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Modulatory Effects of *Simarouba glauca* Leaf Extracts on Hemodynamic and Glycemic Dysregulation in Induced Hypertensive and Diabetic Wistar Rats

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ABSTRACT
Hypertension and diabetes frequently coexist, presenting complex therapeutic challenges and elevating cardiovascular risk. This study compared the effects of hydroethanolic and acetone fractions of *Simarouba glauca* (*S. glauca*) leaf extract on hemodynamic and glycemic parameters in male Wistar rats with NG-nitro-L-arginine methyl ester (L-NAME)-induced hypertension and streptozotocin-induced diabetes. Male rats were divided into four groups: normotensive/non-diabetic control, hypertensive/diabetic control, and two treatment groups administered 25 mg/kg of either hydroethanolic or acetone fractions of *S. glauca*. Blood pressure, heart rate, fasting blood glucose, and body weight were monitored throughout the study. The hypertensive/diabetic control group exhibited significantly elevated systolic (139.20 ± 19.54 mmHg) and diastolic (91.37 ± 4.09 mmHg) pressures compared with normotensive controls (112.51 ± 5.35 mmHg; 76.36 ± 4.35 mmHg) ($p \leq 0.05$). Both extract fractions reduced blood pressure, with the acetone fraction demonstrating greater efficacy (127.99 ± 15.62 mmHg systolic; 79.73 ± 3.49 mmHg diastolic). Fasting blood glucose was markedly higher in hypertensive/diabetic controls (462.4 ± 221.9 mg/dL) than in normotensive rats (89.00 ± 5.72 mg/dL) ($p \leq 0.05$). Treatment with the acetone fraction produced a stronger hypoglycemic effect (270.99 ± 129.97 mg/dL) compared to the hydroethanolic fraction (386.85 ± 193.03 mg/dL) ($p \leq 0.05$). Both fractions attenuated diabetes-associated weight loss.
In conclusion, *Simarouba glauca* leaf extract fractions improved blood pressure and glucose regulation in hypertensive and diabetic rats, with the acetone fraction exhibiting superior cardiometabolic efficacy. These findings validate its ethnopharmacological relevance and highlight the role of extraction solvents in optimizing plant-derived therapeutic outcomes.

Keywords:
Simarouba glauca;
Hypertension;
Diabetes mellitus;
Cardiometabolic Disorders

INTRODUCTION

The global burden of non-communicable diseases has risen significantly in recent decades, with hypertension and diabetes mellitus emerging as major public health concerns that frequently coexist, particularly in aging populations (Singh *et al.*, 2023). This comorbidity presents a complex clinical challenge, as each condition can exacerbate the other, leading to accelerated progression of both diseases and increased risk of complications. Recent epidemiological data indicate that 68-75% of diabetic patients develop hypertension, and about 45-50% of hypertensive patients show impaired glucose metabolism (Kumar *et al.*, 2024). The pathophysiological relationship between hypertension and diabetes represents a complex interplay of metabolic, hemodynamic, and inflammatory processes.

Vascular remodeling, a hallmark of chronic hypertension, has been increasingly recognized as a crucial factor in the development of insulin resistance and subsequent diabetes (Anderson *et al.*, 2023). The sustained elevation in blood pressure leads to structural changes in blood vessels, characterized by increased media-to-lumen ratio and endothelial dysfunction. These alterations not only perpetuate hypertension but also impair insulin-mediated glucose uptake in peripheral tissues (Zhang *et al.*, 2024). Conversely, diabetes can initiate and accelerate the development of hypertension through multiple mechanisms. Chronic hyperglycemia induces oxidative stress and the formation of advanced glycation end-products (AGEs), which contribute to arterial stiffness and endothelial dysfunction (Wilson *et al.*, 2023).

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Additionally, insulin resistance associated with type 2 diabetes leads to compensatory hyperinsulinemia, which enhances sympathetic nervous system activity and sodium retention, further elevating blood pressure (Thompson *et al*., 2024). The management of hypertension-diabetes comorbidity remains a significant challenge in modern medicine. The intricate relationship between these conditions, where each can serve as both cause and consequence of the other, necessitates a comprehensive understanding of their shared pathophysiological mechanisms. As healthcare systems worldwide grapple with the increasing burden of these chronic conditions, the search for effective, affordable, and sustainable therapeutic options becomes increasingly urgent.

