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Antidiabetic and Pancreato-Hepato-Renal Protective Effects of *Entada africana* (Fabaceae) Stem Bark Aqueous Extract in Fructose/Sucrose and Streptozotocin-Induced Type 2 Diabetic Rat

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Abstract

Background: Type 2 diabetes mellitus is a growing public health problem that can lead to multi-organ damage. This study assessed the antidiabetic and antioxidant effects of *Entada africana* stem bark aqueous extract on pancreatic, hepatic, and renal damage in type 2 diabetic rats. **Methods:** Qualitative phytochemical analyses and acute toxicity assessment of the extract were performed. Normal Wistar rats underwent oral glucose tolerance tests after single (75 - 300 mg/kg) and 28-day (300 mg/kg) pretreatment with the extract, and fasting blood glucose was monitored for 2.5 h. Type 2 diabetes was induced in other rats by administering 10% fructose by gavage and 10% sucrose in drinking water for 21 days, followed by streptozotocin (40 mg/kg; *i.p.*) injections on days 22 and 57. Diabetic rats received daily doses (75 - 300 mg/kg) of the extract for 28 days. Body weight and non-fasting blood glucose were measured before treatment and weekly thereafter, and insulin sensitivity, serum and tissue biochemical, and histological parameters were assessed at the end. Glibenclamide (10 mg/kg) served as the standard. **Results:** *E. africana* stem bark aqueous extract contains mucilage, cardiac glycosides, reducing sugars, unsaturated sterols, free quinones, saponins, polyphenols, flavones, flavonols, gallic tannins and triterpenoids, and exhibited low toxicity. The extract (300

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mg/kg) improved glucose tolerance ($p < 0.05$) after 28 days in normal rats. In diabetic rats, it significantly ($p < 0.05$-$p < 0.001$) improved blood glucose, insulin sensitivity, lipid profile, and atherogenic risk index; reduced serum ALT, AST, ALP, Bilirubin, Urea, Uric acid, and Creatinine; and increased liver glycogen, albumin and total protein levels. It also decreased MDA and increased SOD, CAT, and GSH levels in the liver, kidneys and pancreas, improving their integrity. **Conclusion:** The safety, antihyperglycemic, insulin-sensitizing, lipid-modifying, and antioxidant activities, along with pancreato-, hepato-, and nephroprotective effects of *E. africana* stem bark aqueous extract, likely mediated by its phytoconstituents, justify its traditional medicinal use.

Keywords

Fructose/Sucrose/Streptozotocin, Type 2 Diabetes, *Entada africana,* Safe, Insulin Sensitizing, Antihyperglycemic, Antidiabetic, Antioxidant, Hepatoprotective, Nephroprotective, Pancreatoprotective, Rat

1. Introduction

Diabetes mellitus is a major global health challenge, affecting 537 million adults worldwide in 2021 and over 800 million by 2024, with type 2 diabetes (T2D) accounting for ~90% of cases [1]-[4]. T2D is a multifactorial disease marked by insulin resistance and chronic hyperglycemia, which progressively impairs organ structure and function, especially in the liver, kidneys, and pancreas [3] [5]. Hepatic insulin resistance causes uncontrolled glucose production, reduced glucose uptake, and decreased glycogen synthesis, promoting hyperglycemia, hepatic fat accumulation (NAFLD), oxidative stress, and inflammation. Renal insulin resistance alters podocyte function, impairing renal integrity independently of glycemia. Hyperglycemia and hypertriglyceridemia damage microvasculature, leading to NAFLD and diabetic nephropathy. To compensate for rising glucose, the pancreas increases insulin secretion (hyperinsulinemia), enhancing fat storage and exhausting β-cells, ultimately causing β-cell death and diabetes onset [6] [7].

Oxidative stress is a key contributor to early and late diabetic pathophysiology, causing dyslipidaemia, insulin resistance, β-cell dysfunction, impaired glucose tolerance, reduced insulin secretion, metabolic waste accumulation, and organ dysfunction [7]-[10]. Hyperglycemia increases glucose uptake, enhancing glycolysis and the TCA cycle, producing surplus NADH and $FADH_2$ that saturate mitochondrial electron transport chain, causing electron leakage and superoxide radical (O_2^-) formation—the central mechanism of diabetes-associated oxidative stress. As therefore an imbalance between reactive oxygen species (ROS) production and antioxidant defenses, oxidative stress leads to lipid peroxidation, enzyme leakage, biomolecular damage, inflammation, and organ failure or diabetic complications, such as pancreatopathy, hepatopathy and nephropathy [10] [11]. Normally, enzymatic (SOD, CAT) and non-enzymatic (GSH, NO) antioxidants counter ROS, but

in diabetes, these defenses are depleted, highlighting the potential role of exogenous antioxidants.

Although conventional antidiabetic drugs have antioxidant properties, they are limited by side effects, cost, and accessibility, especially in low- and middle-income countries [2] [3]. This motivates research into plant-based remedies, which are rich in natural antioxidants, for diabetes management. While several plants are documented for their antidiabetic and antioxidant effects, many remain unexplored, and further studies are required for others such as *Entada africana* (*E. africana*) to support their reported mechanisms of action.

Entada africana Villiers J.F (*E. africana*), native to Sub-Saharan Africa, including southern Chad and northern Cameroon, is traditionally used to treat diabetes, hypertension, rheumatism, and opportunistic diseases. Phytochemical studies show its leaves and bark are predominantly rich in saponins [12]-[15], and antioxidant, anti-inflammatory, antibacterial, and anticancer activities of leaf and stem bark extracts, as well as in vitro antidiabetic effects of ethanolic leaf fractions are demonstrated [14] [16]. However, the in vivo antidiabetic effects of the aqueous stem bark extract remain unstudied. This study therefore aimed to evaluate the antidiabetic and antioxidant effects of *E. africana* aqueous stem bark extract and its impact on pancreas, liver, and kidney functions in fructose/sucrose- and streptozotocin-induced type 2 diabetic rats.

2. Methods

2.1. Ethical Approval

This work was carried out in scrupulous compliance with the protocol approved by the Institutional Ethics Committee for Human Health of the University of Douala in accordance with ethical clearance number 3999CEI-Udo/09/2023/M.

2.2. Chemicals

Streptozotocin (STZ) was from Sigma Chemical Co. (Saint Louis, MO, USA), Glibenclamide (GB) from Mylan Laboratory, Accu-chek Plus blood glucose test strips and glucometer from Roche Diagnostics (Mann-heim, Germany), and all other reagents and chemicals (Extra pure analytical grade) from common commercial suppliers, were used in this study.

2.3. Plant Materials and Preparation of Extract

The trunk barks of *E. africana* were harvested on Tuesday 14 April 2023 at 09 h 45 min in Tamboursou village, canton Gounou in the sub-prefecture of Gounou-Gaya rural, department of Kabbia, province of Mayo-Kebbi East in southern Chad. After harvesting, a herbarium sample (including leaves, flowers, trunk bark, fruits and seeds) was sent to the Cameroon National Herbarium and identified in comparison with sample number 4738 of herbarium collection specimen number 58983/SRFCam.

The harvested *E. africana* stem barks were dried at ambient temperature, and

the plant aqueous extract was obtained by decoction of 100 g plant stem bark powder in 5000 mL distilled water for 30 min. After 30 min cooling, filtration through cotton wool and Wattman filter paper no.3 yielded Filtrate 1 and Residue 1. Residue 1 was redecocted with 2000 mL distilled water for 30 min, cooled 30 min, and refiltered to obtain Filtrate 2. Filtrates 1 and 2 were combined and oven-dried at 40˚C; the crude extract was weighed and stored dry at 4˚C.

For administration, 2000 mg or 300 mg of crude dried extract were dissolved in 10 mL distilled water to obtain 200 mg/mL (acute toxicity study) or 30 mg/mL (therapeutic study). These solutions were prepared every 3 days as needed and stored at +4˚C. The administered volume (V, mL) was calculated from concentration (C, mg/mL), rat mass (M, g), and dose (D, mg/kg) using $V = D \times M/C$.

2.4. Animals

Female (for acute toxicity study) and male (for therapeutic study) Wistar rats of 2 - 2.5 months, weighing 150 - 170 g were used. They were bred in the animal house of the Biology and Physiology of Animal Organisms unit of the Faculty of Science, at the University of Douala. They were housed in colony cages of three to five (3 - 5) rats each, at ambient temperatures (28˚C ± 2˚C) and humidity (80% - 85%), on a day/night cycle and had free access to tap water and standard rat diet.

2.5. Experimental Procedures

2.5.1. Qualitative Phytochemical Analysis of the Aqueous Extract from *E. africana* Stem Bark

Phytoconstituents highlighted were chosen based on previous studies on *E. africana* [14] [16]. Qualitative phytochemical screening of the aqueous stem bark extract of *E. africana* was carried out following standard procedures as previously described to reveal the presence of constituents: Mucilage and reducing sugars (Fehling test), cardiac glycosides (H_2SO_4/Fehling test), Saponins (Frothing test/Foaming index test), polyphenols ($FeCl_3$/$K_3Fe(CN)_6$ test), Flavonoids, flavones, flavonols and flavonones (Wilstater test), Tannins, cathechic tannins and gallic tannins ($FeCl_3$ test), Triterpenoids (Liebermann-Burchard test), unsaturated steroids, terpenoïds (Salkowski test), β-carotenoids, and Free quinones (precipitation/coloration test, or Petrolium Ether/NaOH test) [17]-[21].

2.5.2. Assessment of the Acute Toxicity of the Aqueous Stem Bark Extract of *E. africana* in Normal Female Rats and Therapeutic Doses Determination

Acute toxicity was evaluated according to OECD guideline 425 for the testing of chemicals, revised [22]. Briefly, 9 nulliparous and non-gravid female rats, 2.5 months old and weighing 160 - 170 g, primarily fasted overnight (12 hours), were divided into 3 groups of 3 rats each: A Control group (NC) receiving distilled water (10 mL/kg); A second group as test group (Ea 2000) receiving by gavage a unique dose of *E. africana* extract at 2000 mg/kg. The third group (Ea 2000 Sat) received the same dose of extract, with a 48-hour time interval to confirm the results obtained.

