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ORIGINAL RESEARCH

Antidiabetic Effect of Hydro-Ethanolic Leaf Extract of *Sclerocarya Birrea* (A. Rich.) Hochst in Wistar Rats

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Introduction: Diabetes mellitus, characterized by chronic hyperglycaemia, remains a major global health burden. Limitations of conventional therapies have led to growing interest in medicinal plants like *Sclerocarya birrea* (A. Rich.) Hochst. widely used in African ethnomedicine. Though prior research has focused more on the stem bark, studies on the leaves, considered more sustainable and traditionally relevant, are still lacking in vivo data. This study assessed the antidiabetic potential of a hydroethanolic leaf extract of *Sclerocarya birrea* in Wistar rats.

Methods: The extract was tested at 25–200 mg/kg in an oral glucose tolerance test (OGTT), and at 100–400 mg/kg in normoglycemic and high fructose-fed, streptozotocin (STZ)-induced type 2 diabetic rats over 21 and 28 days, respectively. Fasting blood glucose, insulin, glycated haemoglobin (HbA1c), glucose transporter type 4 (GLUT4), haematological and biochemical parameters, and histopathological changes in key organs were evaluated.

Results: In the OGTT, the extract significantly reduced postprandial blood glucose at 100 and 200 mg/kg starting from 60 minutes post-glucose load ($p < 0.05$). In normoglycemic rats, repeated administration over 21 days led to a dose-dependent and statistically significant reduction in fasting blood glucose beginning on day 14 and sustained through day 21 ($p < 0.01$). In diabetic rats, fasting blood glucose levels were significantly reduced from day 7 onward, with 400 mg/kg producing effects comparable to glibenclamide by day 28 ($p < 0.01$). Insulin, GLUT4, and HbA1c levels were not significantly altered ($p > 0.05$). Haematological and biochemical parameters remained within normal ranges, and histopathological examination showed preservation of pancreatic and renal tissues in treated groups.

Conclusion: *Sclerocarya birrea* leaf extract significantly lowers blood glucose in both normoglycemic and diabetic rats without adverse effects, supporting its potential as a safe plant-based option for diabetes management. Further research is warranted to clarify its mechanisms and long-term impact.

Keywords: diabetes mellitus, *sclerocarya birrea*, antidiabetic, hydroethanolic extract, streptozotocin

Introduction

Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycaemia resulting from defects in insulin secretion, insulin action, or both.[1] This condition leads to various long-term complications, including cardiovascular disease, neuropathy, nephropathy, and retinopathy, posing significant public health challenges globally. The prevalence of diabetes mellitus has been rising steadily, with an estimated 463 million adults affected in 2019, a number projected to rise to 700 million by 2045.[2] This surge is driven by urbanization,[3] ageing populations, and lifestyle changes, which pose significant public health challenges worldwide.[4,5]

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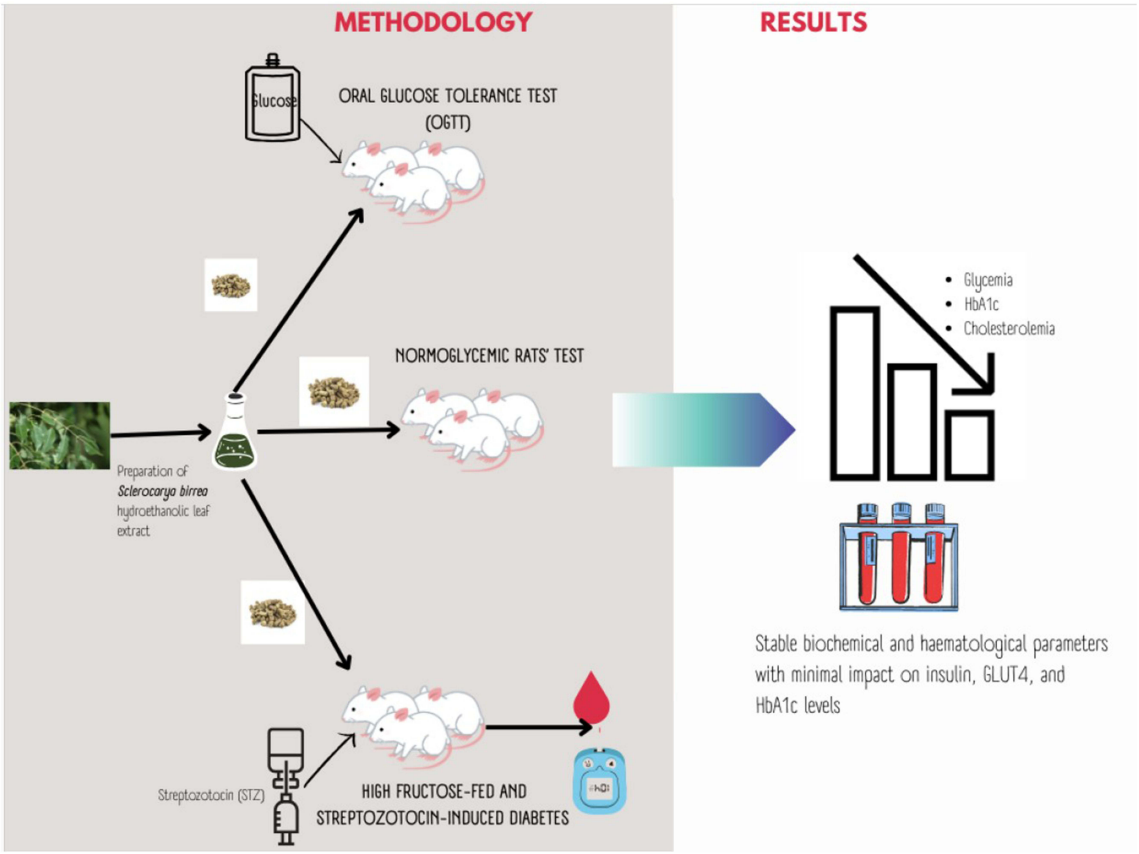
Graphical Abstract



In Sub-Saharan Africa, the prevalence of diabetes is also rising, with estimates indicating that around 24 million people are currently affected, a number expected to double by 2045.[2,6–8] In Burkina Faso, the prevalence of diabetes is approximately 5.8%, indicating an escalating burden of the disease in both rural and urban areas.[9]

The management of diabetes typically encompasses lifestyle modifications, oral hypoglycaemic agents, and insulin therapy.[10,11] However, these treatments are often associated with limitations, including adverse effects, financial constraints, and challenges in patient compliance, thus underscoring the imperative for the exploration of alternative therapeutic interventions, mainly from natural sources.

Sclerocarya birrea (A. Rich.) Hochst., commonly known as marula, is a member of the Anacardiaceae family. The plant is widely distributed across Africa and has been traditionally used to manage a wide range of ailments, including fever, diarrhea, dysentery, inflammation, and infections, in addition to diabetes.[12–14] Its various parts—leaves, bark, and fruits—are employed in African traditional medicine for their antimicrobial, anti-inflammatory, analgesic, infertility, antihypertensive and antidiabetic properties, among others.[15–17] Such diverse ethnomedicinal uses highlight its pharmacological potential. Phytochemical analysis of hydroethanolic and aqueous leaf extracts of Sclerocarya birrea reveals a complex profile rich in bioactive compounds, including flavonoids, polyphenols, saponins, triterpenoids, and tannins, known for their metabolic regulatory effects.[18–23] Recent investigations by Maharaj et al (2022) revealed the presence of three key bioactive flavonoids—myricetin, myricetin-3-O-β-D-glucuronide, and quercetin-3-O-β-D-glucuronide—in spray-dried aqueous leaf extracts of Sclerocarya birrea. These compounds significantly enhanced glucose uptake in differentiated C2C12 myocytes, with compound 1 (myricetin) showing effects (up to 109.1%) comparable to insulin (100%) at 10 µg/mL.

