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Effect of *Simarouba glauca* Fractions on Haematopoietic Indices in Induced Hypertensive-Diabetic Wistar Rats

Osagie-Eweka E.S.D[1*] & Samuel I. Ojeaburu[2]
[1,2]Department of Biochemistry, Faculty of Life Sciences, University of Benin, Benin City, Nigeria
[*]Corresponding Author Email: samuel.ojeaburu@uniben.edu

ABSTRACT
Hypertension and diabetes frequently coexist, compounding therapeutic challenges and substantially elevating cardiovascular risk. This study evaluated the effects of hydroethanolic and acetone fractions of *Simarouba glauca* (*S. glauca*) leaf extract on glycemic and hematological parameters in male Wistar rats with combined NG-nitro-L-arginine methyl ester (L-NAME)–induced hypertension and streptozotocin-induced diabetes. Rats were assigned to four groups: a normotensive, non-diabetic control; a hypertensive, diabetic control; and two treatment groups that received 25 mg/kg of either the hydroethanolic or acetone fraction of *S. glauca* orally for four weeks. Post-treatment hematological analysis revealed significant increases in white blood cell (WBC) counts in both extract-treated groups, suggesting enhanced immunomodulatory activity. The acetone fraction exhibited a more robust erythropoietic response and superior platelet production compared with the hydroethanolic fraction and control groups. Fasting blood glucose was markedly elevated in hypertensive/diabetic controls (462.40 ± 221.90 mg/dL) relative to normotensive controls (89.00 ± 5.72 mg/dL) ($p \leq 0.05$). The acetone fraction showed a stronger hypoglycemic effect (270.99 ± 129.97 mg/dL) than the hydroethanolic fraction (386.85 ± 193.03 mg/dL) ($p \leq 0.05$). Additionally, both extracts mitigated diabetes-associated weight loss. Collectively, these findings highlight the therapeutic potential of *S. glauca* leaf extracts in the management of hypertension–diabetes comorbidity, with the acetone fraction demonstrating greater efficacy in improving glycemic regulation and hematological function. The results further emphasize the importance of extraction methods in shaping the phytochemical composition and therapeutic outcomes, supporting the potential application of *S. glauca* in the integrated management of metabolic disorders.

Keywords:
Glycemic control, Hematological Parameters, Hypertension–Diabetes Comorbidity, Simarouba glauca

INTRODUCTION

Traditional medicine encompasses the body of medical knowledge, practices, and beliefs that have evolved over centuries within diverse cultural and ecological contexts. It includes a wide spectrum of therapeutic modalities such as herbal remedies, massage therapy, acupuncture, and spiritual healing. These systems are characterized by a holistic approach that integrates physical, mental, emotional, and spiritual well-being, reflecting a comprehensive view of human health and disease (WHO, 2024).

The Role of Medicinal Plants in Traditional Health Systems

Plants have always been central to human survival, health, and culture. Across civilizations—from ancient Egypt and India to indigenous American communities—plants have provided both preventive and curative agents. Their therapeutic value has been transmitted across generations through empirical observation and cultural practice. Beyond their pharmacological potential, medicinal plants often hold spiritual and symbolic importance, representing a bridge between humans and nature. As Sutherland *et al.* (2018) observed, many African traditions view plants as sacred gifts with healing power, used in rituals and ceremonies that invoke spiritual balance and holistic restoration.

Simarouba glauca: Ethnomedicinal Background and Pharmacological Relevance

Among such plants, *Simarouba glauca*—commonly known as the "paradise tree"—has garnered significant attention for its wide-ranging medicinal and ecological applications. Belonging to the family Simaroubaceae and native to tropical regions of the Americas, *S. glauca* has been traditionally employed in the treatment of fever,

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dysentery, diarrhea, and intestinal disorders (Bhatia *et al*., 2012; Gupta *et al*., 2015). The bark, leaves, and seeds are the principal parts used in indigenous medicine. Modern pharmacological investigations have reported diverse biological activities, including antimalarial, antibacterial, antidiabetic, and anticancer effects, attributed to its rich phytochemical profile comprising flavonoids, alkaloids, saponins, tannins, and triterpenoids (Islam *et al*., 2013; Ghosh *et al*., 2021).

Recent studies highlight that extracts of *S. glauca* possess strong antioxidant properties owing to their high phenolic and flavonoid content (Patel *et al.*, 2022; Patel *et al.*, 2024). These antioxidants help neutralize reactive oxygen species (ROS) and reduce oxidative stress, a key contributor to chronic metabolic disorders like diabetes and hypertension. Furthermore, *S. glauca* seed oil is recognized for its nutritional and industrial value. Its high oleic acid content makes it a potential substitute for conventional edible oils and an environmentally friendly raw material for biodiesel production (Jayashanthini, *et al*., 2019). Ecologically, *S. glauca* contributes to soil enrichment and reforestation, with its robust adaptability making it suitable for sustainable agroforestry practices (Mehta *et al*., 2022; Agarwal *et al*., 2023; Khan *et al*., 2023).