The animals were deprived of food and water for 4 h after extract administration. They were continuously observed during the first 4 h, then every 12 h within the first 24 h, and daily for the following 14 days. Behavioral parameters (aggressiveness, contortions, mobility, lethargy, grooming, drowsiness, breathing, vomiting), physical parameters (coat/bristling fur, anal mucosa, nasal discharge, stools/fecal appearance), as well as the number of dead rats per group, were recorded during the 48 hours following extract administration. After 14 days, surviving rats were sacrificed, and major organs (liver, kidneys, lungs, spleen, heart, and brain) were collected and weighed.

Therapeutic doses of 75, 150 and 300 mg/kg were selected based on acute toxicity data and the recommendations of the traditional practitioner, providing safety margins of approximately 27, 13, and 7.

2.5.3. Assessment of the Antihyperglycemic Activity of *E. africana* Stem Bark Aqueous Extract in Normal Rats after Acute and Prolonged Administration

The antihyperglycemic activity of the *E. africana* aqueous stem bark extract was evaluated in normal male rats (2.5 months old and weighing 160 - 170 g) by performing oral glucose tolerance tests (OGTT) after acute and prolonged (28 days) administration of the extract.

For the acute study, thirty (30) normoglycemic rats, previously subjected to a 16-hour fast, were randomized into six groups of five rats each, after and based on their initial blood glucose levels, and treated as follows:

- Normal Control (NC): Normal rats received distilled water (10 mL/kg).
- Hyperglycemic Control (HGC): Normal rats received distilled water (10 mL/kg) followed by D-glucose (3 g/kg).
- Standard Control Glibenclamide (Gli): Normal rats received Glibenclamide (10 mg/kg) followed by D-glucose (3 g/kg).
- Test Groups (Ea 75, Ea 150, and Ea 300): Normal rats received *E. africana* extract at doses of 75, 150, or 300 mg/kg, each followed by D-glucose (3 g/kg).

The treatments (distilled water, glibenclamide, or plant extract doses) were administered by oral gavage immediately after group assignment or 30 min before the second blood glucose measurement (T−30). At Time 0 (T0), immediately after this second measurement, a D-glucose solution (3 g/kg) was administered by oral gavage to rats in the HGC, Gli, and Test (Ea 75, Ea 150, and Ea 300) groups, while the NC group received distilled water (10 mL/kg). Blood glucose levels were then measured at 30, 60, and 120 min post-glucose administration.

Following the acute test, rats in the NC and HGC groups continued to receive distilled water (10 mL/kg), the standard group (Gli) glibenclamide (10 mg/kg), and the test group (Ea 300) *E. africana* aqueous extract (300 mg/kg). Treatments were administered once daily for 28 days to evaluate the prolonged effect on glucose tolerance. On day 28, after a 16-h fast, rats received their respective treatments following baseline blood glucose measurement (T−30). D-glucose (3 g/kg) was then administered by oral gavage to the HGC, Gli, and Ea 300 groups, while

NC rats received distilled water (10 mL/kg) immediately after T0 glycemia. Blood glucose levels were subsequently measured at 30, 60, and 120 min post-glucose administration.

2.5.4. Assessment of Prolonged Effects of the Stem Bark Aqueous Extract of *Entada africana* in a Type 2 Diabetic Rat Model

1) ***Induction of type 2 diabetes mellitus in rats***

Type 2 diabetes mellitus (T2DM) was induced following the modified protocol of [23] as showed in "**Figure 1**". Briefly, 56 normal male rats (2 - 2.5 months old, 150 - 170 g) received 10% fructose daily by gavage and 10% sucrose ad libitum in drinking water for 21 days, followed on day 22 by a single intraperitoneal injection of streptozotocin (STZ, 40 mg/kg) after a 12-h fast. On day 56, rats with controlled postprandial blood glucose (≤120 mg/dL) were fasted for 12 h and subjected to an oral glucose tolerance test on day 57. Then, only Animals that failed to maintain the hyperglycemia threshold after the first injection and exhibiting glucose intolerance (2-h blood glucose >140 mg/dL) immediately received a second STZ injection (40 mg/kg i.p.). Normal control rats received distilled water (10 mL/kg) by gavage and tap water as drinking water for 21 days, followed by intraperitoneal injections of STZ vehicle (0.9% NaCl) on days 22 and 57. On day 60, rats with postprandial blood glucose ≥300 mg/dL were considered diabetic. After each STZ injection, 5% sugar water was provided ad libitum for 24 h to reduce STZ toxicity. During the 60-day induction period, glycemic variations were monitored using insulin sensitivity tests (days 17 and 28), glucose tolerance tests (day 57), and screening tests (days 28, 56, and 60), while body weight was recorded every 3 days.

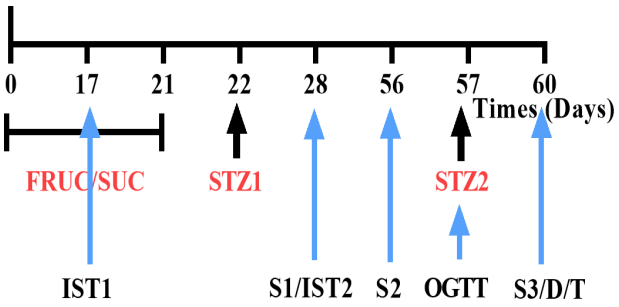

Figure 1. Induction process of type 2 diabetes in Wistar strain rats. FRUC = Fructose; SUC = Sucrose; FRUC/SUC = Fructose and Sucrose co-administration; STZ1 and STZ2 = Streptozotocin injections 1 and 2; IST1 and IST2 = Insulin sensitivity tests 1 and 2; S1, S2 and S3 = Screenings 1, 2 and 3; D = Distribution in groups; T = Treatments starting.

2) ***Distribution of rats and Treatment***

After screening for diabetes at the end of induction (day 60), a total of 36 rats, including 6 normal rats and 30 diabetic rats, were divided by randomization of blood glucose levels into 6 groups of 6 rats each and treated as follows:

- Group 1 or normal control (NC): consisting of normoglycaemic rats receiving distilled water (10 ml/kg);
- Group 2 or diabetic control (DC): diabetic rats receiving distilled water (10

ml/kg);

- Group 3 or standard (Gli): diabetic rats receiving the Glibenclamide at a dose of 10 mg/kg;
- Groups 4, 5 and 6: diabetic rats treated with *E. africana* stem bark aqueous extract at doses of 75, 150 and 300 mg/kg respectively.

Treatments were administered once daily in the morning for 28 days after diabetes induction (days 60 - 88). Postprandial blood glucose was measured 2 h after feeding on days 60, 68, 75, 82, and 89, while body weight was recorded every 3 days to calculate weekly mean values. At the end of treatment, an insulin sensitivity test was performed on day 89 after blood glucose determination, followed by a 12-h fast prior to sacrifice on day 90.

3) ***Glucose Tolerance and Insulin Sensitivity Tests, and Blood Glucose Measurement during diabetes induction and treatment***

Oral Glucose Tolerance test was performed on day 57 of the induction period as followed: Rats previously fasted for 16 hours (normal and test rats) were given D-glucose (3 g/kg) after the initial blood glucose measurement at T0, then blood glucose was measured again at 30, 60, 90 and 120 minutes later [24].

Insulin sensitivity test was performed during induction period (days 17 and 28), and at the end of treatment period (day 89), in non-fasting rats. Briefly, after blood glucose levels determination at 0 minute (T0), the insulin solution (2 IU/kg) was immediately administered intraperitoneally to all the animals, and then blood glucose levels were again determined at 10, 20, 30 and 60 min [9] [24].

Overall, blood glucose levels were measured during screening, insulin sensitivity, and glucose tolerance tests using an ACCU-CHEK® Active glucometer and compatible test strips. After a small tail-tip incision, a drop of blood was applied to the reactive zone of the inserted strip. Glucose reacts with glucose dehydrogenase, producing a color change whose intensity is measured by reflectometry and automatically converted into blood glucose concentration, displayed on the meter screen within 5 seconds.

4) ***Sacrifice, Blood and organs collection, serum biochemical analysis and organs relative weight determination***

On day 90, animals were anesthetized with diazepam (50 mg/kg) and ketamine (10 mg/kg) and sacrificed by decapitation. Arteriovenous blood was collected into dry tubes, centrifuged at 3000 rpm for 15 min, and the serum obtained was stored at −20˚C for biochemical analyses. Serum total protein, albumin, creatinine, urea, uric acid, ALT, AST, alkaline phosphatase, total bilirubin, triglycerides, total cholesterol, LDL-C, and HDL-C were determined spectrophotometrically using commercial assay kits (Biosino Bio-Technology and Science Inc., Beijing, China). Atherogenic risk index and insulin resistance index were calculated as (AI = [Total Cholesterol]/[HDL-C]) [25] and (IR = [Triglycerides]/[HDL-C]) [26] respectively

Organs (liver, kidneys, heart, pancreas, adrenal glands, brain, and abdominal fat) were excised, rinsed in 0.9% NaCl, blotted dry, and weighed to calculate relative organ mass. Parts of organs were used for glycogen (liver), oxidative stress

and histomorphological (pancreas, liver and kidney) determinations.

5) Determination *of hepatic glycogen levels in diabetic rats*

The Hepatic glycogen was assayed according to the method described by [6]. At the end of treatment, rats were sacrificed and approximately 1 g of liver tissue was excised, rinsed, and homogenized in 3 mL of 4% trichloroacetic acid. The homogenate was centrifuged at 4500 rpm for 5 min, and the supernatant was collected. Glycogen was precipitated by adding 95% ethanol (2 v/v), followed by heating to boiling. After cooling, the mixture was centrifuged at 4500 rpm for 10 min, and the resulting pellet was hydrolyzed with 2 mL of 2.5 N sulfuric acid by heating for 30 min. After cooling, the hydrolysate was neutralized with dinitrophenolphthalein indicator and 2.5 N sodium hydroxide until a pink-red color appeared. The glucose released was quantified using the GOD–POD method with a commercial reagent (Biosino, Hong Kong, China), and absorbance was measured at 500 nm using a spectrophotometer (Biolabo, France).