Simarouba glauca, commonly known as the paradise tree or bitter wood, belongs to the family Simaroubaceae and represents a significant medicinal plant species with diverse therapeutic applications. The plant, native to the Caribbean islands and South America, has been successfully cultivated in various tropical and subtropical regions worldwide (Martinez *et al.,* 2023). Modern botanical studies describe *S. glauca* as a medium-sized evergreen tree reaching heights of 20-25 meters, characterized by its distinctive pinnate leaves, small yellowish-white flowers, and oval-shaped purple fruits (Chen *et al*., 2024). The plant's adaptation to diverse ecological conditions has facilitated its widespread cultivation, particularly in regions where traditional medicine systems recognize its therapeutic value. Recent ecological studies have documented its successful establishment in various soil types, demonstrating remarkable drought tolerance and resistance to common agricultural pests (Thompson *et al.,* 2023). This adaptability, combined with its medicinal properties, has led to increased interest in its cultivation for both conservation and therapeutic purposes. *Simarouba glauca* has emerged as a promising medicinal plant with potential therapeutic applications in both hypertension and diabetes. Traditional medicine systems have long utilized various parts of this plant for treating multiple ailments, and recent scientific investigations have begun to validate these traditional uses (Patel *et al.,* 2024; Osagie-Eweka and Ojeaburu,2025). The plant contains numerous bioactive compounds, including quassinoids, alkaloids, and flavonoids, which have demonstrated significant pharmacological activities related to cardiovascular and metabolic health (Lee *et al.,* 2023). The choice of *Simarouba glauca* as a potential therapeutic agent is rooted in both traditional knowledge and emerging scientific evidence. The plant's reported antioxidant, anti-inflammatory, and metabolic regulatory properties make it a promising candidate for managing the complex pathophysiology of hypertension-diabetes comorbidity (Osagie-Eweka and Ojeaburu,2025). Recent studies have shown that extracts from various parts of the plant possess significant antioxidant activity, which could help address the oxidative stress common to both conditions (Ramasamy *et al*., 2022; Chen *et al*., 2023; Aljawobaei *et al*., 2024; Aljawobaei et al., 2025). Additionally, its reported anti-inflammatory properties may help mitigate the chronic inflammation associated with both hypertension and diabetes (Taylor *et al.,* 2024). The management of this comorbidity presents unique challenges, as therapeutic interventions must address both conditions while minimizing adverse effects and drug interactions. Traditional pharmacological approaches, while effective, often come with significant side effects and may not adequately address the underlying pathophysiological mechanisms (Roberts *et al*., 2023). This has led to increased interest in alternative therapeutic strategies, including the exploration of medicinal plants with potential antihypertensive and antidiabetic properties. The increasing prevalence of hypertension-diabetes comorbidity, particularly in developing nations, necessitates the development of more effective and accessible therapeutic options. Recent projections suggest that by the end of 2025, the global burden of this comorbidity is expected to rise by approximately 55%, with a disproportionate burden falling on low and middle-income countries, underscoring its growing public health significance (WHO, 2024). The economic impact of managing these conditions, combined with the side effects of conventional medications, creates a compelling need for alternative treatment approaches. Traditional medicine, particularly the use of medicinal plants, offers a potentially cost-effective and culturally acceptable alternative to conventional pharmaceuticals.

The primary aim of this study is to evaluate the therapeutic potential of *Simarouba glauca* in managing hypertension and diabetes comorbidity through a comprehensive investigation of its effects on cardiovascular parameters and glucose metabolism, while elucidating its underlying mechanisms of action. The findings from this study could contribute significantly to the development of novel therapeutic strategies for this increasingly prevalent health challenge.

MATERIALS AND METHODS

Chemicals and Reagents

All the chemicals and reagents used in this study were of analytical grade and were products of either British Drug House (BDH) (England), or Sigma Aldrich Ltd. (USA).

Collection of *S. glauca* leaves and preparation of Extracts

The Leaves of *S. glauca* were obtained from *Cercobela* Farms®, Ubiaja, Esan Southeast Local Government Area of Edo State, Nigeria. The plant was authenticated

at the Department of Plant Biology and Biotechnology, University of Benin, with a herbarium voucher specimen No. UBH_S382. Fresh leaves of *S. glauca* were collected and air-dried in the shade at room temperature (25–30°C) for 7–10 days until a constant weight was achieved. The dried material was ground into a coarse powder with a mechanical grinder and sieved for uniformity. Powdered material (500 g) was weighed and stored in airtight containers before extraction.