Previous studies have primarily focused on the stem bark and fruits of *Sclerocarya birrea*, with findings demonstrating that the stem bark extract exhibits antidiabetic activity.[24–26] Maharaj et al (2022) demonstrated that the aqueous extract of *Sclerocarya birrea* leaves exhibited antidiabetic activity in vitro, primarily through enzyme inhibition. However, its efficacy and safety profile in in-vivo models remain underexplored, and the potential mechanisms of action have not been fully elucidated.

Despite the traditional use of leaves in some communities, scientific investigations have disproportionately concentrated on the bark, which raises sustainability and ethical concerns, as bark harvesting may endanger plant survival. Leaves, in contrast, are more readily renewable, easier to harvest, and have also been shown to contain significant bioactive phytochemicals. Thus, the leaf extract represents a more sustainable and promising alternative for therapeutic development. Notably, the leaves of *Sclerocarya birrea* are already utilized in the formulation of *Diabefla*, a traditional antidiabetic remedy that has received special market authorization and is commercialized in pharmacies in Burkina Faso, further underscoring their potential for safe and effective use in diabetes management.[27,28]

There remains a clear research gap concerning the in-vivo efficacy, safety, and mechanism of action of the hydroethanolic leaf extract of *Sclerocarya birrea* in animal models of diabetes. Addressing this gap could offer new insights into plant-based therapeutic options and validate traditional practices with scientific rigor.

Building on this rationale, the present study investigates the antidiabetic effects of the hydroethanolic leaf extract of *Sclerocarya birrea* in Wistar rats through three main objectives: analyzing its impact on postprandial hyperglycaemia in diabetic rats, evaluating its effects in normoglycemic rats, and assessing its influence on high fructose-fed streptozotocin-induced diabetic rats while exploring potential mechanisms of action.

Methodology

Chemicals and Reagents

Streptozotocin (purchased from Sigma-Aldrich Chemical Co., St. Louis, MO, USA), Glibenclamide (purchased from Nigeria-German Chemicals Plc, Ota, Nigeria), and other chemicals and reagents used for this study were of pure analytical grade.

Plant Material and Extraction

The leaves of *Sclerocarya birrea* (A. Rich.) Hochst were collected in the Bichi area of Kano, Kano State, Nigeria. The plant material was authenticated by Dr Samuel Odewo of the Forestry Research Institute of Nigeria (FRIN) in Ibadan, where a voucher specimen with voucher number 2024080188878 was deposited. The collected leaves were then subjected to a drying process under shaded conditions at ambient temperature, after which they were pulverized into a fine powder using a mechanical grinder.

A hydroethanolic extract (80:20) was prepared by macerating 1 kg of the powdered leaves in 5 L of a solvent mixture of ethanol and distilled water (80:20 v/v) for 72 hours at room temperature. The mixture was then filtered using Whatman No. 1 filter paper, and the filtrate was concentrated under reduced pressure using a rotary evaporator at 40°C to yield a semisolid extract. The resulting extract was further dried in a vacuum desiccator to obtain a solid extract, which was stored in an airtight container at 4°C until further use.

The dried hydroethanolic extract was freshly reconstituted each day in distilled water at concentrations corresponding to the required doses (100, 200, and 400 mg/kg), and administered orally at a dose volume of 10 mL/kg, in accordance with standard pharmacological practices for plant extract studies. The extraction process yielded 12% w/w of dried hydroethanolic leaf extract.

Animals and Experimental Design

Male Wistar rats (10–12 weeks old, weighing 190–200 g) were obtained from the Laboratory Animal Centre, College of Medicine, University of Lagos, Nigeria. The animals were housed under standard laboratory conditions, including a temperature of 27 ± 3°C and relative humidity of 65%, with a 12-hour light/dark cycle. The rats were acclimatized for a period of two weeks prior to the initiation of the experiments and were provided with a standard pellet diet (Vital Feed Nig. Ltd) and water ad libitum. The experimental protocols were approved by the Health Research Ethics Committee of the College of Medicine, University of

Lagos, Nigeria (Approval Number: CMUL/ACUREC/06/24/149). The study was conducted in accordance with internationally accepted principles for the care and use of laboratory animals.

Oral Glucose Tolerance Test (OGTT)

The oral glucose tolerance test (OGTT) was conducted on healthy Wistar rats that had been subjected to an overnight fast (18 hours). The animals were randomly assigned to seven groups of five animals each.

- Standard Control Group: Received 10 mL/kg of normal saline orally.
- Untreated Control Group: Received 2 g/kg of glucose orally without any treatment.
- Positive Control Group: Orally received Glibenclamide (10 mg/kg).
- Treated Groups: Received the hydroethanolic extract of Sclerocarya birrea leaves at 25 mg/kg, 50 mg/kg, 100 mg/kg, or 200 mg/kg, administered orally.

Thirty minutes following the administration of treatment, a glucose solution (2 g/kg) was administered to all groups. Blood samples were collected from the retro-orbital sinus under ether anaesthesia at 30, 60, 90, and 120 minutes following glucose administration. Blood glucose levels were measured using glucose oxidase-peroxidase reactive strips and a glucometer (Accu-Chek, Roche Diagnostics GmbH, Germany).

Effect of Extract on Normoglycemic Rats

The experiment was conducted on healthy rats who had fasted overnight for 12 hours, following the method described by Lanjhiyana et al (2011). Twenty-five rats were randomly divided into five groups (with experimental treatment doses based on optimal OGTT response), each consisting of five animals:

- Group I: Received normal saline (control group).
- Group II: Received 10 mg/kg of Glibenclamide (positive control).
- Group III: Received 100 mg/kg of hydroethanolic extract of *Sclerocarya birrea*.
- Group IV: Received 200 mg/kg of hydroethanolic extract of *Sclerocarya birrea*.
- Group V: Received 400 mg/kg of hydroethanolic extract of *Sclerocarya birrea*.

The choice of extract doses was guided by findings from the initial OGTT phase of the study, which showed an optimal glycemic response from 100 mg/kg. The hydroethanolic extract was administered daily for 21 days. Whole blood samples were collected from the tail vein for fasting blood sugar (FBS) measurements on day 0 (before treatment) and 6 hours post-treatment on days 1, 7, 14, and 21. Fasting blood sugar levels were measured using an AccuChek glucometer (Roche Diagnostics GmbH, Germany) and recorded in mg/dL.