6) *Pancreato-Hepato-Renal Antioxidant Analyses*

At the 90th day (D90) of experiment, the liver, kidney and pancreas were removed from each rat, rinsed in 0.9% NaCl solution, blotted dry and weighed. They were then ground in Tris-HCl buffer (pH = 7.4), centrifuged at 3000 rpm for 15 minutes, and the obtained homogenates were stored at −20˚C in the freezer for assay of the oxidative stress markers (MDA, SOD, CAT and GSH), using the different usually described protocols [27]-[29].

7) *Histopathological analysis of pancreas, liver, and kidney*

The pancreas, liver, and kidney from all experimental animals were fixed in 10% buffered formalin. Histological analysis was performed according to standard laboratory procedures [30], including fixation, trimming, dehydration, embedding, sectioning, hematoxylin–eosin staining, mounting, and microscopic observation.

2.5.5. Statistical Analysis of Data

All data were expressed as the mean ± Standard Error of the Mean (SEM). Statistical analysis of data was done using GraphPad Prism 8.0.1 software (San Diego, CA, USA). Mean values among experimental groups were compared using Analysis of variance (ANOVA) tests: Two-way ANOVA with Bonferroni's post-test for comparing repeated measures data such as body weight and blood glucose; One-way ANOVA with Mann-Whitney for comparing groups regarding serum biochemical and oxidative stress parameters, and others. Differences were considered significant at $p < 0.05$.

3. Results

3.1. Qualitative Phytochemical Screening of the Aqueous Stem Bark Extract of *Entada africana*

The qualitative phytochemical analysis of the aqueous stem bark extract of *E. africana* revealed the presence of mucilage, cardiac glycosides, reducing sugars, unsaturated sterols, free quinones, saponins, polyphenols, flavonoids, flavones, fla-

vonols, gallic tannins, and triterpenes. Flavonones, catechic tannins, and *β*-carotenoids were absent (Table 1).

Table 1. Qualitative phytochemistry of the aqueous stem bark extract of *E. Africana*.

Phytoconstituents	Present/Absent
Mucilage	+
Cardiac glycosides	+
Reducing sugars	+
Unsatured sterols	+
Free quinones	+
Saponins	+
Polyphenols	+
- Flavonoids	+
. Flavones	+
. Flavonols	+
. Flavonones	-
- Tannins	/
. Cathechic tannins	-
. Gallic tannins	+
Terpenes	/
- Triterpenoids	+
- β-Carotenoids	-

(+) = Present; (-) = Absent; (/) = not verified.

3.2. Acute Toxicity of the Aqueous Stem Bark Extract of *E. africana*: General Physical, Morphometric and Behavioral Status

The acute toxicity study showed that the aqueous stem bark extract of *E. africana* at 2000 mg/kg caused no mortality or changes in behavioral, physical, or morphometrical parameters in treated rats compared to controls, either within the first 72 h or up to 14 days post-administration (Table 2).

This dose also did not significantly affect food and water intake. Although food consumption significantly decreased ($p < 0.001$) from week 1 to week 2 within each group, body weight gain significantly increased ($p < 0.0001$) over the same period without differences between groups (Figure 2).

The LD50 of the extract is therefore greater than 2000 mg/kg, corresponding to a toxicity category of 5 according to the GHS.

3.3. Antihyperglycemic Effects of *E. africana* Stem Bark Aqueous Extract in Acute and Prolonged Administration in Normal Rats

During the first 30 minutes after administration of the treatments (acute or prolonged), blood glucose levels did not differ significantly between groups or from

T-30 within each group (Figure 3(A) and Figure 3(B)). D-glucose administered at T0 significantly increased ($p < 0.001$–$p < 0.0001$) blood glucose, peaking at 30 - 60 minutes, then gradually declining until 120 minutes.

Table 2. Physical and behavioral status, and organs relative masses in female rats treated with the *E. africana* aqueous stem bark extract dose of 2000 mg/kg.

Parameters/Organs	Treatments		
	NC	Ea2000	Ea 2000 Sat
Number of rats	3	3	3
Mobility	N	N	N
Lying Posture	N	N	N
Grooming	A	A	A
Abdominal Contortion	A	A	A
Aggressiveness	A	A	A
Lethargy	N	N	N
Respiration/Breathing	N	N	N
Bristling fur/Piloerection	A	A	A
Anal Mucosa	N	N	N
Vomiting	A	A	A
Fecal appearance	N	N	N
Mortality (%)	0	0	0
Liver	3.5 ± 0.1	3.5 ± 0.1	3.4 ± 0.1
Left Kidney	0.4 ± 0.0	0.3 ± 0.0	0.4 ± 0.0
Right Kidney	0.4 ± 0.0	0.4 ± 0.0	0.4 ± 0.0
Heart	0.4 ± 0.0	0.3 ± 0.1	0.3 ± 0.0
Lungs	1.0 ± 0.1	1.0 ± 0.0	1.0 ± 0.1
Brain	0.9 ± 0.1	1.0 ± 0.0	1.0 ± 0.0
Spleen	0.5 ± 0.0	0.5 ± 0.1	0.6 ± 0.1

Each data represents the Mean ± SEM. N = 3; NC: normal control; *Ea* 2000: *E. africana* at the dose of 2000 mg/kg; *Ea* 2000 sat: *E. africana* at the dose of 2000 mg/kg (satellite); N = Normal; A = Absent.

However, the calculated area under the curve (AUC) for blood glucose significantly increased in hyperglycemic control (HGC) rats compared to normal controls (NC) by 70.78% ($p < 0.01$) in acute treatment (Figure 3(A)) and 77.65% ($p < 0.01$) in prolonged treatment (Figure 3(B)). *E. africana* extract (75 - 300 mg/kg) in acute treatment did not significantly lower glucose after the load, though a non-significant maximum reduction of 2.89% ($p > 0.05$) occurred at 300 mg/kg (Figure 3(A)). In normal rats treated for 28 days, 300 mg/kg extract significantly reduced hyperglycemia by 14.18% ($p < 0.05$) compared to HGC (Figure 3(B)).

Glibenclamide (10 mg/kg) reduced glucose-induced hyperglycemia by 27.40% ($p < 0.05$) after acute treatment (Figure 3(A)) and 27.25% ($p < 0.01$) after 28 days (Figure 3(B)) compared to HGC.

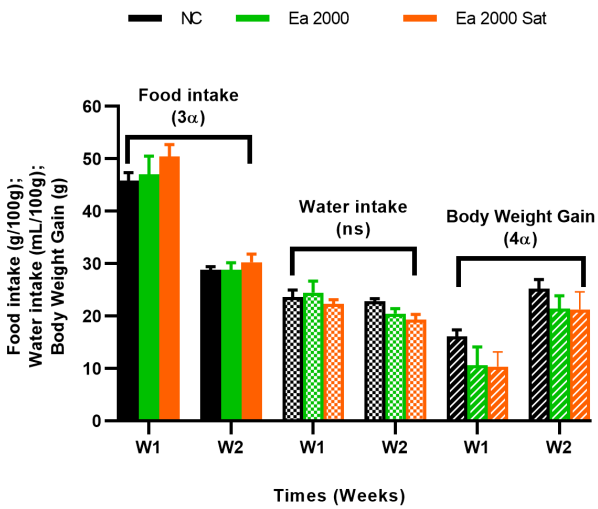

Figure 2. Food intake, water intake and body weigh gain in female rats treated with a single dose of 2000 mg/kg of the aqueous stem bark extract of *E. Africana.* Each bar represents the Mean ± ESM; n = 3; ns: not significant ($p > 0.05$); $^{3\alpha}p < 0.001$, $^{4\alpha}p < 0.0001$: significant difference compared to W1; NC: Normal Control; *Ea* 2000: *Entada africana* extract at the dose of 2000 mg/kg; *Ea* 2000 sat: *Entada africana* extract at the dose of 2000 mg/kg satellite; W1 and W2: Weeks 1 and 2.

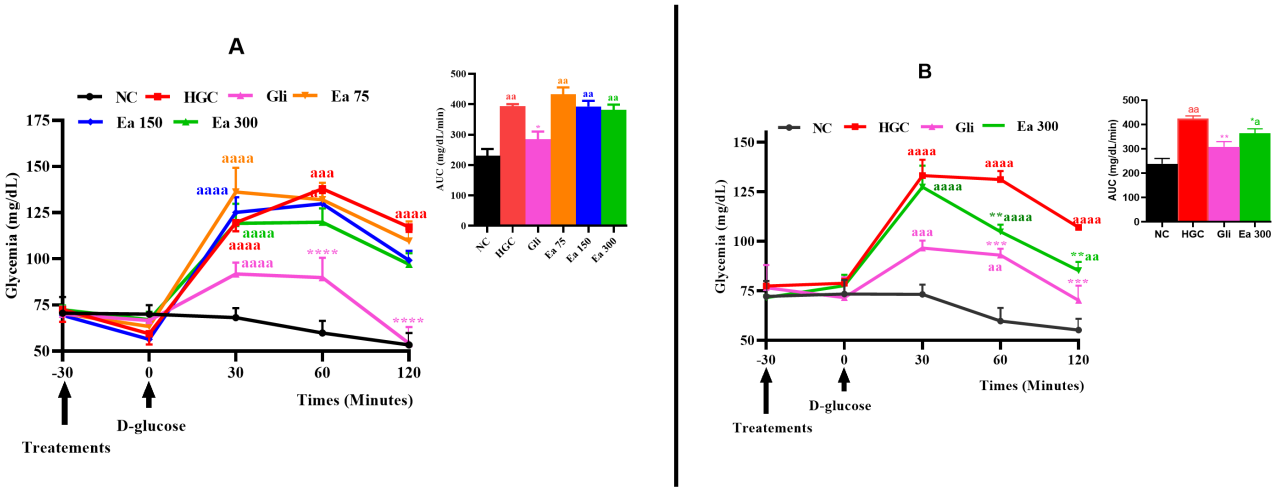

Figure 3. Antihyperglycemic effects in normoglycemic rats after acute (A) and prolonged (B) treatment. Each point or bar represents the mean ± SEM; n = 5; $^{a}p < 0.05$; $^{aa}p < 0.01$; $^{aaa}p < 0.001$; $^{aaaa}p < 0.0001$: significant difference compared to the normal control; *p < 0.05; **p < 0.01; ***p < 0.001: significant difference compared to the hyperglycemic control; NC: normal control; HGC: hyperglycemic control; Gli: Glibenclamide; Ea 75, Ea 150, Ea 300: *Entada africana* aqueous extract at the different doses indicated.