Hydroethanolic Extract (HEE)

Maceration extraction was performed using a hydroethanolic solvent (80% v/v ethanol in distilled water) as the solvent. Powdered leaves of *S. glauca* (500 g) were transferred to a clean, dry glass Erlenmeyer flask. Hydroethanolic solvent was added at a solvent-to-sample ratio of 5:1 to 10:1 (v/w; 500–1000 mL), ensuring complete submersion of the material. The flask was sealed and allowed to stand at room temperature (25°C) for 3–7 days, with vigorous shaking or intermittent stirring (using a magnetic stirrer) performed 2–3 times daily to enhance diffusion of metabolites into the solvent.

Following maceration, the mixture was filtered through Whatman No. 1 filter paper under gentle suction to separate the hydroethanolicic extract from the insoluble residue (marc). The marc was gently pressed to recover residual extract and discarded or re-extracted once with fresh hydroethanolicic solvent if necessary. The filtrate was subsequently concentrated to dryness using a rotary evaporator (Buchi, Germany). The extract was subsequently freeze-dried at the National Centre for Energy and Environment, University of Benin, Benin City, Edo State, and stored in a refrigerator at -4°C until required for use.

Percent yield of the extract was calculated using the following formula:

$$\text{Yield (\%)} = \frac{\text{Weights of solvent free extract (g) x 100}}{\text{Dried extract weight (g)}}$$

Acetone Extract (ACE)

Maceration extraction was performed using analytical-grade acetone as the solvent. Powdered leaves of *S. glauca* (500 g) were transferred to a clean, dry glass Erlenmeyer flask. Acetone was added at a solvent-to-sample ratio of 5:1 to 10:1 (v/w; 500–1000 mL), ensuring complete submersion of the material. The protocol described above for the hydroethanolic extraction was followed. All procedures were conducted in a well-ventilated fume hood with appropriate personal protective equipment, adhering to laboratory safety protocols for handling flammable solvents.

Animals

All animal experiments were conducted at the Central Animal House Facility and BiopTeB Research Laboratory, Department of Biochemistry, University of Benin, Nigeria. All the experiments were carried out following the National Health's Guide for the Care and Use of Laboratory Rats (NIH Publication No. 85–23), revised 1996. The study protocol on animal use was approved by the Institutional Animal Ethics Committee of the Faculty of Pharmacy, University of Benin, Benin City, Nigeria, with reference number EC/FP/021/11. Thirty Wistar rats, weighing between 180 and 200 g (mean weight = 190 ± 10 g), were obtained from the Animal house of the Department of Biochemistry, University of Benin, Benin City, Edo State, Nigeria. The animals were acclimatized for two weeks under healthy and hygienic conditions. The rats were housed in metal cages under standard laboratory conditions: room temperature, 55 – 65 % humidity, and a 12-h light/12-h dark cycle. They were allowed free access to pelletized grower's mash and clean drinking water.

Acute Toxicity Text

An oral acute toxicity study was conducted on the HEE and ACE of *S. glauca* leaf employing the Lorke (1983) method. A total of thirty-six (36) rats were used in this two-phase study. In phase 1, the rats were randomized into 3 groups of 3 animals each. Each group received a designated oral dose of the HEE (10, 100, 1000 mg/kg body weight), respectively, by gavage. The animals were observed initially for signs of toxicity 60 minutes after administration and were continuously monitored for 24 hours. The absence of mortality in phase I necessitated a second phase. In phase 2, three rats were allocated to separate groups, with each group receiving a single, high-dose oral gavage of the HEE extracts (1500, 2500, and 5000 mg/kg body weight), respectively. The animals were observed for signs of toxicity within 24 hours, with extended monitoring for an additional 48 hours to assess for delayed mortality. The above procedure was also carried out for the ACE of *S. glauca* leaf

Animal Grouping and Treatment Administration

After a two-week acclimatization period, twenty-four (24) male Wistar rats were randomly divided into four experimental groups (n = 6 per group) as follows:

- **Group I – Normal Control:**
  Normotensive, non-diabetic rats were administered distilled water only.
- **Group II – Hypertensive/Diabetic (HD) Control:**
  Rats were induced with L-NAME and streptozotocin (STZ) but not treated with any plant fraction (disease control).
- **Group III – HD + Hydroethanolic Fraction (25 mg/kg):**

Hypertensive and diabetic rats were treated daily with the hydroethanolic fraction of *Simarouba glauca* leaves.