Effect of Sclerocarya Birrea Extract on High Fructose-Fed and Streptozotocin-Induced Diabetic Rats

The induction of Type 2 diabetes (T2D) was accomplished through the implementation of a modified method previously outlined by Kale et al (2018). This method entailed the administration of fructose (20% w/v) *ad libitum* for a period of eight weeks, followed by a single intraperitoneal injection of streptozotocin (STZ) injection (40 mg/kg i.p). dissolved in a citrate buffer. This procedure was conducted subsequent to the eight-week pre-treatment period with fructose. Rats with blood glucose levels above 200 mg/dL were considered diabetic and were used for the study. Seventy-two (72) hours following the STZ injection, forty-eight (48) diabetic rats were divided into six groups of eight rats each.

- Group I: Normal control group, received 0.9% sodium chloride (10 mL/kg, p.o).
- Group II: Untreated diabetic control group.
- Group III: Received 100 mg/kg of Sclerocarya birrea leaf extract (p.o).

- Group IV: Received 200 mg/kg of Sclerocarya birrea leaf extract (p.o).
- Group V: Received 400 mg/kg of Sclerocarya birrea leaf extract (p.o).
- Group VI: Positive control group, received 5 mg/kg of Glibenclamide (p.o).

The extract doses in Groups III to V were selected based on findings from the initial OGTT phase of the study, which indicated an optimal glycemic response from 100 mg/kg.

The duration of the study was 28 days, during which the body weights of the animals were recorded weekly. On days 1, 7, 14, 21 and 28, fasting blood glucose levels were estimated using a glucometer (Accu-Check® Active) and glucose test strips. Following the conclusion of the study, blood and tissue samples were collected for biochemical, haematological, insulin, Glucose Transporter Type 4 (GLUT4), glycated haemoglobin (HbA1c) assays and histological evaluation.

Haematological Parameters

A 2 mL blood sample was collected for haematological analysis using an automated haematological analyser. Approximately 50 µL of blood was aspirated into the analyser to generate a complete blood count (CBC) result.

Biochemical Parameters

Serum samples were analyzed for biochemical markers, including triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC), alanine transaminase (ALT), aspartate transaminase (AST), urea, creatinine, and bilirubin. These measurements were conducted using commercial kits supplied by Randox Laboratories Ltd. (Crumlin, UK) in accordance with the manufacturer's protocols.

Glycated Haemoglobin (HbA1c) Assay

Lysing of the Whole Blood

The assay was conducted in accordance with the manufacturer's specifications, employing the HbA1c Kit (Fortress Diagnostics, UK). In summary, fresh haemolysate was prepared for each blood sample. Subsequently, 250µL of haemolysis reagent was dispensed into a test tube. Then, 20 µL of well-mixed whole blood samples were added to the test tube with the haemolysis reagent, mixed vigorously and left to stand for 5 minutes.

HbA1c Assay Method

In accordance with the manufacturers' specifications, a wavelength of 700 nm, a temperature of 37°C, and a cuvette measurement of 1 cm light path against distilled water were employed. Next, 75 µL of the haemolysed sample was transferred into a test tube, after which 480 µL of the provided working reagent was added. The mixture was then incubated and agitated for 5 minutes at 37°C. The resulting value of the light absorption (A1), was then measured. Subsequently, 210 µL of the provided Enzyme/Chromogen was added to the test tube solutions, and the resulting Absorbance (A2) was measured following a 3-minute incubation at 37°C. The delta Absorbance (ΔA) was then calculated using the established formula to estimate the HbA1c levels.

$\Delta A = A2-(A1*0.725)$

Mechanistic Study

Insulin Assay

Following manufacturers' specifications, the present assay was conducted utilising the Rat INS (Insulin) ELISA Kit (Elabscience, USA). Briefly, the plate wells were prepared with a dilution of the standard, a blank well, and a sample well. Subsequently, 100 µL of biotinylated detection antibodies working solution was added to each well, which was then incubated for 60 minutes at 37°C. Thereafter, w the plate was washed thrice. Then, 100 µL of the Avidin-Horseradish Peroxidase (HRP) Conjugate was added and re-incubated for 30 minutes at 37°C. Following this, the plate was rewashed five times, then 90 µL of the substrate reagent was added and re-incubated for 15 minutes at 37°C. Subsequently, 50 µL of stop solution was added, and the plate was read at 450nm using a microplate reader after determining the optical density (OD). The experiment was performed in duplicates.

Calculation of Results

The mean of the duplicate readings for each standard and sample was calculated, and then the mean zero standard optical density was subtracted. A four-parameter logistic curve was then plotted on log-log graph paper, with standard concentration on the x-axis and OD values on the y-axis, in order to ascertain the insulin concentration.

The actual insulin concentration was then determinate by multiplying the calculated insulin concentration by the dilution factor.

Glucose Transporter 4 (GLUT4) Assay

In accordance with the manufacturer's specifications, the assay was conducted utilising the Rat GLUT4 (Glucose Transporter 4) ELISA Kit (Elabscience, USA). In summary, 100 µL of standard, blank, and sample were added to the plate wells and incubated for 90 minutes at 37°C. Thereafter, 100 µL of biotinylated detection antibodies working solution was added to each well and then incubated for 60 minutes at 37°C. Subsequently, the plate was washed thrice then 100 µL of the Avidin-Horseradish Peroxidase (HRP) Conjugate was added and re-incubated for 30 minutes at 37°C. Thereafter, the plate was rewashed five times. Subsequently, 90 µL of the substrate reagent was added and re-incubated for a further 15 minutes at 37°C. Then, 50 µL of stop solution was added. The plate was then read at 450nm using a microplate reader after determining the optical density (OD).

Calculation of Results

The mean duplicate readings for each standard and sample were calculated, and then the mean zero standard optical density was subtracted. To calculate GLUT4 concentration, a four-parameter logistic curve was plotted on log-log graph paper with standard concentration on the x-axis and OD values on the y-axis. The actual concentration was then calculated as the product of the calculated GLUT4 concentration and the dilution factor.

Histopathological Examination

Tissue samples from the liver, kidney and pancreas were prepared in accordance with the protocol delineated by Baker and Silverston (1985). Histological slides of these tissues were examined under a light microscope at 40× magnification.[29] Histopathological lesions were scored using semi-quantitative approach as follows: 0 for normal, 1 (1%e30%) for mild, 2 (31%e70%) for moderate, and 3 (>70%) for severe.

Statistical Analysis

Data were expressed as the mean ± standard error of the mean (SEM). The significance of differences between the control and treated groups was determined using a one-way analysis of variance (ANOVA) followed by Dunnett's multiple comparison test. A p-value of < 0.05 was considered to be statistically significant. All statistical analyses were performed using GraphPad Prism 7 (GraphPad Software Inc., La Jolla, CA, USA).

Results

Effect of Sclerocarya Birrea Treatment on Oral Glucose Tolerance Test (OGTT)

The Oral Glucose Tolerance Test (OGTT) revealed significant variations across treatment groups over time (Figure 1). The control group exhibited relatively stable glucose levels, while the untreated control (2g/kg glucose only) demonstrated elevated glucose levels, reaching a peak at 60 minutes. *Sclerocarya birrea* treatments at 200, 100, and 50 mg/kg demonstrated notable glucose lowering effects, with the greatest reductions observed in the 100 mg/kg and 200 mg/kg groups. Glibenclamide produced a marked reduction in glucose levels, especially at 90 and 120 minutes.

