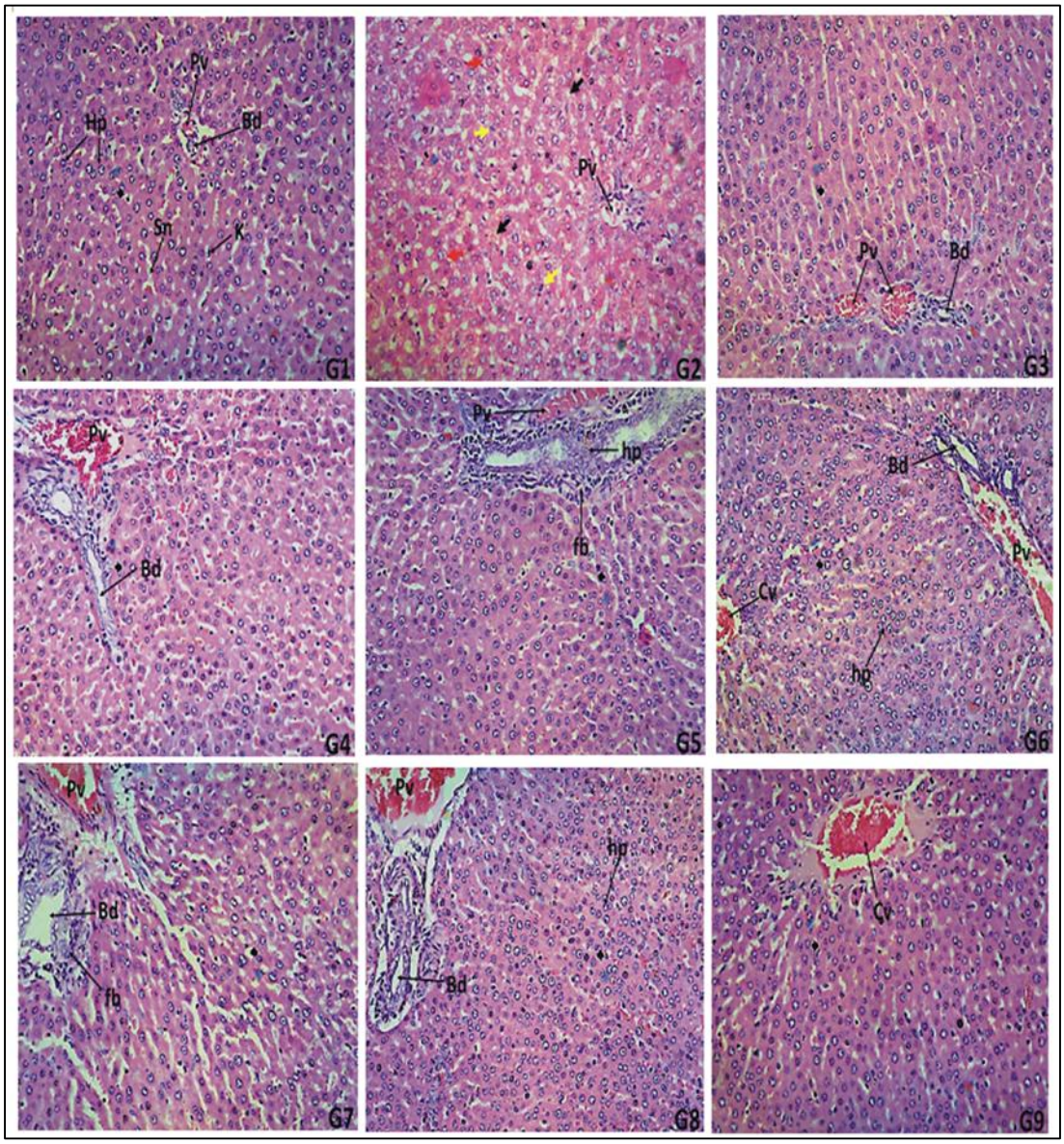

Figure 3 Photomicrograph of a section of the liver of Wistar rats: G1 = Normal Control; liver tissue showing normal hepatic architecture. G2 = Diabetic control; liver tissue demonstrating an atrophying hepato-architecture with areas of degenerated hepatic cells. G3 = Diabetic + Insulin treated; liver tissue showing normal hepatic architecture. G4 = Diabetic + 500 mg/kg *G. latifolium* (methanol fraction) treated; liver tissue showing normal hepatic architecture. G5 = Diabetic + 500 mg/kg *G. latifolium* (ethyl-acetate fraction) treated; liver tissue showing mildly affected hepatic architecture. G6 = Diabetic + 500 mg/kg *T. occidentalis* (methanol fraction) treated; liver tissue showing mildly affected hepatic architecture. G7 = Diabetic + 500 mg/kg *T. occidentalis* (ethyl-acetate fraction) treated; liver tissue showing mildly affected hepatic architecture. G8 = Diabetic + 250 mg/kg *G. latifolium* + 250 mg/kg *T. occidentalis* (methanol fraction) treated; liver tissue showing mildly affected hepatic architecture. G9 = Diabetic + 250 mg/kg *G. latifolium* + 250 mg/kg *T. occidentalis* (ethyl-acetate fraction) treated; liver tissue showing normal hepatic architecture

3.6. Effect of *Gongronema latifolium, Telfairia occidentalis* and its combined fraction on Histopathology of Kidney Tissue of Diabetic and Non-diabetic Rats