3.4. Blood Glucose Variations, Insulin Sensitivity and Glucose Tolerance during Induction of Type 2 Diabetes

Blood glucose levels changed throughout the diabetes induction phases in rats (**Figure 4(A)**). Baseline levels on day 0 (D0) remained stable after 17 days of 10% fructose and 10% sucrose administration. One week after the first streptozotocin injection (STZ1), blood glucose rose significantly ($p < 0.0001$), increasing by 140.97% versus normal controls (NC) and 155.95% versus D0. Levels normalized

by day 56, then rose again at day 60 after the second STZ injection (STZ2), reaching three times the normal value ($p < 0.0001$) and 50.56% higher than D28 ($p < 0.0001$).

Insulin sensitivity decreased non-significantly by 16.21% ($p > 0.05$) after 17 days of 10% fructose/sucrose administration (Figure 4(B)), but dropped significantly (158.46%, $p < 0.001$) after STZ1 on day 28 compared to NC (Figure 4(C)). Glucose tolerance was also reduced by 15.77% ($p < 0.05$) versus NC on day 57 (Figure 4(D)).

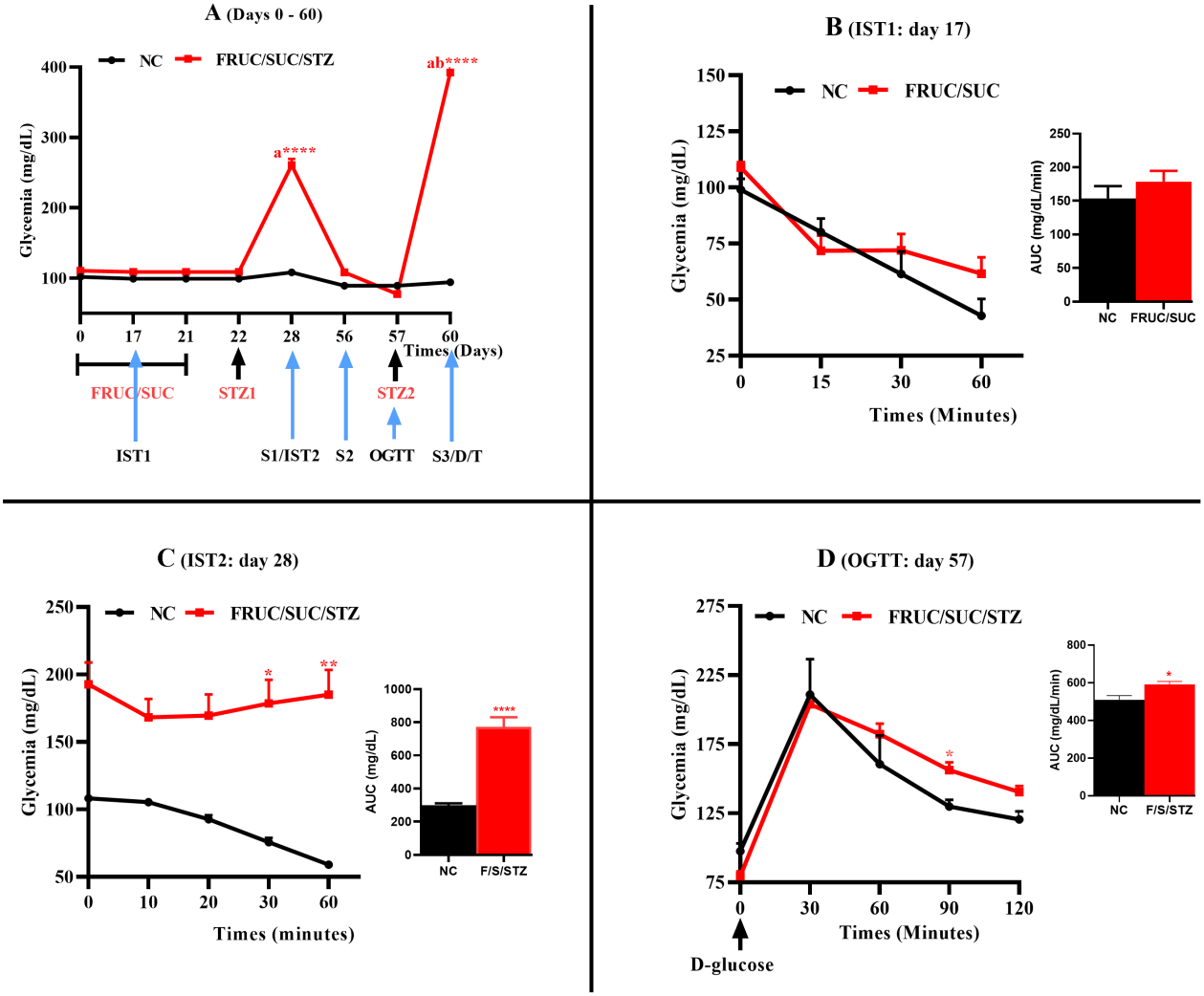

Figure 4. Changes in blood glucose (A), insulin sensitivity (B and C) and glucose tolerance (D) during diabetes induction. Each point or bar represents the mean ± SEM; n = 6 – 56; *$p < 0.05$; **$p < 0.01$; ****$p < 0.0001$: significant difference from normal control; [a]$p < 0.0001$: significant difference from blood glucose at day 0 (D0); [b]$p < 0.0001$: significant difference from blood glucose at day 28 (D28); IST1 and IST2: Insulin Sensitivity Test at days 17 and 28, respectively; DS1, DS2 and DS3: Diabetes Screenings 1, 2 and 3 at experimental days 28, 56 and 60, respectively; OGTT = Oral Glucose Tolerance Test at day 57; D: distribution; T: treatment; NC: normal control; FRUC/SUC: Fructose/Sucrose; STZ: Streptozotocin; FRUC/SUC/STZ or F/S/STZ: Fructose/Sucrose/Streptozotocin.

By day 60, the rats exhibited clear impaired glycemic control, with chronic hyperglycemia, reduced glucose tolerance, and insulin resistance.

3.5. Effects of *Entada africana* Aqueous Extract on Blood Glucose Levels and Insulin Sensitivity in Type 2 Diabetic Rats

After diabetes induction, diabetic control (DC) rats maintained significantly elevated blood glucose levels ($p < 0.001$–$p < 0.0001$) until day 89 compared with normal controls (NC)) (Figure 5(A)). In contrast, 28 days of treatment with *Entada africana* aqueous stem bark extract or glibenclamide significantly reduced blood glucose levels from day 68 to day 89 ($p < 0.05$–$p < 0.0001$), with values normalized relative to DC rats by the end of the experiment (Figure 5(A)).

Furthermore, insulin sensitivity decreased by 44.73% ($p < 0.01$) in DC rats versus NC (Figure 5(B)). Treatment with the extract at 75 mg/kg dose significantly increased insulin sensitivity by 31.46% ($p < 0.05$), while doses of 150 and 300 mg/kg and glibenclamide produced non-significant increases of 17.23%, 13.84%, and 23.40%, respectively, compared with DC rats (Figure 5(B)).

Overall, the 75 mg/kg dose of *E. africana* more effectively improved blood glucose levels and insulin sensitivity in diabetic rats than glibenclamide (Figure 5(A) and Figure 5(B)).

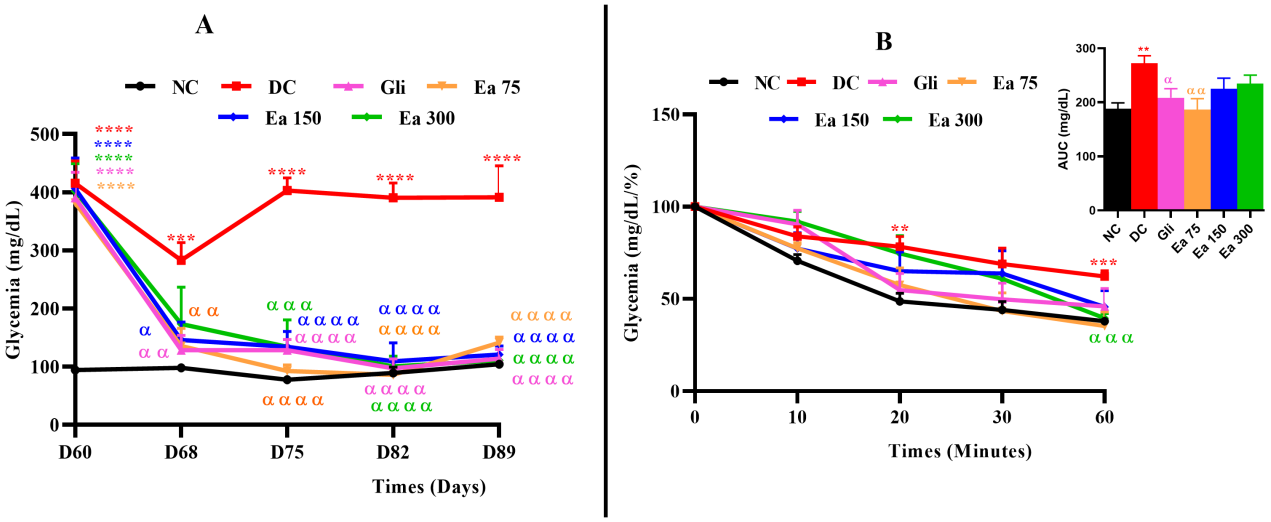

Figure 5. Changes in blood glucose levels (A) and insulin sensitivity (B) respectively during and at the end of 28 days of treatment in type 2 diabetic rats. Each point or bar represents the mean ± SEM; n = 6; **p < 0.01; ***p < 0.001; ****p < 0.0001: significant difference from normal control; $^{\alpha}p < 0.05$; $^{\alpha\alpha}p < 0.01$; $^{\alpha\alpha\alpha}p < 0.001$; $^{\alpha\alpha\alpha\alpha}p < 0.0001$: significant difference compared with the diabetic control; NC: Normal control; DC: Diabetic control; Gli: Glibenclamide; *Ea* 75, *Ea* 150, *Ea* 300: *Entada africana* at the different doses indicated.