Effect of Extract on Normoglycemic Rats

Following a 21-day administration in normoglycemic rats, all doses of *Sclerocarya birrea* (100, 200, and 400 mg/kg) demonstrated a significant reduction in blood glucose levels from day 14 through day 21, in a dose-dependent manner (Figure 2). At day 7, only glibenclamide produced a statistically significant reduction in blood glucose levels. The stronger effects of including glibenclamide as well *Sclerocarya birrea* was observed at day 14.

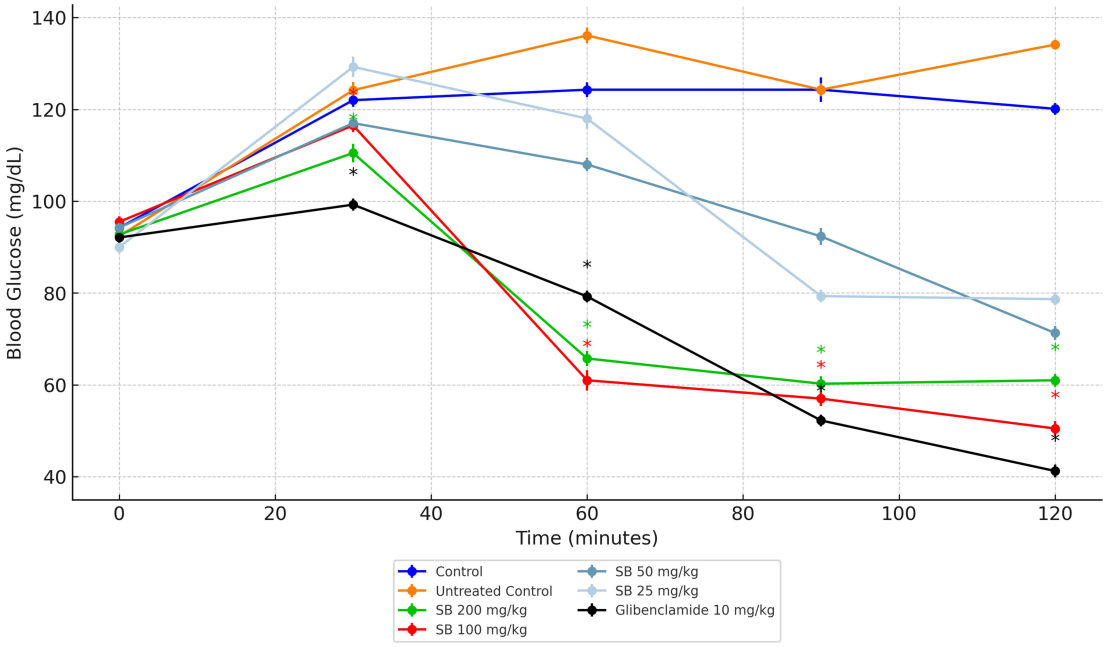


Figure 1 Effects of Sclerocarya birrea treatment and glibenclamide on blood glucose levels during the oral glucose tolerance test (OGTT) in different treatment groups over time. Values are expressed as mean ± SEM (n = 5), * indicates P < 0.05 versus control group using two-way ANOVA followed by the Dunnett multiple comparison test.
Abbreviations: NC, normal control; SB, Sclerocarya birrea; GLI, glibenclamide.

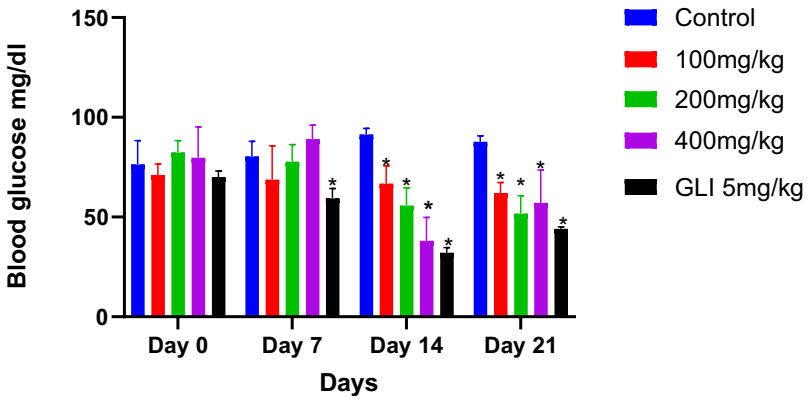


Figure 2 Dose related effect of Sclerocarya birrea leaf extract on normo-glycaemic rats. Values are expressed as mean ± SEM (n = 5), * indicates P < 0.05 versus control group using two-way ANOVA followed by the Dunnett multiple comparison test.
Abbreviation: GLI, glibenclamide.

Effect of Sclerocarya Birrea on High Fructose-Fed and Low-Dose Streptozotocin-Induced Diabetic Rats

Blood Glucose Levels

As anticipated, one-way ANOVA revealed no statistically significant differences in fasting blood glucose levels among groups at baseline (day 0), thereby confirming adequate randomization and comparable glycaemic status prior to treatment initiation. From day 7 onward, significant intergroup differences emerged, as depicted in Figure 3, indicating a progressive antihyperglycemic effect of *Sclerocarya birrea*. The glucose-lowering response was comparable to that observed with glibenclamide (5 mg/kg) on days 14 and 21, and became more pronounced by day 28, underscoring the sustained efficacy of the extract over the treatment period.

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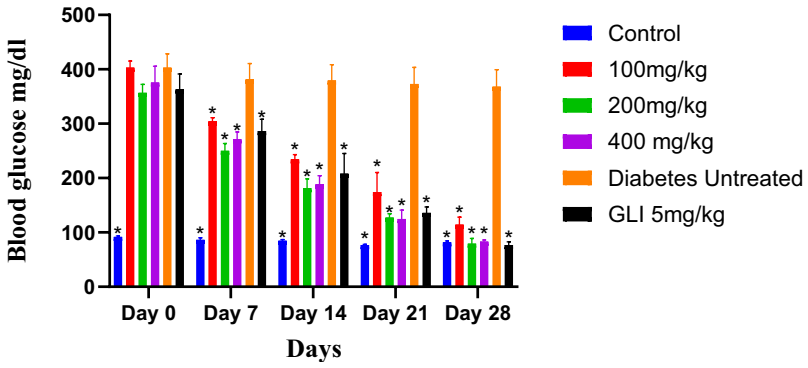

Figure 3 Dose related effect of Sclerocarya birrea leaf extract in streptozotocin induced diabetic rats. Values are expressed as mean ± SEM (n = 5), * indicates P < 0.05 versus untreated diabetes group using two-way ANOVA followed by the Dunnett multiple comparison test.

Glycated Haemoglobin (HbA1c), Insulin and GLUT4

Table 1 summarizes the effects of *Sclerocarya birrea* extract and glibenclamide on HbA1c, insulin, and GLUT4 levels in diabetic rats. HbA1c values showed variability among treatment groups, with the lowest mean observed in the control group and the highest in the GLI 5 mg group. Insulin concentrations were lower in the 100 mg/kg, 200 mg/kg, and control groups compared to diabetic untreated rats, and higher in the 400 mg/kg group. GLUT4 expression was reduced at 100 mg/kg and 200 mg/kg doses and increased at 400 mg/kg relative to the diabetic untreated group. However, none of these differences reached statistical significance based on ANOVA followed by Dunnett's test.