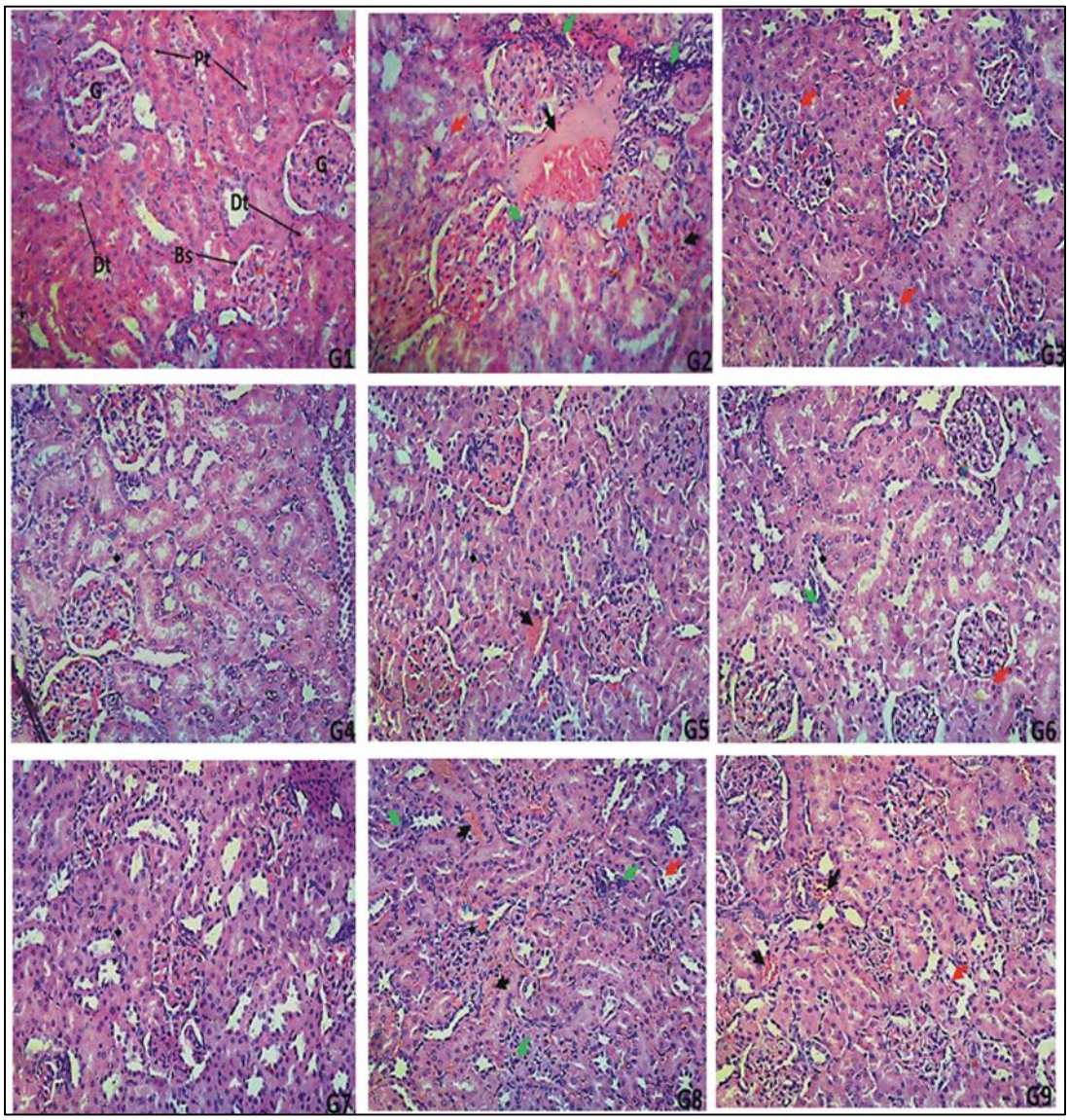

Figure 4 Photomicrograph of a transverse section of the kidney of Wistar rats: G1 = Normal Control; Kidney tissue demonstrating a normal renal architecture. G2 = Diabetic control; kidney tissue demonstrating an atrophying renal micro-architecture with areas of degenerated cells. G3 = Diabetic + Insulin treated; kidney tissue showing a protected renal micro-architecture. G4 = Diabetic + 500 mg/kg *G. latifolium* (methanol fraction) treated; kidney tissue demonstrating a protected renal micro-architecture. G5 = Diabetic + 500 mg/kg *G. latifolium* (ethyl-acetate fraction) treated; kidney tissue showing mildly altered renal micro-architecture. G6 = Diabetic + 500 mg/kg *T. occidentalis* (methanol fraction) treated; kidney tissue showing mildly affected renal architecture. G7 = Diabetic + 500 mg/kg *T. occidentalis* (ethyl-acetate fraction) treated; kidney tissue showing a protected renal micro-architecture. G8 = Diabetic + 250 mg/kg *G. latifolium* + 250 mg/kg *T. occidentalis* (methanol fraction) treated; kidney tissue showing protected micro-architecture. G9 = Diabetic + 250 mg/kg *G. latifolium* + 250 mg/kg *T. occidentalis* (ethyl-acetate fraction) treated; kidney tissue showing a protected kidney micro-architecture

4. Discussion

The liver and kidney are complex organs that play important roles in maintaining good health. It is responsible for diverse functions, including detoxification, metabolism, immunity, fluid balance, homeostasis and vitamin storage [17]. The liver