3.6. Effects of *E. africana* Stem Bark Aqueous Extract on Body Mass, Relative Organ Masses and Protein Levels in Diabetic Rats

As shown in "Figure 6(A)", body mass did not differ significantly between normal and diabetic rats during the induction period. In contrast, diabetic control (DC) rats exhibited a significant decrease in body mass from day 75 to day 89 ($p < 0.01$–$p < 0.0001$) compared with NC and D60 values (Figure 6(B)), accompanied by a 42.91% reduction in total protein levels ($p < 0.001$) versus NC (Figure 6(C)).

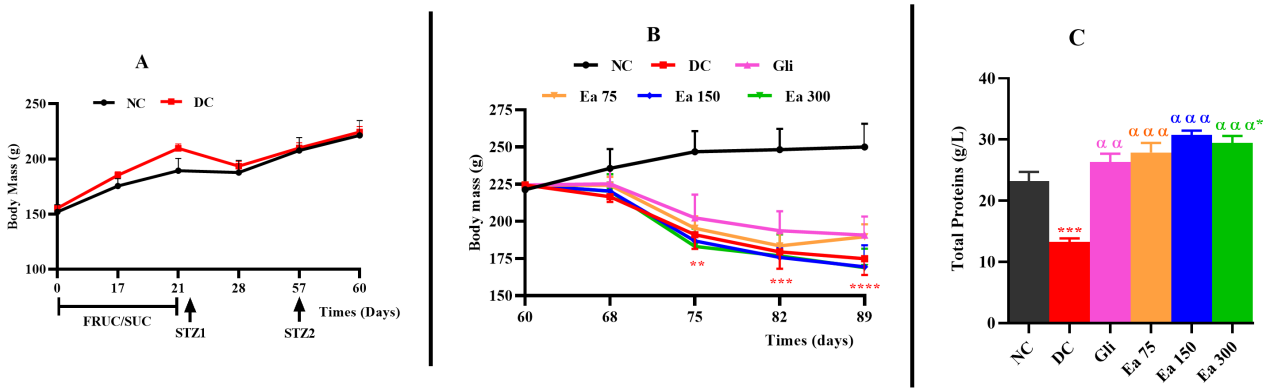

Figure 6. Weight gain during diabetes induction (A) and treatment (B) periods, and serum total protein levels (C) in diabetic rats treated with *Entada africana* stem bark aqueous extract. Each point represents the mean ± SEM; n = 6; *p < 0.05; **p < 0.01; ***p < 0.001; ****p < 0.0001: significant difference compared with the normal control; ααp < 0.01; αααp < 0.001: significant difference compared with the diabetic control; FRUC/SUC: Fructose/sucrose; STZ 1 and 2: Streptozotocin 1 and 2; NR: Normal rats; DR: Diabetic rats; Gli: Glibenclamide; *Ea 75*, *Ea 150*, *Ea 300*: *Entada africana* at the different doses indicated.

Treatment with *E. africana* aqueous extract or glibenclamide did not significantly prevent weight loss in diabetic rats. However, the extract at 75, 150, and 300 mg/kg significantly increased serum total protein levels compared with DC rats (1.11-, 1.32-, and 1.22-fold, respectively; $p < 0.001$). Serum protein levels in rats treated with 150 and 300 mg/kg also increased by 32.46% ($p < 0.01$) and 26.76% ($p < 0.05$), respectively, versus NC.

Only abdominal fat mass increased significantly in DC rats (2.13-fold, $p < 0.05$) compared with NC. Notably, the 75 mg/kg dose of *E. africana* significantly reduced abdominal fat by 82.61% ($p < 0.01$) in treated diabetic rats versus DC (Table 3).

Table 3. Relative organ masses in diabetic rats after 28 days of treatment.

Organs	Treatments					
	NC	DC	Gli	Ea 75	Ea 150	Ea 300
Brain	0.6 ± 0.1	0.8 ± 0.7	0.7 ± 0.4	0.8 ± 0.1	0.9 ± 0.2	0.8 ± 0.1
Pancreas	0.2 ± 0.1	0.2 ± 0.1	0.1 ± 0.0	0.2 ± 0.1	0.2 ± 0.1	0.2 ± 0.1
Liver	3.3 ± 0.2	3.0 ± 0.1	2.6 ± 0.1	2.8 ± 0.1	4.0 ± 0.2	3.2 ± 0.1
Kidneys	0.2 ± 0.1	0.3 ± 0.2	0.2 ± 0.2	0.3 ± 0.2	0.3 ± 0.1	0.3 ± 0.2
Heart	0.3 ± 0.1	0.3 ± 0.1	0.2 ± 0.1	0.3 ± 0.1	0.4 ± 0.2	0.4 ± 0.3
Adrenal glands	0.08 ± 0.07	0.09 ± 0.01	0.07 ± 0.02	0.08 ± 0.03	0.08 ± 0.01	0.08 ± 0.01
Abdominal Fat	1.08 ± 0.05	2.3 ± 0.1*	1.6 ± 0.5	0.4 ± 0.1 αα	1.5 ± 0.3	0.8 ± 0.3

The values are expressed as mean ± SEM; n = 5; ααp < 0.01: significant difference compared to the diabetic control; NC: Normal Control; DC: Diabetic Control; Gli: Glibenclamide; Ea 75, Ea 150, Ea 300: *Entada africana* at the different doses indicated; Adren. glds.: Adrenal glands; Abdo. Fat: Abdominal Fat.

3.7. Effects of *Entada africana* Stem Bark Aqueous Extract on Lipid Profile of Type 2 Diabetic Rats

Compared with normal control (NC) rats, diabetic control (DC) rats exhibited

significantly increased ($p < 0.01$–$p < 0.001$) serum triglycerides (169.64%), total cholesterol (72.73%), and LDL-cholesterol (31.5-fold), along with a marked reduction in HDL-cholesterol (85.6%; $p < 0.01$) (Table 4). DC rats also showed elevated atherogenic (6.5-fold; $p < 0.01$) and insulin resistance indices (144.45%; $p < 0.01$) compared with NC (Table 4).

Table 4. Lipid profile changes in aqueous extracts of *Entada africana* treated diabetic rats.

Treatments	Parameters					
	Triglycerides (mmol/L)	Total Chol. (mmol/L)	LDL-Chol. (mmol/L)	HDL-Chol. (mmol/L)	AI	RI
NC	1.12 ± 0.1	0.11 ± 0.01	0.11 ± 0.01	1.25 ± 0.06	0.09 ±0.1	0.81 ± 0.1
DC	3.02 ± 0.1**	0.19 ±0.01**	3.57 ± 0.2**	0.18 ± 0.6**	0.65 ± 0.02**	1.98 ± 0.1**
Gli	1.37 ± 0.1^{aaa}	0.13 ± 0.01^{aaa}	1.45 ± 0.2^{a}**	1.74 ± 0.1^{a}**	0.07 ± 0.01^{aa}	0.86 ± 0.1^{aa}
Ea 75	0.68 ± 0.2^{aaa}	0.09 ± 0.01^{aaa}	0.65 ± 0.1^{aa}*	1.64 ± 0.1^{aa}*	0.05 ± 0.01^{aa}	0.38 ± 0.1^{aa}*
Ea 50	0.79 ± 0.1^{aaa}	0.15 ± 0.01^{aa}*	0.57 ± 0.^{1}^{aa}**	1.66 ± 0.06^{aa}*	0.09 ± 0.01^{aa}	0.5 ± 0.1^{a}
Ea 300	0.77 ± 0.1^{aaa}	0.08 ± 0.01^{aaaa}	0.71 ± 0.01^{aa}**	1.31 ± 0.08^{aa}	0.06 ± 0.01^{aa}	0.45 ± 0.1^{aa}

Each point represents the mean ± MSE; n = 5; **p < 0.01; ***p < 0.001: significant difference from normal control; ^{aa}p < 0.05; ^{aa}p < 0.01; ^{aaa}p < 0.001; ^{aaaa}p < 0.0001: significant difference from diabetic control; Total Chol.: Total cholesterol; LDL-Chol.: Low density lipoprotein; HDL-Chol.: High density lipoprotein; AI: Atherogenic index; RI: Resistance index; NC: Normal control; DC: Diabetic control; Gli: Glibenclamide; Ea 75, Ea 150, Ea 300: *Entada africana* at the different doses indicated.

Treatment of diabetic rats with the aqueous stem bark extract of *E. africana* significantly reduced ($p < 0.01$–$p < 0.001$) serum triglycerides, total cholesterol, and LDL-cholesterol at all doses (75, 150, and 300 mg/kg) compared with DC. The greatest reductions were observed for triglycerides (77.5% at 75 mg/kg), total cholesterol (57.89% at 300 mg/kg), and LDL-cholesterol (84.03% at 150 mg/kg). The extract at 300 mg/kg normalized serum HDL-cholesterol, increasing its level by 7.28-fold compared with DC ($p < 0.01$), whereas doses of 75 and 150 mg/kg increased HDL nearly 8-fold relative to DC ($p < 0.01$) and by 31.2% and 32.8%, respectively, compared with NC ($p < 0.05$). All extract doses significantly normalized the atherogenic and insulin resistance indices, with the 75 and 300 mg/kg doses showing the most pronounced effects on the lipid profile (Table 4).

Glibenclamide (10 mg/kg) also significantly reduced serum triglycerides (54.65%), total cholesterol (31.1%), and LDL-cholesterol (59.47%) ($p < 0.01$–$p < 0.001$), increased HDL-cholesterol approximately 9-fold ($p < 0.01$), and normalized atherogenic and insulin resistance indices compared with DC (Table 4).