Haematological Parameters

Table 2 presents haematological parameters following administration of *Sclerocarya birrea* extract at doses of 100, 200, and 400 mg/kg in diabetic rats, compared with diabetic untreated, healthy controls, and glibenclamide-treated animals. White blood cell counts were highest in the diabetic untreated group and remained elevated in all treated groups. Differential leukocyte counts (lymphocytes, monocytes, neutrophils) showed variability across groups, with relatively higher lymphocyte percentages observed in control and glibenclamide groups. Haemoglobin, RBC, HCT, and platelet levels remained generally stable, with no marked deviations. Mean corpuscular indices (MCV, MCH, MCHC) also showed no consistent directional changes across treatment conditions, and none of the haematological parameters differed significantly between the diabetic untreated and any other group ($p > 0.05$, ANOVA with Dunnett's post hoc test).

Table 1 Effects of Sclerocarya Birrea Extract and Glibenclamide on HbA1c, Insulin, and GLUT4 Levels in Diabetic and Control Rats (n = 8 per Group)

Group	HbA1c (% ± SEM)	Insulin (mIU/L ± SEM)	GLUT4 (ng/mL ± SEM)
Diabetic untreated	7.83 ± 1.69	5.77 ± 0.98	6.70 ± 0.98
100 mg/kg	6.17 ± 4.22	4.13 ± 0.40	5.23 ± 0.76
200 mg/kg	8.23 ± 0.95	4.00 ± 0.36	5.37 ± 0.55
400 mg/kg	7.10 ± 2.50	8.30 ± 3.73	7.60 ± 0.75
Control	3.33 ± 0.35	4.07 ± 0.50	4.70 ± 0.10
GLI 5 mg	9.87 ± 2.67	5.27 ± 1.44	6.43 ± 1.37

Notes: Data are expressed as mean ± standard error of the mean (SEM), *n* = 8 rats per group.One-way analysis of variance (ANOVA) was used followed by Dunnett's post hoc test to compare all treatment groups with the diabetic untreated group. No statistically significant differences were found ($p > 0.05$ for all comparisons). HbA1c (%): Glycated Haemoglobin Percentage, Insulin (miu/L): Insulin concentration (milli international units per liter), GLUT 4 (ng/mL): Glucose Transporter Type 4 concentration.

Table 2 Effects of Sclerocarya Birrea Extract and Glibenclamide on Haematological Parameters in Diabetic and Control Rats (n = 8 per Group)

Haematological Parameters	100mg/kg	200mg/kg	400mg/kg	Diabetes Untreated	Control	GLI 5mg
WBC x 103 /ul	13.80±8.16	12.70±5.64	12.27±6.35	13.73±8.39	8.37±1.57	7.83±2.28
L %	24.07±8.87	27.27±3.45	20.50±10.25	22.40±5.00	32.03±8.41	41.43±34.42
M %	27.43±8.11	29.47±4.62	24.00±13.98	27.70±7.24	25.97±2.00	19.27±11.02
N %	48.50±12.08	43.27±1.21	55.50±7.88	49.90±10.05	42.03±10.29	39.30±24.85
Hb g/dl	15.33±0.91	15.20±0.87	15.17±0.67	15.13±1.07	15.70±0.79	14.07±1.79
RBC x 106 /ul	9.47±0.24	8.92±0.45	8.05±1.97	9.31±0.31	6.35±5.10	8.32±1.32
HCT %	51.77±5.10	53.87±2.84	52.07±4.01	50.90±5.12	52.47±2.71	47.57±4.74
MCV fl	54.73±5.58	60.47±2.24	67.90±19.60	54.73±5.76	56.20±3.30	39.40±30.09
MCH pg	16.17±1.15	17.00±0.52	19.87±6.62	16.23±1.46	16.73±0.98	16.93±1.00
MCHC g/dl	29.63±1.46	28.20±1.85	29.13±2.20	29.73±1.19	29.87±0.21	29.50±0.95
PLT x 103 /ul	889.67±33.49	622.67±474.35	654.00±279.21	909.67±78.00	870.00±128.00	776.33±195.58

Notes: Data are presented as mean ± standard error of the mean (SEM), with n = 8 rats per group. Haematological parameters were measured at the end of the treatment period. No statistical significance testing is shown in this table.

Abbreviations: WBC, White Blood Cell count (×10^3/μL); L, Lymphocytes (%); M, Monocytes (%); N, Neutrophils (%); Hb, Haemoglobin (g/dL); RBC, Red Blood Cell count (×10^6/μL); HCT, Haematocrit (%); MCV, Mean Corpuscular Volume (fL); MCH, Mean Corpuscular Haemoglobin (pg); MCHC, Mean Corpuscular Haemoglobin Concentration (g/dL); PLT, Platelet count (×10^3/μL).

Biochemical Parameters

Table 3 summarizes the biochemical parameters measured in control, diabetic untreated, and treated rats receiving *Sclerocarya birrea* extract or glibenclamide. Total protein levels were generally higher in all treated groups compared to controls and diabetic untreated rats. Cholesterol and LDL-C concentrations were elevated in the 100 mg/kg group, with HDL values showing only minor variation between groups. Liver enzymes (SGPT, SGOT, ALP) and renal markers (urea, creatinine) remained within comparable ranges across all groups. No statistically significant differences were observed between the diabetic untreated group and any of the treatment groups for any parameter ($p > 0.05$, ANOVA with Dunnett's post hoc test).

Table 3 Effects of Sclerocarya Birrea Extract and Glibenclamide on Biochemical Parameters in Diabetic and Control Rats (n = 8 per Group)

Biochemistry Parameters	Control	100mg/kg	200mg/kg	400mg/kg	Diabetes Untreated	GLI 5mg
PRO2 g/L	67.07±4.73	74.43±3.25	72.23±7.59	73.90±4.19	70.63±3.58	74.27±2.83
CHOL2 mmol/L	2.50±0.09	2.94±0.32	2.38±0.20	2.54±0.13	2.30±0.25	2.26±0.17
HDL2 mmol/L	1.34±0.06	1.59±0.30	1.49±0.04	1.52±0.07	1.50±0.19	1.39±0.04
ALP2 U/L	171.47±46.95	281.97±38.98	154.67±17.42	189.00±60.74	229.57±25.98	176.27±26.49
ALB2g/L	34.03±2.18	36.43±2.36	35.73±1.19	37.70±1.78	35.63±1.21	36.57±1.86
UREA2 mmol/L	6.23±0.77	6.10±1.40	6.77±0.51	6.25±0.83	5.32±0.94	6.42±0.54
BIT2 μmol/L	1.79±0.09	1.81±0.41	2.01±0.33	2.07±0.15	1.82±0.41	1.89±0.21
SGPT U/L	48.85±3.82	62.77±18.38	53.83±3.36	56.93±2.30	58.63±11.86	51.70±5.65
SGOT U/L	121.07±5.91	150.80±44.63	126.43±11.45	125.50±11.45	115.80±8.15	130.27±23.67
CRE μmol/L	78.53±7.33	74.53±2.97	77.60±6.06	77.61±6.47	72.99±4.62	76.38±2.97
TG mmol/L	0.48±0.05	0.68±0.16	0.53±0.05	0.40±01.2	0.42±0.15	0.42±0.05
LDLC2 mmol/L	0.94±0.12	1.04±0.09	0.65±0.16	0.84±0.10	0.60±0.16	0.68±0.13

Notes: Data are presented as mean ± standard error of the mean (SEM), *n* = 8 rats per group. No statistically significant differences were detected between the diabetic untreated group and any treatment group ($p > 0.05$, ANOVA followed by Dunnett's test).