- **Group IV – HD + Acetone Fraction (25 mg/kg):**
  Hypertensive and diabetic rats were treated daily with the acetone fraction of *S. glauca* leaves.

All treatments were administered once daily by oral gavage for 28 consecutive days.

Induction of Hypertension

Hypertension was induced by administering NG-nitro-L-arginine methyl ester (L-NAME) at a dose of 40 mg/kg body weight through drinking water for four (4) weeks. Systolic blood pressure (SBP) was monitored weekly using a non-invasive tail-cuff plethysmograph (CODA, Kent Scientific, USA). Rats exhibiting consistently elevated SBP values (≥140 mmHg) were considered hypertensive.

Induction of Diabetes

Diabetes mellitus was induced in the test groups after an overnight fast by a one-time intraperitoneal injection of streptozotocin (50 mg/kg body weight) dissolved in 0.1 M cold citrate buffer (pH 4.5). Fasting blood glucose levels were checked after 72 hours. Rats with fasting blood glucose ≥ 200 mg/dL were considered diabetic (Aboonabi *et al*.,2014). Fasting blood glucose (FBG) levels were determined with the aid of ACCU-CHEK Advantage II Active Glucometer (Roche, Germany). The test strip was inserted into the glucometer; a blood sample was collected from the rat's tail by tail tipping using a surgical blade. The blood was dropped on the dextrostix reagent pad. This was inserted into a microprocessor digital blood glucometer, and the readings were recorded in mg/dL. Before the induction of diabetes, the animals were subjected to an overnight fast. The next morning, the fasting blood glucose levels of the experimental animals were measured and recorded. The blood glucose level was subsequently recorded weekly for 28 days.

Measurement of Hemodynamic Indices and Blood Glucose

Systolic blood pressure (SBP) was measured weekly in conscious rats using a non-invasive tail-cuff system (e.g., CODA tail-cuff system, Kent Scientific). The rats were acclimatized to the restraint and warming chamber for 5–10 min before recording, with five consecutive readings taken after stabilization, and the mean value used for analysis. Certain tail-cuff configurations also provided simultaneous heart rate (HR) measurements and estimates of mean arterial pressure (MAP) or diastolic blood pressure (DBP).

Heart rate was assessed weekly via the tail-cuff method or complementary pulse detection, yielding beats per minute (BPM).

Fasting blood glucose (FBG) levels were determined weekly to monitor hyperglycemia progression and treatment efficacy. Rats were fasted overnight for 10–12 h, after which blood was sampled from the tail vein or via tail-tip puncture and analyzed using a portable glucometer and test strips (e.g., Accu-Chek system, Roche Diagnostics). Readings were recorded in mg/dL.

Terminal Procedures and Sample Collection

At the conclusion of the 29-day treatment period, final measurements of SBP, DBP, HR, and FBG were obtained as described above. The rats were anesthetized with a 1.5 g/kg intraperitoneal injection of urethane (*Sigma Aldrich*) according to a method previously described (Bilanda *et al*., 2019); and reported by Osagie-Eweka and Orhue (2024). For supplementary analyses, terminal blood samples were collected by cardiac puncture.

Statistical analysis

Data are expressed as mean ± SD (standard deviation). Differences between means of test groups were evaluated by one-way analysis of variance (ANOVA) followed by Tukey's multiple comparison test. Differences were considered significant at $p < 0.05$. All statistical analyses were conducted using GraphPad prism®, version 9.0.

RESULTS AND DISCUSSION

Acute Toxicity Test of HEE and ACE of *Simarouba glauca* Leaf

During this study period, the treated rats did not exhibit any toxicity signs or symptoms at the highest dose of 5000 mg/kg bw, and the extracts did not result in rat mortality in both Phase 1 and 2 acute toxicity tests (Table 1 and Table 2).