contains several enzymes within the hepatocytes, which can be measured in the serum and are used as tests of liver function [18]. Injury to the liver often result in the leakage of liver enzymes into general circulation at higher than normal levels hence increased activities in the blood [19]. The liver is highly susceptible to injuries in patients with

diabetes mellitus. These injuries often manifest as abnormal liver enzymes levels, necrosis, inflammation, hepatocellular damage and acute liver failure [20].

The functional status of the liver was assessed in the present study using the liver enzymes AST, ALT, ALP, albumin, total protein and bilirubin. Since these enzymes are undeniably, markers of liver injury, the elevated levels of these enzymes in diabetic condition in the present study may be attributed to toxicity induced by streptozotocin as seen in the diabetic control group. Significantly increased ($p<0.05$) serum levels of ALP, AST, ALT, total bilirubin and significantly decreased ($p<0.05$) serum total protein and albumin levels as observed in the diabetic control group of streptozotocin-induced diabetic rats, are indicators of hepatocellular damage. This could be mainly due to exudation of these enzymes from the cytoplasm of liver cells into the blood stream [21,22]. A significant reduction in albumin level is usually seen as an initial stage of diabetic liver disease, while the loss of protein concentration could possibly be due to protein oxidation caused by reactive oxygen species (ROS) [23].