3.8. Effects of *Entada africana* Stem Bark Aqueous Extract on Liver Function in Type 2 Diabetic Rats

3.8.1. Effects of the Plant Extract on Hepatic Glucose Levels (Glycogen Storage)

"Figure 7" illustrates the effect of *E. africana* aqueous extract on hepatic glucose

(glycogen) levels in normal and diabetic rats. Diabetic rats exhibited a significant 52.9% reduction in liver glucose storage compared with normal controls ($p < 0.01$). Treatment with the extract significantly increased hepatic glucose in diabetic rats by 78.08% at 75 mg/kg ($p < 0.01$) and normalized it at 300 mg/kg, with a 121.8% increase versus diabetic controls. The 150 mg/kg dose produced a non-significant increase of 16.44% ($p > 0.05$). Glibenclamide also significantly elevated hepatic glucose levels by 76.71% ($p < 0.01$) compared with diabetic controls.

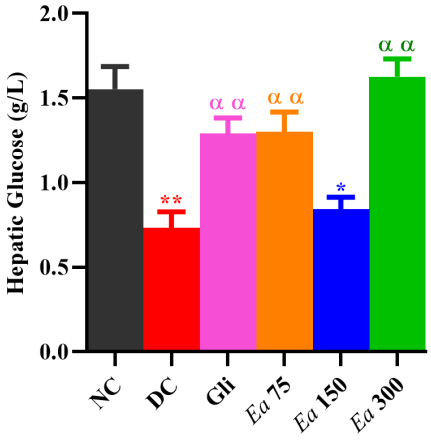

Figure 7. Hepatic glucose levels (liver glycogen storage) in normal and diabetic rats. Each bar represents the mean ± SEM; n = 6; *p < 0.05, **p < 0.01: significant difference compared to the normal control; ααp < 0.01: significant difference compared to the diabetic control; NC: Normal control; DC: diabetic control; Gli: Glibenclamide; Ea 75, Ea 150, Ea 300: *Entada africana* at the different doses indicated.

3.8.2. Effects of the Plant Extract on Levels of Serum Liver Function Markers

Diabetic control rats showed significant increases ($p < 0.001$) in serum ALT (45.87%), AST (86%), total bilirubin (67.96%), and ALP (six-fold) compared with normal controls (Table 5).

Treatment with *E. africana* aqueous stem bark extract significantly reduced ($p < 0.05$–$p < 0.01$) these elevated parameters at all doses. Maximal reductions were observed for ALT (29.55% at 300 mg/kg), AST (53.76% at 75 mg/kg), total bilirubin (46.35% at 75 mg/kg), and ALP (59.63% at 300 mg/kg).

Glibenclamide also significantly decreased ALT (29.55%, $p < 0.01$), AST (36.56%, $p < 0.001$), and ALP (66.10%, $p < 0.01$) versus diabetic controls. Notably, the 75 mg/kg dose of *E. africana* produced a greater reduction in AST (53.76%) than glibenclamide (36.56%) (Table 5).

3.9. Effects of the Stem Bark Aqueous Extract of *Entada africana* on Kidney Function in Type 2 Diabetic Rats

Serum kidney function markers in non-treated and treated diabetic rats are presented in "Table 6". Diabetic control rats showed significant increases ($p < 0.01$) in uric acid (26.10%), urea (4.85-fold), and creatinine (9.30-fold), along with a

marked reduction in serum albumin (91.61%, $p < 0.01$) compared with normal controls.

Table 5. Serum markers of liver function in plant extract-treated diabetic rats.

Treatments	Parameters			
	ALT (mmo/L)	AST (mmo)	ALP (U/L)	BIL (μmol/L)
NC	2.43 ± 0.03	0.51 ± 0.02	122.9 ± 6.07	2.07 ± 0.1
DC	3.53 ± 0.20***	0.93 ± 0.02***	861.0 ± 10.6***	3.45 ± 0.1***
Gli	2.48 ± 0.00 ᵃᵃ	0.6 ± 0.04 ᵃᵃᵃ	291.9 ± 32.8 ᵃᵃ **	1.65 ± 0.1 ᵃᵃ
Ea 75	2.69 ± 0.07 ᵃᵃ **	0.43 ± 0.01 ᵃᵃᵃ##	353.3 ± 19.05 ᵃᵃᵃ **	1.86 ± 0.1 ᵃᵃᵃ
Ea 50	2.50± 0.05 ᵃᵃ	0.70± 0.05 ᵃᵃ **	3495 ± 12.7 ᵃᵃ **	2.31 ± 0.1 ᵃᵃᵃ
Ea 300	2.45 ± 0.08 ᵃᵃ	0.51 ± 0.01 ᵃᵃᵃ	347.6 ± 10.4 ᵃᵃᵃ **	2.17 ± 0.1 ᵃᵃᵃ

Each value represents the mean ± MSE; n = 5; **p < 0.01; ***p < 0. 001: significant difference from normal control; ᵃᵃp < 0.01; ᵃᵃᵃp < 0.001: significant difference from diabetic control; ##p < 0.01: significant difference from Glibenclamide; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; BIL: Total Bilirubin; NC: Normal control; DC: Diabetic control; Gli: Glibenclamide; Ea 75, Ea 150, Ea 300: *Entada africana* at the different doses indicated.

Table 6. Serum markers of kidney function in *E. Africana* extract-treated diabetic rats.

Treatments	Parameters			
	Uric Acid (μmol/L)	Urea (mmol/L)	Creatinine (μmol/L)	Albumin (g/L)
NC	163.2 ± 1.5	0.41 ± 0.01	50.8 ± 0.06	44.46 ± 1.7
DC	205.8 ± 3.5***	2.4 ± 0.07 **	522.7 ± 15.6**	3.73 ± 0.08**
Gli	178.8 ± 7.9 ᵃᵃ	0.83 ± 0.07 ᵃᵃ **	50.25 ± 0.2 ᵃᵃᵃ	48.48 ± 1.06 ᵃᵃ
Ea 75	177.5 ± 7.5 ᵃᵃ	1.04 ± 0.05 ᵃᵃ **	50.0 ± 8.3 ᵃᵃᵃ	40.37 ± 0.2 ᵃᵃ
Ea 150	144.3± 5.01 ᵃᵃᵃ##	0.72 ± 0.01 ᵃᵃ **	90.0 ± 10.0 ᵃᵃ	37.38 ± 0.9 ᵃᵃ *
Ea 300	184.4 ± 5.8 ᵃ *	0.66 ± 0.04 ᵃᵃ *	68.75 ± 10.0 ᵃᵃᵃ	36.73 ± 1.2 ᵃᵃ *

Each point represents the mean ± MSE; n = 5; *p < 0.05; **p < 0.01; ***p < 0.001: significant difference from normal control; ᵃp < 0.05; ᵃᵃp < 0.01; ᵃᵃᵃp < 0.001: significant difference from diabetic control; ##p < 0. 01: significant difference compared with Glibenclamide; NC: Normal control; DC: Diabetic control; Gli: Glibenclamide; Ea 75, Ea 150, Ea 300: *Entada africana* at the different doses indicated.

Treatment with *E. africana* aqueous stem bark extract significantly reduced ($p < 0.01$–$p < 0.001$) uric acid, urea, and creatinine levels at all doses. Maximal reductions were observed for uric acid (29.9% at 150 mg/kg), urea (72.5% at 300 mg/kg), and creatinine (90.43% at 75 mg/kg). The extract also significantly increased ($p < 0.01$) serum albumin at all doses (75, 150, and 300 mg/kg), by approximately 9.82-, 9.02-, and 8.85-fold, respectively, versus diabetic controls. The 150 mg/kg dose improved uric acid levels more effectively than glibenclamide by 19.30% ($p < 0.01$).

Glibenclamide also significantly reduced ($p < 0.01$) serum uric acid (13.12%),

urea (65.5%), and creatinine (90.39%) and increased ($p < 0.01$) serum albumin by 12-fold compared with diabetic controls (Table 6).

3.10. Effects of *Entada africana* Stem Bark Aqueous Extract on Pancreato-Hepato-Renal Oxidative Stress Markers in Type 2 Diabetic Rats

3.10.1. Effects of the Plant Extract on Pancreatic Oxidative Stress Markers

In diabetic control (DC) rats, pancreatic malondialdehyde (MDA) levels increased 4.15-fold compared with normal controls ($p < 0.01$), while pancreatic SOD, catalase (CAT), and GSH significantly decreased by 35.31% ($p < 0.001$), 71.17% ($p < 0.01$), and 68.16% ($p < 0.01$), respectively (Table 7).

Table 7. Pancreatic, Liver and kidney oxidative stress markers values or activities in *E. Africana* stem bark aqueous extract-treated diabetic rats.