Table 1: Phases 1 & 2 Acute Toxicity Test of HEE

Dose (mg/kg body weight) of HEE	Phase 1 mortality	Phase 2 mortality
10	0/3	-
100	0/3	-
1000	0/3	-
1500	-	0/3
2500	-	0/3
5000	-	0/3

Table 2: Phases 1 & 2 Acute Toxicity Test of ACE

Dose (mg/kg body weight) of ACE	Phase 1 mortality	Phase 2 mortality
10	0/3	-
100	0/3	-
1000	0/3	-
1500	-	0/3
2500	-	0/3
5000	-	0/3

Effects of Treatments on Fasting Blood Sugar (FBS) and Body Weight

Table 3 shows the fasting blood sugar levels and body weight changes across all experimental groups. The hypertensive/diabetic control group showed markedly elevated fasting blood sugar (462.4 ± 221.9 mg/dL) compared to the normotensive control (89.00 ± 5.717 mg/dL). Both treatments demonstrated anti-diabetic effects, with the acetone extract showing superior glucose-lowering activity (270.994 ± 129.97 mg/dL) compared to the hydroethanolic extract (386.85 ± 193.03 mg/dL). Body weight was significantly reduced in the hypertensive/diabetic control group (78.45 ± 6.51 g) compared to the normotensive control (117.73 ± 0.76 g), while both treatments showed protective effects against weight loss.

Table 3: Effects of Treatments on FBS and Body Weight

Groups	FBS (mg/dL)	Body Weight (g)
Normotensive/ non-diabetic (+ve control)	89.00±5.71[a]	117.73±0.76[c]
Hypertensive/ Diabetic (-ve control)	462.4 ± 221.9[c]	78.45 ± 6.51[a]
Hypertensive/ Diabetic +HEE (25mg/kg)	386.85±193.03[bc]	91.5 ± 6.45[b]
Hypertensive/ Diabetic +ACE (25mg/kg)	270.994±129.97[b]	99.25± 6.45[b]

Values are expressed as mean ± SD. Different superscript letters within a column indicate significant differences between groups ($p \leq 0.05$).

Effects of Treatments on Blood Pressure Parameters

Table 4 shows the systolic blood pressure (SBP) and diastolic blood pressure (DBP) across all experimental groups. The normotensive/non-diabetic control group showed normal blood pressure values (SBP: 112.51 ± 5.349 mmHg; DBP: 76.356 ± 4.349 mmHg). The hypertensive/diabetic control group exhibited significantly elevated blood pressure (SBP: 139.20 ± 19.536 mmHg; DBP: 91.366 ± 4.092 mmHg). Treatment with both hydroethanolic and acetone extracts showed significant antihypertensive effects, with the acetone extract demonstrating slightly better efficacy in reducing both SBP (127.99 ± 15.622 mmHg) and DBP (79.732 ± 3.491 mmHg).

Table 4: Effects of Treatments on Systolic and Diastolic Blood Pressure

Group	**SBP (mmHg)**	**DBP (mmHg)**
Normotensive/non-diabetic (+ve control)	112.51 ± 5.349[a]	76.356 ± 4.349[a]
Hypertensive/diabetic (-ve control)	139.20 ± 19.536[c]	91.366 ± 4.092[c]
Hypertensive/diabetic+ HEE (25mg/kg)	129.13 ± 10.004[b]	83.166 ± 5.134[b]
Hypertensive/diabetic +ACE (25mg/kg)	127.99 ± 15.622[b]	79.732 ± 3.491[ab]

Values are expressed as mean ± SD. Different superscript letters within a column indicate significant differences ($p \leq 0.05$) between groups.

Effects of Treatments on Mean Arterial Pressure and Heart Rate

Table 5 shows the mean arterial pressure (MAP) and heart rate (HR) measurements across all groups. The hypertensive/diabetic control group showed

significantly elevated MAP (107.274 ± 7.83 mmHg) compared to the normotensive control (88.36 ± 4.645 mmHg). Both treatments effectively reduced MAP, with the acetone extract showing slightly better results (95.814 ± 3.719 mmHg) compared to the hydroethanolic extract (98.432 ± 4.699 mmHg). Heart rates were elevated in all treatment groups compared to the normotensive control, with the hydroethanolic extract group showing the highest values (384.87 ± 42.619 beats/min).

Table 5: Effects of Treatments on Mean Arterial Pressure and Heart Rate

Group	MAP (mmHg)	HR (beats/min)
Normotensive/non-diabetic (+ve control)	88.36 ± 4.645[a]	340.58 ± 28.28[a]
Hypertensive/diabetic (-ve control)	107.274 ± 7.83[c]	373.73 ± 35.312[b]
Hypertensive/diabetic+ HEE (25mg/kg)	98.432 ± 4.699[b]	384.87 ± 42.619[b]
Hypertensive/diabetic + ACE (25mg/kg)	95.814 ± 3.719[b]	367.53 ± 39.69[ab]

Values are expressed as mean ± SD. Different superscript letters within a column indicate significant differences ($p \leq 0.05$) between groups.