Abbreviations: PRO2, Total Protein (g/L); CHOL2, Total Cholesterol (mmol/L); HDL2, High Density Lipoprotein Cholesterol (mmol/L); ALP2, Alkaline Phosphatase (U/L); ALB2, Albumin (g/L); UREA2, Urea (mmol/L); BIT2, Bilirubin (μmol/L); SGPT, Serum Glutamate Pyruvate Transaminase (U/L); SGOT, Serum Glutamate Oxaloacetate Transaminase (U/L); CRE, Creatinine (μmol/L); TG, Triglycerides (mmol/L); LDLC2, Low Density Lipoprotein Cholesterol (mmol/L); GLI, Glibenclamide.

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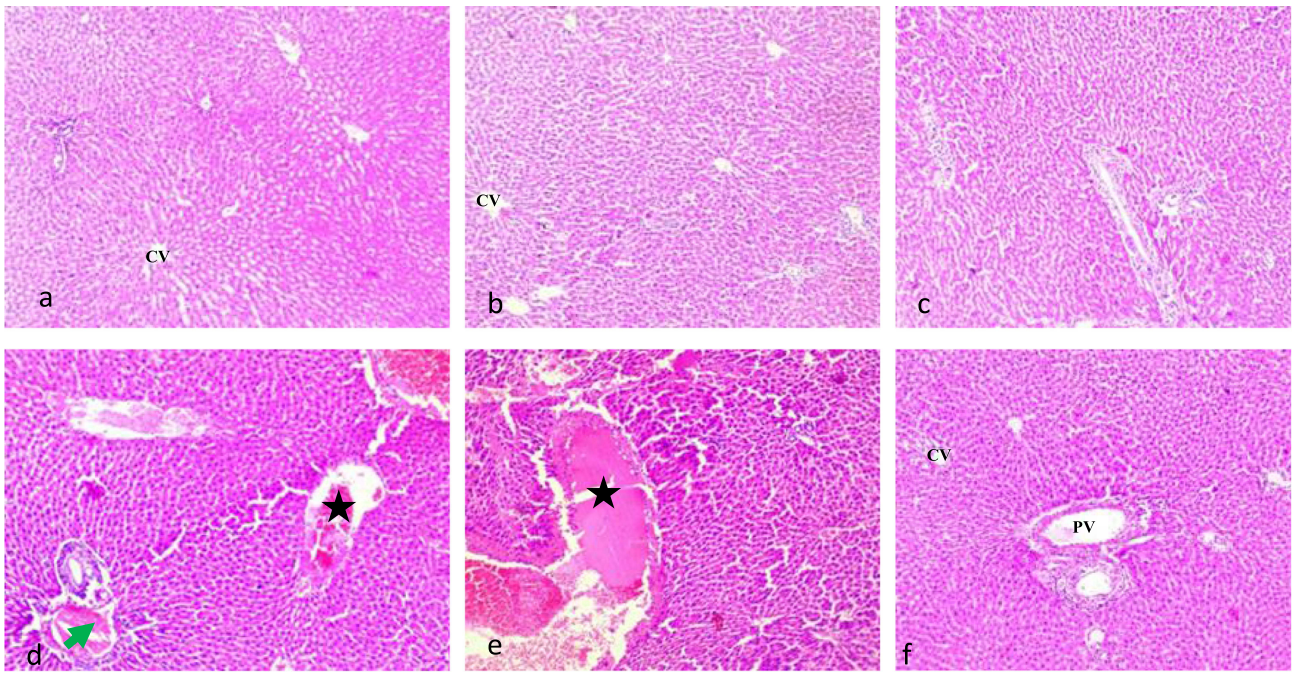

Figure 4 Photomicrograph of a section of the liver from each group. (**a**) Untreated; (**b**) Control; (**c**) 100 mg/kg; (**d**) 200 mg/kg; (**e**) 400 mg/kg; (**f**) Glibenclamide 5 mg/kg. (**a, b, c** and f) Normal liver tissue with radially arranged hepatocyte plates, central vein (CV), portal vein (PV), basophilic nuclei, and acidophilic cytoplasm. No abnormalities observed. (**d** and **e**) Liver tissue showing vascular congestion (star) and oedema, with floccular pink fluid in the portal/periportal zones (green arrow) and congested red blood cell aggregates.

Histopathological Studies

A histological analysis of the GLI 5 mg/kg (Glibenclamide) (Figures 4f, 5f and 6f) and control groups (Figures 4b, 5b and 6b) revealed normal tissue architecture in the liver (Figure 4), pancreas (Figure 5), and kidneys (Figure 6), with no abnormalities observed. In the untreated diabetic group (Figures 4a, 5a and 6a), the liver remained normal, while the pancreas exhibited severe degenerative changes, including vacuolar alterations and necrosis. The kidneys displayed vascular congestion.

Sclerocarya birrea treatment at 100 mg/kg (Figures 4c, 5c and 6c) revealed normal liver tissue, but the pancreas exhibited atrophic islets with lymphocytic infiltration and vascular congestion. Higher doses (200 mg/kg and 400 mg/kg) (Figures 4d, e, 5d, e and 6d, e) revealed vascular congestion and oedema in the liver and kidneys, while the pancreas remained unaffected. Vascular changes were observed in the kidneys across all treatment groups (Figures 4–6).

Discussion

The findings from this study demonstrate the potential efficacy of *Sclerocarya birrea* hydroethanolic leaf extract in mitigating hyperglycaemia in diabetic rat models, including those with streptozotocin (STZ) induced diabetes. In accordance with earlier research on the antidiabetic properties of *Sclerocarya birrea*, the present study demonstrated a substantial decrease in blood glucose levels in both the oral glucose tolerance test (OGTT) and in diabetic rats. The glucose-lowering effects of the extract were found to be comparable to those of the conventional antidiabetic agent, Glibenclamide. These results support the hypothesis that *Sclerocarya birrea* leaf extract may have a beneficial role in glucose regulation, potentially serving as an alternative therapeutic option for diabetes management.