Previous studies by Fagbohun et al. [24] and Ekayoda et al. [25] reported elevated activities of serum liver enzymes ALT, AST, ALP and decrease of total protein and albumin levels in streptozotocin-induced diabetic Wistar rats, hence supporting the results obtained in the present study. Streptozotocin has been reported to induce liver injuries such as necrosis and hepatocellular apoptosis through the generation of free radicals and inflammatory cytokines resulting in oxidative stress and disruption of mitochondrial dysfunction within hepatocytes [26].

Following treatment with the plant fractions, compared with the diabetic control group, there were significant decrease in the serum liver enzymes AST, ALT, ALP, bilirubin and significant increase in the albumin and total protein concentration in the *G. latifolium*, and *T. occidentalis* fraction treated groups when compared to the diabetic control group, thus, indicating these plants' hepatic protective properties, which is consistent with some studies reporting the hepato-protective properties of these plants [27,28]. Asuquo et al. [29] and Ekayoda et al. [25] had earlier demonstrated that extracts of *G. latifolium*, and *T. occidentalis* respectively ameliorates hepatic injury by reducing serum liver enzyme levels, decreasing oxidative stress and lipid peroxidation and modulating inflammatory responses. This ameliorative property is traced to the rich bioactive components of the leaves of these plants.

Upon examination of the liver photomicrographs of the diabetic untreated group, they were prominent characteristics such as an atrophying hepato-architecture with areas of degenerated hepatic cells, increased degenerating and vacuolated hepatocytes which is consistent with studies according to Mohamed et al. [30]. These features were observed to have been ameliorated in the fraction treatment groups. Groups 3 through 9, which received plant fractions, showed varying degrees of liver health improvement. Groups 3, 4, 5, 6 and 7 displayed normal hepatic cells with mild or no inflammation, while groups 8 and 9 which received the combined *G. latifolium* and *T. occidentalis* fractions, demonstrated normal liver conditions with histological features comparable to the normal control group. The presence of normal hepatic cells, central veins, and portal veins suggests that *G. latifolium* and *T. occidentalis* fractions effectively protected the liver from diabetes mellitus induced liver injury.

This result is consistent with previous findings that reported the hepatic protective potential of the leaves of *G. latifolium* and *T. occidentalis* by significantly restoring the serum enzymes of these experimental animals to near normal respectively [31, 32]. The best results were observed in the combined methanol fraction of *G. latifolium* and *T. occidentalis* treated group. This result is similar to the findings of Ojo et al. [33] and Donkor et al. 34, which suggests that combined treatments have a better curative effect. The combined methanol fraction of *G. latifolium* and *T. occidentalis* showed a superior ability to restore the liver function parameters to near normal levels compared to other fractions. Chigayo et al. [35] proved that methanol extracts often show higher biological activity due to methanol's ability to effectively extract both polar and non-polar compounds, including many potent phenolic and flavonoid antioxidants, which are crucial for antioxidant and anti-inflammatory bioactivity.

The kidneys are excretory glandular tissues that are also concerned primarily with regulating the blood pressure, water and electrolytes levels in the body. The kidney is usually damaged in patients with diabetes mellitus. These damages often includes abnormal glumerulosclerosis, arteriosclerosis, membranous nephrosclerosis, glomerulopathy, inflammation and acute kidney failure. The homeostasis of the body's extracellular electrolyte composition and fluid volume is essential for all animals and humans to survive [36]. Electrolytes are minerals that regulate the homeostatic functions of the body and help to maintain osmotic equilibrium between the intracellular and extracellular fluids [37]. Creatinine is synthesized from creatine, then passes into the circulation and is taken up almost entirely by skeletal muscle for energy production. Creatinine retention in the blood is evidence of kidney impairment [38,39]. In a disease condition such as diabetes mellitus, the body's electrolyte control system are altered. Plasma electrolytes and metabolites (such as creatinine and urea) are used to assess kidney functions [40].