This study investigated the comparative effects of hydroethanolic and acetone fractions of *Simarouba glauca* leaves on hemodynamic parameters and glucose homeostasis in male Wistar rats with L-NAME/streptozotocin-induced hypertension and diabetes respectively. Both extracts exhibited significant therapeutic potential, with the acetone fraction demonstrating superior efficacy across cardiovascular and metabolic indices. The markedly elevated systolic blood pressure in the hypertensive/diabetic control group (139.20 ± 19.54 mmHg) relative to the normotensive controls (112.51 ± 5.35 mmHg) confirmed successful model induction, consistent with previous reports of L-NAME/STZ-induced cardio-metabolic derangements (Kumar *et al.*, 2024). Treatment with both extracts significantly reduced systolic pressure, with the acetone fraction achieving slightly greater improvement (127.99 ± 15.62 mmHg vs. 129.13 ± 10.00 mmHg), likely due to its higher concentration of quassinoids and phenolic compounds with vasodilatory and antioxidant properties (Kumar *et al.*, 2023).

In terms of diastolic blood pressure, the acetone fraction again proved more effective, restoring values to near-normal levels (79.73 ± 3.49 mmHg) relative to normotensive controls (76.36 ± 4.35 mmHg). Considering the established link between diastolic dysfunction and cardiovascular risk in diabetes (Patel *et al.*, 2023), this suggests a possible selective action on vascular smooth muscle tone, in line with mechanisms proposed by Miller *et al.*, (2023). The reduction in mean arterial pressure (acetone: 95.81 ± 3.72 mmHg; hydroethanolic: 98.43 ± 4.70 mmHg) relative to disease control (107.27 ± 7.83 mmHg) further affirms the broad vascular benefits of *S. glauca*, supporting its traditional use in cardiovascular health management (Lee *et al.*, 2023). The superior effect of the acetone fraction may reflect a more efficient extraction of non-polar bioactive constituents, as suggested by recent phytochemical studies.

Heart rate analysis revealed distinct patterns across treatment groups. The hydroethanolic extract group showed a higher mean rate (384.87 ± 42.62 bpm) compared to both the normotensive control (340.58 ± 28.28 bpm) and acetone group (367.53 ± 39.69 bpm), suggesting potential variations in autonomic modulation. This observation aligns with growing evidence of mechanistic diversity among plant-based cardiovascular modulators (Miller *et al.*, 2024). The acetone fraction also demonstrated remarkable glycemic control, significantly lowering fasting blood glucose (270.99 ± 129.97 mg/dL) relative to the hypertensive/diabetic control (462.40 ± 221.90 mg/dL) and hydroethanolic fraction (386.85 ± 193.03 mg/dL). This reflects a more effective modulation of glucose-regulating pathways, consistent with emerging evidence on the antidiabetic activity of plant-derived bioactive (Roberts *et al.*, 2023). Body weight patterns further support these metabolic benefits. The disease control group experienced marked weight loss (78.45 ± 6.51 g) relative to normotensive controls (117.73 ± 0.76 g), while both extracts mitigated this effect. Notably, the

acetone fraction promoted better weight preservation (99.25 ± 8.02 g) than the hydroethanolic extract (91.50 ± 6.45 g), suggesting enhanced insulin sensitivity and improved metabolic balance. These findings align with previous reports on phytochemical interventions improving body weight and energy utilization in diabetic-hypertensive models (ADA, 2024).

Overall, the combined improvements in cardiovascular and metabolic outcomes underscore *S. glauca's* dual therapeutic potential. The acetone fraction's superior activity may be attributed to stress-adaptive secondary metabolites that enhance endothelial function and glucose utilization (Martinez *et al*., 2023). These findings corroborate the growing recognition of solvent polarity as a determinant of phytochemical yield and pharmacological activity (Patel *et al*., 2024), emphasizing the importance of optimizing extraction methodologies in medicinal plant research.

CONCLUSION

The present study demonstrates that both hydroethanolic and acetone fractions of *Simarouba glauca* leaves possess significant antihypertensive and antihyperglycemic properties in L-NAME/STZ-induced hypertensive-diabetic rats. However, the acetone fraction exhibited superior overall efficacy, reflecting its richer concentration of active constituents. These results validate the ethnopharmacological use of *S. glauca* in cardiovascular and metabolic disorders and support its potential development as a dual-action therapeutic agent for managing hypertension-diabetes comorbidity.

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