To the best of our knowledge, no previous studies have specifically investigated the effects of *Sclerocarya birrea* leaves on the Oral Glucose Tolerance Test (OGTT). The present study demonstrates a significant reduction in blood glucose levels in *Sclerocarya birrea* treated groups, especially at 100 mg/kg and 200 mg/kg doses, suggesting that the extract aids in the regulation of postprandial hyperglycaemia. The potential mechanism by which the plant extract exerts its effects may involve several pathways, including the inhibition of α-glycosidases and α-amylases enzymes, leading to a reduction in glucose absorption from the gastrointestinal tract, and/or stimulation of peripheral glucose utilization

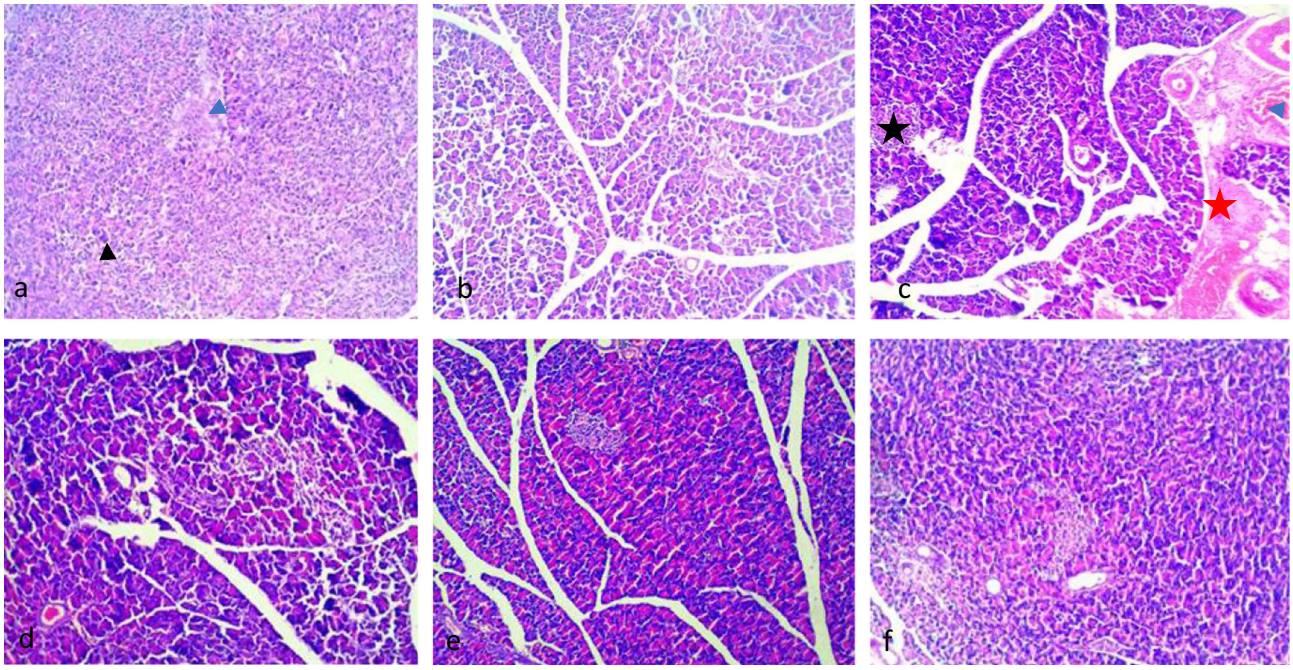

Figure 5 Photomicrograph of a section of the pancreas from each group. (**a**) Untreated; (**b**) Control; (**c**) 100 mg/kg; (**d**) 200 mg/kg; (**e**) 400 mg/kg; (**f**) Glibenclamide 5 mg/kg. (**a**) Anomalous pancreas exhibiting normal exocrine acini, accompanied by severe degenerative and vacuolar changes in the outer cellular zone of pancreatic islets, as indicated by features such as karyopyknosis (arrowhead), and necrosis (blue arrowhead). (**b, d, e** and **f**) Healthy pancreas featuring exocrine acini and intact islets of Langerhans. There is an absence of inflammatory cells or abnormalities. (**c**) Pancreatic islets with atrophy, dense lymphocytic infiltration (black star), vascular congestion (blue arrowhead), and oedema in blood vessels with floccular pink fluid (red star).

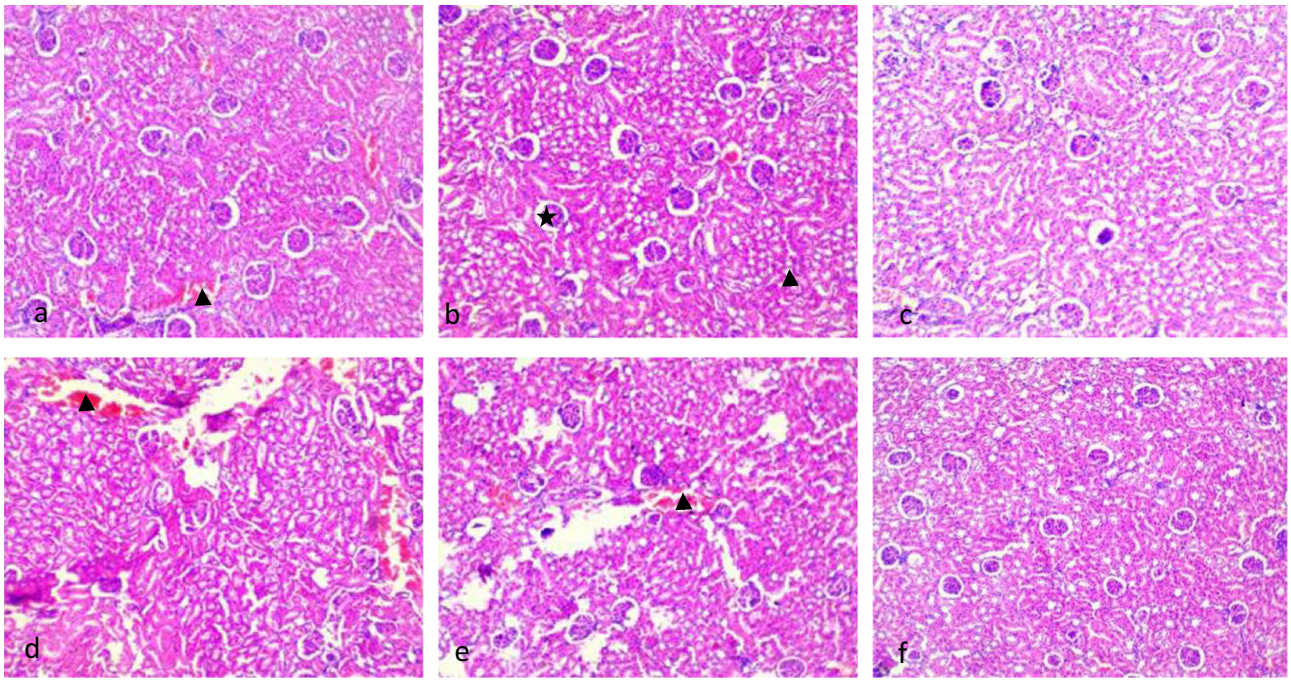

Figure 6 Photomicrograph of a section of the kidney from each group. (**a**) Untreated; (**b**) Control; (**c**) 100 mg/kg; (**d**) 200 mg/kg; (**e**) 400 mg/kg; (**f**) Glibenclamide 5 mg/kg. (**a, d** and **e**) The Kidney tissue displays features indicative of vascular congestion, including normocellular glomerular tufts, viable renal tubules, and congested blood vessels (black arrowhead). (**b, c** and **f**) The kidney tissue exhibits characteristics consistent with normalcy, featuring normocellular glomerular tufts (black star) and renal tubules (black arrowhead), with no abnormalities observed.

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through a mechanism analogous to that of chlorpropamide and/or metformin. The findings of this study are in agreement with those of by Victoria Montesinos et al (VictoriaMontesinos et al, 2021), who noted significant decreases in blood glucose levels in a 90 day clinical trial involving prediabetic subjects taking *Sclerocarya birrea* extract. However, a comparison should be made with caution, as the drug tested in the trial was an extract from the stem bark, whereas the present study utilized an extract from the leaves. The underlying mechanism of this glucose-lowering effect may involve enhanced GLUT4 translocation, as supported by previous studies,[18,30] that identified myricetin and quercetin derivatives in *Sclerocarya birrea* leaves as stimulants of glucose uptake in myocytes through insulin-like mechanisms.[18] The extract is hypothesised to facilitate glucose entry into peripheral tissues, thereby contributing to improved glucose tolerance and reduced postprandial spikes in glucose.