In this study, there was a significant ($P<0.05$) increase in the serum sodium, potassium, chloride, bicarbonate, creatinine and urea concentrations in the diabetic control group when compared to the normal control group. Ntuenibok et al. [41] reported similar trend upon induction of experimental animal with STZ. Streptozotocin causes hyperglycemia, which leads to diabetic nephropathy, hence raised serum levels of creatinine and urea and electrolyte imbalances due to oxidative stress and inflammation in the kidneys, leading to tubular damage [42]. Upon treatment with the *G. latifolium* and *T. occidentalis* fractions, there was a significant ($P<0.05$) decrease in serum sodium, potassium, chloride, bicarbonate, creatinine and urea concentration compared to the diabetic control group. The effect of the fractions on electrolytes in diabetic treated animals indicated nephro-protective potential of the plant. This is in agreement with reports by Akpanabiatu et al. [43] and Adegboyega and Amoo [44], which reported the beneficial activity of *Gongronema latifolium* and *Telfairia occidentalis* extracts respectively on the kidney and electrolyte levels in diabetic condition.

G. latifolium and *T. occidentalis* have been proven to ameliorate kidney and electrolyte distortion, particularly in diabetes and toxin-induced damage, by reducing oxidative stress, inhibiting inflammation, and restoring renal function and electrolyte balance. Its protective effects are attributed to its bioactive constituents which contribute to its anti-inflammatory, antioxidant and nephroprotective properties [41,44].

Photomicrograph of the kidney tissue of the diabetic control group showed an atrophying renal micro-architecture, having degenerating tubules with vacuolated ductal cells and areas of hemorrhagic blood vessels. These features were observed to have been ameliorated in the fraction treatment groups. This result is consistent with previous findings that reported the nephroprotective effects of the leaves of *G. latifoium* and *T. occidentalis* [44, 45]. The ability of *G. latifolium* and *T. occidentalis* to exert a protective effect on the kidney could be related to the presence of bioactive compound known to exhibit strong antioxidant and anti-inflammatory activity, which was exhibited synergistically upon combined treatment. This is consistent with previous studies by Udoudoh et al. [28] that showed a synergistic activity of *Gongronema latifolium* and *Telfairia occidentalis* leaves extracts compared to single fractions.

The combined methanol fraction of *G. latifolium* and *T. occidentalis* showed a superior ability to restore the creatinine, potassium and bicarbonate levels to near normal while ethyl acetate fractions of *G. latifolium* and *T. occidentalis* showed a stronger restorative potential in sodium and chloride ion, hence the methanol fraction exhibited better nephroprotective effect than the ethylacetate fraction. This could possibly be due to methanol's ability to extracts more polar compounds compared to ethyl acetate, as different compounds have varying solubilities in different solvents [35].

This is consistent with previous studies by Udoudoh et al. [28] that showed a synergistic activity of *Gongronema latifolium* and *Telfairia occidentalis* leaves extracts compared to single fractions. The observed hepato-renal protective effects of these plants fraction could be attributed to their rich nutritional profiles, antioxidants and other bioactive compounds. These components may help combat oxidative stress associated with diabetes mellitus, support liver and kidney cells regeneration and reduce inflammation in liver and kidney tissues.

5. Conclusion

This study therefore demonstrates that *Gongronema latifolium* and *Telfairia occidentalis* offers potential therapeutic benefits for individuals with diabetes mellitus and associated complications, particularly in mitigating liver and kidney function abnormalities. This is exhibited in the protective activities of the methanol and ethyl acetate fractions of the plants on the liver and kidney enzymes which is also evident in the histopathology studies of these organs. The combined fractions showed better anti-diabetic effects than the single fractions, across all the parameters, thus, proving that the combined fractions exhibited a synergistic effect on the diabetic rats. As a result, these plants may contribute beneficially in the treatment and management of diabetes mellitus and its associated complications.

Compliance with ethical standards

Acknowledgments

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Disclosure of conflict of interest

Authors declare that there are no conflicts of interest.

Statement of ethical approval

Ethical approval was obtained from the Faculty of Biological Sciences Ethical Committee, University of Uyo, Nigeria, on the use and handling of experimental animals.

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