Treatments	Parameters			
	MDA (µM/mg protein)	SOD (IU/mg protein)	CAT (µM H_2O_2/min /mg protein)	GSH (µM/mg protein)
		PANCREAS		
NC	1.64 ± 0.14	12.46 ± 0.1	1.63 ± 0.06	8.26 ± 0.12
DC	6.80 ± 0.33**	8.06 ± 0.02***	0.47 ± 0.2**	2.63 ± 0.13*
Gli	3.47 ± 0.15 ᵃᵃ **	12.07 ± 0.16 ᵃᵃ	0.71 ± 0.05 ᵃ **	7.70 ± 0.1ᵃᵃ
Ea 75	2.57 ± 0.13 ᵃᵃ ##	0.15 ± 0.24 ᵃᵃ *	084 ± 0.06 ᵃ **	4.54 0.15 ᵃᵃ **
Ea 150	2.28 ± 0.12 ᵃᵃ ##	8.23 ± 0.08**	0.39 ± 0.03**	3.67 ± 0.1 ᵃᵃ **
Ea 300	1.39 ± 0.09 ᵃᵃ ##	8.94 ± 0.01 ᵃ *	0.35 ± 0.02**	6.95 ± 0.01 ᵃᵃ *
		LIVER		
NC	3.26 ± 0.1	4.11 ± 0.02	0.19 ± 0.0	4.16 ± 0.04
DC	9.23 ± 0.2**	3.74 ± 0.06**	0.12 ± 0.0**	1.41 ± 0.06**
Gli	3.2 ± 0.02 ᵃᵃ	4.41 ± 0.09 ᵃᵃ	0.27 ± 0.01 ᵃᵃ **	4.13 ± 0.07 ᵃᵃ
Ea 75	19 ± 0.07 ᵃᵃ *	3.98 ± 0.06	.34 ± 0.01 ᵃᵃ *##	4.52 ± 0.08 ᵃᵃ *
Ea 150	1.25 ± 0.08 ᵃᵃ *	4.7 ± 0.07 ᵃᵃ	0.29 ± 0.01 ᵃᵃ **	2.5 ± 0.09 ᵃᵃ **
Ea 300	1.27 ± 0.1 ᵃᵃ *	4.42 ± 0.1 ᵃ	0.24 ± 0.01 ᵃ **	4.63 ± 0.07 ᵃᵃ *##
		KIDNEY		
NC	2.6 ± 0.2	4.5 ± 0.02	0.22± 0.0	7.82 ± 0.07
DC	8.56 ± 0.3**	3.63 ± 0.1*	0.03 ± 0.0**	1.26 ± 0.05**
Gli	4.58 ± 0.2 ᵃᵃ **	3.67 ± 0.06*	0.26 ± 0.01ᵃᵃ	1.97 ± 0.05 ᵃᵃ **
Ea 75	2.48 ± 0.2 ᵃᵃ##	3.07 ± 0.06**	0.21 ± 0.01ᵃᵃ	4.75 ± 0.1 ᵃᵃ## *
Ea 150	2.32 ± 0.2 ᵃᵃ##	2.79 ± 0.1**	0.13 ± 0.01ᵃᵃ **	1.68 ± 0.08 ᵃ **
Ea 300	2.41 ± 0.1 ᵃᵃ##	4.14 ± 0.06 ᵃᵃ##	0.22 ± 0.0 ᵃᵃ	6.24 ± 0.1 ᵃᵃ##

Each value represents the mean ± MSE; n = 5; *$p < 0.05$; **$p < 0.01$: significant difference compared with the normal control; ᵃ$p < 0.05$; ᵃᵃ$p < 0.01$: significant difference compared with the diabetic control; ##$p < 0.01$: significant difference compared with Glibenclamide; NC: Normal control; DC: Diabetic control; Gli: Glibenclamide; Ea 75, Ea 150, Ea 300: *Entada africana* extract at the different doses indicated.

Treatment with *E. africana* aqueous stem bark extract significantly reduced MDA at all doses ($p < 0.01$) and increased pancreatic SOD, CAT, and GSH levels ($p < 0.05$–$p < 0.01$) versus DC rats. Maximal effects included a 79.56% reduction in MDA at 300 mg/kg, increases in SOD (25.93%) and CAT (78.72%) at 75 mg/kg, and a 164.26% (2.64-fold) increase in GSH at 300 mg/kg (Table 7).

Glibenclamide (10 mg/kg) reduced pancreatic MDA by 48.97% ($p < 0.01$) and increased SOD (49.75%, $p < 0.01$), CAT (51.06%, $p < 0.05$), and GSH (~2.93-fold, $p < 0.01$) compared with DC rats.

All extract doses (75, 150, and 300 mg/kg) were significantly ($p < 0.01$) and dose-dependently more effective than glibenclamide in reducing pancreatic MDA, with additional reductions of 25.94%, 34.29%, and 59.94%, respectively (Table 7).

3.10.2. Effects of the Plant Extract on Hepatic Oxidative Stress Parameters

Compared with normal controls, diabetic control rats showed significantly increased hepatic malondialdehyde (MDA) levels (183.13%, $p < 0.01$) and reduced SOD (9.02%), CAT (36.84% - 62.71%), and GSH (66.11%) activities/levels ($p < 0.01$) (Table 7).

In diabetic rats, *E. africana* aqueous extract at all doses and glibenclamide significantly decreased MDA ($p < 0.01$) and increased or normalized SOD, CAT, and GSH levels ($p < 0.05$–$p < 0.01$) compared with diabetic and normal controls. Notably, the 75 mg/kg and 300 mg/kg extract doses were significantly more effective ($p < 0.01$) than glibenclamide in increasing hepatic CAT (25.93%) and GSH (12.11%) levels, respectively (Table 7).

3.10.3. Effects of the Plant Extract on Kidney Oxidative Stress Parameters

In diabetic (DC) rats, kidney lipid peroxidation increased markedly, with MDA levels rising 3.29-fold compared with normal controls ($p < 0.01$), while kidney SOD, CAT, and GSH significantly decreased by 19.33%, 86.36%, and 83.89%, respectively ($p < 0.05$–$p < 0.01$) (Table 7).

Treatment with *E. africana* aqueous extract at 75, 150, and 300 mg/kg doses significantly reduced kidney MDA levels by 71.03%, 72.90%, and 71.85% ($p < 0.01$) and increased SOD, CAT, and GSH levels ($p < 0.05$–$p < 0.01$) compared with DC rats. Increases included SOD (14.05% at 300 mg/kg), CAT (7-, 4.33-, and 7.33-fold), and GSH (3.77-fold, 33.33%, and 4.95-fold, respectively).

Glibenclamide significantly decreased kidney MDA by 46.50% ($p < 0.01$) and increased CAT (8.67-fold) and GSH (56.35%) versus DC rats (Table 7).

Compared with glibenclamide, all extract doses (75, 150 and 300 mg/kg) were more effective in reducing kidney MDA ($p < 0.01$), with additional decreases of 45.85%, 49.34%, and 47.38%, respectively. The 75 and 300 mg/kg doses also improved kidney SOD and GSH more than glibenclamide, increasing GSH by 2.41- and 3.17-fold and SOD by 12.81% at 300 mg/kg (Table 7).

3.11. Histological Effects of *Entada africana* Stem Bark Aqueous Extract on Liver, Kidney and Pancreas in Diabetic Rats

"Figure 8" illustrates histological sections of the pancreas, liver, and kidney from

normal, untreated diabetic, and treated diabetic rats.

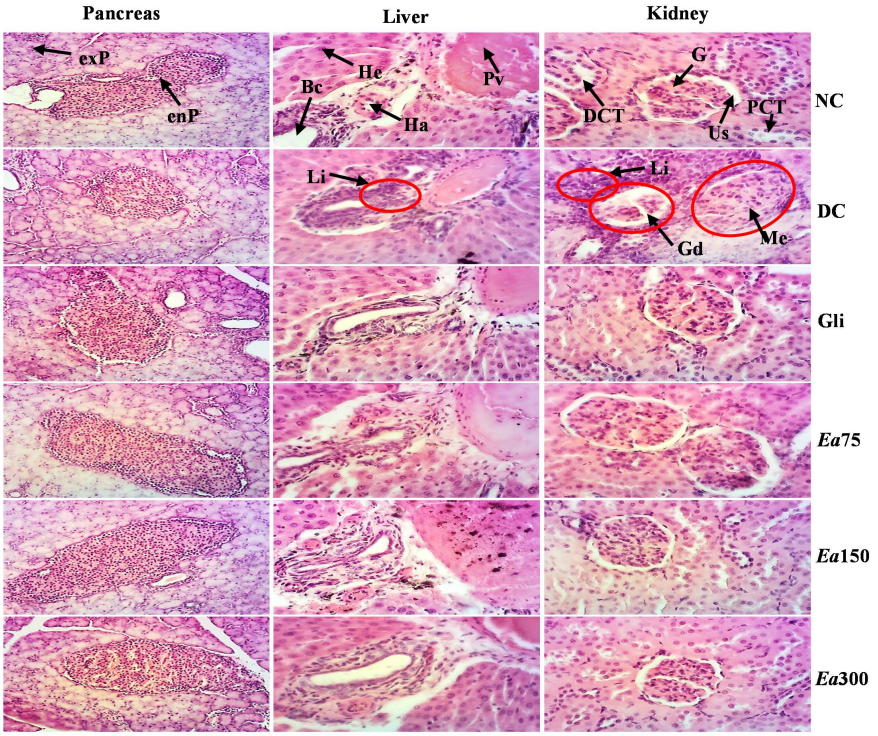

Figure 8. Histology of liver, kidney and pancreas from *E. africana*-treated diabetic rats (HE x200). Pv: portal vein; Ha: hepatic artery; Bc: biliary canaliculus; He: hepatocytes; Li: leukocyte infiltration; G: glomerulus; Us: urinary space; DCT: distal convoluted tubules; PCT: proximal convoluted tubules; Gd: glomerular degeneration; Me: mesangial expansion; exP: exocrine pancreas; enP: endocrine pancreas; NC: Normal Control; DC: Diabetic Control; Gli: Glibenclamide; Ea 75, Ea 150, Ea 300: *Entada africana* at the different doses indicated.

In the pancreas, normal rats presented well-organized acini and well-developed islets of Langerhans, whereas diabetic control rats showed reduced islet size. Normal rat livers showed intact parenchyma with a portal vein, hepatic artery, bile canaliculi, and well-defined hepatocytes, whereas diabetic control rats displayed leukocyte infiltration in the portal area. Normal kidneys exhibited preserved renal parenchyma with intact glomeruli, urinary spaces, and proximal and distal tubules, while diabetic controls showed leukocyte infiltration, glomerular degeneration, and mesangial expansion (Figure 8).

Treatment with *E. africana* aqueous extract or glibenclamide improved hepatic and renal histological alterations and increased islet size compared with untreated diabetic rats. The 75 mg/kg extract dose showed greater effects on renal and pancreatic tissues, while the 300 mg/kg dose was more effective on liver histology (Figure 8).

4. Discussion

Type 2 diabetes mellitus (T2D) is a complex and multifactorial disease characterized by chronic hyperglycemia and insulin resistance. These metabolic abnormal-

ities progressively affect nearly all organ systems and are responsible for severe complications. Effective management combining antidiabetic drugs, lifestyle changes and regular medical monitoring is essential to prevent or delay these outcomes [31]-[33]. Thus, the present study scientifically evaluated the therapeutic potential of the aqueous stem bark extract of *Entada africana* in the management of type 2 diabetes and its associated organ complications. This investigation was deeply motivated and guided by previously reported and current phytochemical and toxicological data obtained on the plant.