A number of studies have demonstrated the efficacy of stem bark extracts of *Sclerocarya birrea* in reducing hyperglycaemia in normoglycemic rats. However, this study represents the first to investigate the effects of leaf extracts in this context. In normoglycemic rats, *Sclerocarya birrea* leaves administered over 21 days exhibited a dose-dependent decrease in blood glucose levels, which was statistically significant by day 14. This effect demonstrates the extract's ability to maintain glucose homeostasis without causing hypoglycaemia in nondiabetic conditions, suggesting a modulating effect on glucose levels rather than a purely hypoglycaemic action. The substantial decrease in blood glucose levels evident in normoglycemic rats following 21 days of *Sclerocarya birrea* leaf extract administration is presumably attributable to its bioactive flavonoid glycosides, such as myricetin-3-O-β-D-glucuronide and quercetin-3-O-β-D-glucuronide, as identified in previous studies.[18] These compounds have been shown to enhance glucose uptake via mechanisms including AMPK pathway activation and GLUT4 translocation, which improve peripheral glucose utilization and mimic insulin action. The dose-dependent nature of the response in this study may be explained by increased bioavailability of these active molecules at higher extract concentrations, enhancing their therapeutic effects. The delayed onset of significant glucose-lowering effects until day 14 could be indicative of the time required for sufficient accumulation of bioactive or modulation of metabolic pathways, consistent with the pharmacodynamics of plant-based therapies.

In the streptozotocin (STZ)-induced diabetic model, treatment with *Sclerocarya birrea* resulted in significant reductions in fasting blood glucose levels over the 28-day period, with results comparable to those observed with the standard drug, glibenclamide. These findings is corroborated by Maharaj et al,[18] who demonstrated that *Sclerocarya birrea* facilitated glucose uptake in muscle cells. Given that STZ-induced diabetes models are associated with insulin resistance and beta-cell dysfunction, the observed effect suggests that *Sclerocarya birrea* may improve insulin sensitivity or enhance insulin secretion. The improvement in blood glucose levels also suggests potential interaction with insulin pathways and perhaps GLUT4 activity, as reported in the muscle cell studies by Maharaj et al,[18] where myricetin-3-Oβ-D-glucuronide from *Sclerocarya birrea* leaves enhanced glucose uptake, pointing toward a possible modulation of GLUT4 translocation and cellular glucose uptake. The findings of the study demonstrated that higher doses of *Sclerocarya birrea* (100–400 mg/kg) did not result in significant alterations to HbA1c and insulin levels in diabetic rats when compared to the untreated diabetic group. The limited impact on HbA1c may reflect the relatively short study duration in comparison to the lifespan of red blood cells in rats, which is approximately 45–65 days,[31] potentially limiting the observable changes in glycated haemoglobin; with the potential for more comprehensive studies to reveal further information regarding HbA1c changes over time. Studies in prediabetic humans[32] have demonstrated reduced insulin resistance and improved glucose tolerance with *Sclerocarya birrea*, suggesting that any potential impact of the extract on long-term glycaemic markers like HbA1c may require extended administration periods, which were beyond the scope of this 28-day study.

The study observed nonsignificant changes in haematological profiles across treated groups, suggesting that *Sclerocarya birrea* does not adversely affect haematological parameters, aligning with findings by previous studies (Bationo et al, 2016; Coulidiaty et al, 2024; Maharaj et al, 2022; Victoria Montesinos et al, 2021) where haematology remained stable across treatment groups in diabetic models. In biochemical parameters, there was a no alteration of lipid profiles in treated groups, with slightly lowered LDL and stable HDL levels. While not statistically significant in this study, this trend aligns with human trials indicating a slight cholesterol lowering effect in prediabetics taking *Sclerocarya birrea* (Victoria Montesinos et al, 2021) and not yet published clinical trial results from our team. This minor impact on lipid profiles may stem from the antioxidant and anti-inflammatory actions of *Sclerocarya birrea* leaves phytochemicals,[33,34] which may improve lipid metabolism indirectly via reduced inflammation and oxidative stress.

Histopathological evaluations indicated that *Sclerocarya birrea* treatment at higher doses preserved pancreatic and renal tissue integrity in diabetic rats. The untreated diabetic rats displayed pancreatic atrophy, necrosis, and renal vascular congestion, which were markedly reduced in the treated groups. The preservation of pancreatic tissue is particularly noteworthy, as beta-cell protection is crucial for maintaining endogenous insulin production.[35] This finding is consistent with the observations reported in studies employing a combination of plant extracts, including *Sclerocarya birrea, Nauclea latifolia*, and *Piper longum*, which demonstrated the preservation of hippocampal neurons and pancreatic tissues in diabetic rats.[36] These results suggest that *Sclerocarya birrea* may contribute to the prevention of diabetes-induced tissue damage and dysfunction, at least in part, through enhanced glucose regulation and insulin sensitization.

The glucose-lowering effects of *Sclerocarya birrea* may be partly attributable to mechanisms such as GLUT4 modulation and insulin sensitization, as previously suggested in muscle cell studies, although these pathways were not directly assessed in this study. Indeed, Maharaj et al demonstrated that the active compounds in *Sclerocarya birrea*, such as myricetin and quercetin derivatives, stimulate GLUT4 translocation to the cell membrane in muscle cells, enhancing glucose uptake independently of insulin.[18] This outcome is probably attributable to the bioactive components of the extract, which mimic the action of insulin, thereby facilitating glucose transport into cells. Furthermore, although not significant, trends in reduced HbA1c and stable insulin levels suggest that *Sclerocarya birrea* may enhance insulin sensitivity without exerting a direct effect on insulin secretion, supporting its potential as an adjunct in insulin-resistant conditions.

Further studies focusing on long-term glycaemic control and direct assessments of insulin receptor pathways would provide further insight into the role of *Sclerocarya birrea* in insulin-mediated glucose metabolism. Moreover, future molecular studies should investigate its direct effects on GLUT4 expression and translocation to validate its action on glucose uptake pathways in diabetic tissues.

Conclusion

This study demonstrates that the hydroethanolic leaf extract of *Sclerocarya birrea* exhibits significant antidiabetic effects, effectively reducing blood glucose levels in both normoglycemic and type 2 diabetic rat models, as well as reducing hyperglycaemia in the oral glucose tolerance test (OGTT). The extract was well tolerated and did not induce adverse changes in haematological or biochemical parameters. Although no significant changes were observed in insulin, GLUT4, or HbA1c levels within the study duration, histological observations indicated preservation of pancreatic and renal tissue architecture in treated groups, suggesting a potential protective effect. These findings support the therapeutic promise of *Sclerocarya birrea* leaf extract as a safe, plant-based adjunct for diabetes management. Further studies are recommended to explore its long-term effects and mechanisms in clinical settings.

Data Sharing Statement

Data will be made available on request from the corresponding author.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence this work.

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