Qualitative phytochemical analysis of the aqueous stem bark extract of *E. africana* revealed the presence of mucilage, cardiac glycosides, reducing sugars, unsaturated sterols, free quinones, saponins, polyphenols, flavonoids (flavones and flavonols), gallic tannins and triterpenoids. These phytoconstituents, as well as isolated compounds such as myricetin, robinetin, and pyrogallol previously reported in *E. africana* stem bark extracts, have been consistently identified [13] [16] [34]-[41]. They are known to possess multiple biological activities, notably antihyperglycemic, antihyperlipidemic, antioxidant, hepatoprotective, cardioprotective, nephroprotective and anti-inflammatory properties, all of which are relevant to diabetes management [14].

Acute toxicity test showed no mortality or adverse effects at a single oral dose of 2000 mg/kg of the aqueous stem bark extract of *E. africana* in normal female rats, indicating an LD50 greater than 2000 mg/kg. According to the Globally Harmonized System (GHS), this extract can therefore be classified as having low toxicity (Category 5 or unclassified) [22]. Other studies reported LD50 values of 146.7 mg/kg for methanolic extract and 3.8 g/kg for ethylacetate extract in mice, suggesting that toxicity depends on the extraction solvent and animal species [42] [43]. Methanolic extracts were also reported to be non-cytotoxic in KB and Vero cell lines [42]. Similar low toxicity profiles have been reported for other medicinal plants traditionally used against diabetes [44]-[46].

Pharmacological evaluation, including toxicological studies, also encompasses the assessment of therapeutic efficacy, both preventive and curative. The Oral Glucose Tolerance Test (OGTT) is widely used clinically to screen and diagnose T2D and prediabetes [47] [48], and experimentally to assess glucose handling and antidiabetic efficacy in animal models [48]-[50]. In this study, 28-days administration of the aqueous stem bark extract of *E. africana* significantly attenuated the post-load blood glucose increase in normal rats, particularly at the 300 mg/kg dose. Similar antihyperglycemic effects were previously reported following subchronic administration of methanolic extracts of *E. africana* stem bark in rabbits [42]. These findings strongly support the antihyperglycemic potential of *E. africana* and its ability to improve glucose tolerance.

To further investigate the plant's antidiabetic effects, a well-established type 2 diabetes model was used, combining a high-sugar diet (fructose/sucrose) with low-dose streptozotocin (STZ) [23] [51]-[53]. In this study, normal rats receiving a 10% fructose/sucrose diet followed by STZ (40 mg/kg) developed hallmark features of T2D, including reduced insulin sensitivity, impaired glucose tolerance

and persistent chronic hyperglycemia. These alterations result from the synergistic diabetogenic effects of both agents: the high-sugar diet induces insulin resistance, while STZ partially impairs pancreatic β-cell function and insulin secretion. Excess fructose metabolism in the liver promotes accumulation of free fatty acids and diacylglycerol (DAG), which activates protein kinase C (PKC) and disrupts metabolic insulin signaling through serine-threonine phosphorylation of insulin receptor substrates [54]-[61]. STZ further contributes by inducing oxidative stress and nitric oxide production, leading to β-cell necrosis and insulinopenia [62] [63]. Together, these mechanisms reproduce a pathological state closely resembling advanced human T2D [23] [52].

Treatment of diabetic rats with the aqueous stem bark extract of *E. africana* significantly reduced hyperglycemia and insulin resistance compared with untreated diabetic controls. These effects suggest that the extract can both prevent hyperglycemia in normal rats and reduce it in diabetic rats. Such effects may involve inhibition of digestive enzymes and intestinal glucose transporters, thereby slowing glucose absorption [64]. This hypothesis is supported by reports that methanolic extracts of *E. africana* leaves inhibit α-amylase and α-glucosidase more effectively than acarbose in vitro [65]. Since inhibition of these enzymes is a key strategy in diabetes management, *E. africana* appears to be a promising source of antidiabetic compounds.

In addition, the extract may hypothetically exert direct insulinotropic effects by activating enzymes involved in glycogenesis and insulin secretion [66]. Computational studies have shown that pyrogallol, myricetin and robinetin previously reported in *E. africana* extracts can activate glucokinase and ATP-sensitive potassium channels, thereby promoting glycogenesis and insulin release [16]. Indirect insulinotropic effects may also occur through incretin-related mechanisms. Although direct evidence linking *E. africana* to GLP-1 secretion is lacking, myricetin has been reported to act as a GLP-1 receptor agonist [67]-[69], suggesting a potential contribution to glycemic control and body weight regulation. Furthermore, myricetin has been reported to stimulate GLUT2 expression and glucose uptake in pancreatic cells [70], supporting a role for enhanced glucose transport and storage. Improved insulin sensitivity observed in treated rats may also reflect inhibition of enzymes associated with insulin resistance and lipogenesis, as reported for other antidiabetic plants such as *Moringa oleifera* [7] [71] and *Artabotrys thomsonii* [53].

Lipid metabolism disorders are a major feature of diabetes and are closely linked to insulin resistance and glucose metabolism [72]. Untreated diabetic rats exhibited dyslipidemia characterized by increased triglycerides, total cholesterol and LDL-cholesterol, decreased HDL-cholesterol, and elevated atherogenic risk and insulin resistance indices, indicating a very high risk of cardiovascular diseases [73]. Similar lipid abnormalities have been widely reported in fructose/STZ-induced diabetes [7] [23] [53] [74]. Hyperglycemia promotes excessive acetyl-CoA production, leading to increased triglyceride synthesis and cholesterol trans-

fer [73] [75]. Treatment with the aqueous stem bark extract of *E. africana* significantly improved lipid profiles, with effects comparable to or exceeding those of glibenclamide. These hypolipidemic effects suggest a potential role in preventing cardiovascular complications of diabetes. Comparable lipid-lowering effects were reported with saponin extracts of *Entada phasoelides* [76], although contrasting results have been observed with methanolic extracts of *E. africana* in rabbits [42]. The lipid-lowering mechanisms may involve inhibition of ACAT activity, reduced cholesterol absorption, modulation of lipoprotein oxidation and regulation of SREBP-dependent triglyceride synthesis [7] [77] [78]. Myricetin previously reported in *E. africana* has also been shown to reduce hepatic lipid synthesis and inflammation, enhance fatty acid oxidation through PPAR-α activation, and downregulate SREBPs [79]-[82].

Diabetic rats showed significant body weight loss and reduced serum protein levels despite increased abdominal fat mass, likely due to muscle wasting, enhanced proteolysis and impaired amino acid uptake associated with insulin resistance and STZ toxicity [83]. Although *E. africana* extract did not reverse weight loss, it increased proteinemia and normalized creatininemia, suggesting improved protein metabolism and insulin sensitivity. The persistent weight loss may reflect reduced fat mass through enhanced lipolysis, potentially mediated by flavonoids and saponins activating AMPK [84] [85]. Improved serum protein levels may also result from reduced protein degradation and advanced glycation associated with oxidative stress [86]-[88].

As the central metabolic organ, the liver is particularly affected by diabetes. Diabetic rats exhibited elevated ALT, AST, ALP and bilirubin levels, indicating hepatic dysfunction, which was confirmed histologically by leukocyte infiltration [89]-[92]. Hepatic glucose content was reduced in diabetic controls, reflecting impaired glycogen storage due to hepatic insulin resistance and enhanced glycogenolysis [93]. Treatment with the aqueous stem bark extract of *E. africana* and glibenclamide significantly normalized liver enzymes, improved liver morphology and increased hepatic glucose levels. Similar hepatoprotective effects of *E. africana* have been reported in acetaminophen-induced hepatotoxicity [36]. These effects may be attributed to bioactive compounds such as polyphenols, triterpenes, alkaloids and saponins, and supported by computational evidence that pyrogallol, myricetin and robinetin from *E. africana* activate glucokinase and ATP-sensitive potassium channels, promoting glycogenesis and insulin release [16].

The kidney was also markedly impaired by diabetes, as shown by increased serum creatinine, urea and uric acid and decreased albumin levels [94] [95]. Hypercreatininemia reflects reduced glomerular filtration and metabolic disturbances associated with insulin resistance and muscle mass loss [96]. Hyperuremia and elevated uric acid may contribute to renal injury through urate crystal deposition, inflammation and oxidative stress [97] [98]. Hypoalbuminemia further indicates altered nutritional and renal status [3] [86] [99] [100]. These biochemical disturbances were consistent with histological findings of leukocyte infiltration, glomerular degeneration and mesangial expansion. Treatment with *E. africana* extract

significantly improved renal function markers and preserved renal architecture, likely through the combined actions of flavonoids, saponins and tannins and improved glycemic and lipid control [86] [100].

Oxidative stress plays a central role in diabetes-related tissue injury. Fructose/sucrose and STZ administration induced oxidative stress, evidenced by increased lipid peroxidation (MDA) and depletion of antioxidant defenses (CAT, SOD, GSH) in liver, kidney and pancreas [101]-[103]. The aqueous stem bark extract of *E. africana* significantly restored antioxidant enzyme activities, increased GSH levels and reduced MDA. Similar antioxidant effects have been reported for *E. africana* in vitro and for *Entada phasoelides* in diabetic rats [35] [36] [76]. These effects may hypothetically be attributed to bioactive compounds, including polyphenols, flavonoids, tannins and triterpenoids. Pyrogallol, robinetin and myricetin identified in *E. africana* extracts have been reported to scavenge reactive oxygen species, inhibit lipid peroxidation and protect cell membranes, despite reported context-dependent toxicity of pyrogallol at high doses [82] [104]-[110].

5. Conclusion

The aqueous stem bark extract of *Entada africana* exhibits antihyperglycemic, hypolipidemic, insulino-sensitizing, antioxidant, hepatoprotective, nephroprotective and pancreatoprotective effects in type 2 diabetic rats. These effects, likely mediated by its numerous bioactive phytoconstituents, result from the modulation of metabolic and oxidative mechanisms underlying diabetes-induced organ injury. These findings support the traditional use of *E. africana* and suggest its potential as a complementary therapy in diabetes management, warranting further studies on long-term safety and therapeutic development.

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Conflicts of Interest

The authors have not declared any conflict of interests.

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