Hypertension and Diabetes Mellitus: A Dual Global Health Challenge

Hypertension and diabetes mellitus are among the most prevalent non-communicable diseases worldwide, jointly contributing to substantial morbidity and mortality. According to the World Health Organization (2021), over 1.13 billion people are affected by hypertension, a major risk factor for cardiovascular disease, stroke, and chronic kidney failure. Similarly, the International Diabetes Federation (2019) estimates that approximately 463 million individuals are living with diabetes, a figure projected to increase dramatically by 2030. Diabetes mellitus is characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action, or both (ADA, 2020).

Pathophysiological Interplay Between Hypertension and Diabetes

The coexistence of hypertension and diabetes, often termed hypertensive-diabetic comorbidity, poses a significant clinical challenge due to the synergistic effects of metabolic and vascular dysfunction. Insulin resistance, hyperinsulinemia, sodium retention, endothelial dysfunction, and chronic low-grade inflammation form the pathophysiological link between the two conditions (Reynolds *et al*., 2018; Zheng *et al*., 2018). These mechanisms accelerate the progression of atherosclerosis, increase vascular stiffness, and impair renal function, ultimately predisposing individuals to myocardial infarction, stroke, and premature mortality.

Hypertension is clinically defined by persistently elevated arterial pressure, typically above 140/90 mmHg (Zhou *et al*., 2019). It is broadly categorized as primary (essential) or secondary (non-essential). Primary hypertension, accounting for about 90–95% of cases, arises from multifactorial interactions among genetic predisposition, environmental influences, and lifestyle factors such as diet and physical inactivity. Secondary hypertension, by contrast, results from identifiable causes including renal artery stenosis, chronic kidney disease, and endocrine disorders such as hyperaldosteronism or pheochromocytoma. The coexistence of hypertension and diabetes is multifactorial and self-perpetuating. Insulin resistance and hyperinsulinemia contribute to sympathetic overactivity and renin–angiotensin–aldosterone system (RAAS) activation, leading to increased vascular tone and sodium retention. Conversely, chronic hypertension causes endothelial injury and vascular remodeling, impairing glucose uptake and insulin signaling. Furthermore, oxidative stress and inflammation represent common biochemical pathways that exacerbate both diseases (Reynolds *et al*., 2018). Shared lifestyle risk factors—obesity, poor nutrition, and sedentary behavior—further amplify the incidence and progression of this dual condition.

Therapeutic Gaps and the Role of Phytomedicine

Current pharmacotherapies for hypertension (such as ACE inhibitors, calcium channel blockers, and diuretics) and diabetes (such as biguanides and sulfonylureas) are effective but may produce undesirable side effects, including electrolyte imbalance, hepatotoxicity, and hypoglycemia. Hence, the exploration of phytotherapeutic agents has gained momentum, especially those capable of addressing multiple targets such as oxidative stress, endothelial dysfunction, and hematological imbalance simultaneously.

Plant-derived compounds often possess multifaceted bioactivity, offering antioxidant, anti-inflammatory, and hematopoietic effects that may alleviate systemic complications of metabolic disorders. Studies have shown that phytochemicals such as flavonoids, terpenoids, and saponins can improve vascular integrity, stimulate erythropoiesis, and modulate immune responses (Leite *et al*., 2020). These properties underscore the therapeutic relevance of medicinal plants like *Simarouba glauca* in managing complex comorbid conditions such as hypertension-diabetes overlap.

Given the increasing global burden of hypertension and diabetes and the growing recognition of plant-based therapies as viable alternatives or adjuncts to conventional treatments, *Simarouba glauca* presents a promising research candidate. Its previously reported antidiabetic, antihypertensive, antioxidant, and hematopoietic activities suggest a potential integrative role in modulating the physiological disturbances associated with these metabolic disorders (Osagie-Eweka *et al*., 2023; Osagie-Eweka and Ojeaburu,2025; Ojeaburu and Osagie-Eweka, 2025)

Haematological alterations are among the earliest systemic manifestations in diabetes and hypertension, including anemia, altered leukocyte count, and platelet dysfunction (Zvetkova *et al*., 2024). Evaluating the effects of *Simarouba glauca* on hematopoietic parameters in experimental hypertensive-diabetic models may thus provide critical insights into its therapeutic potential and safety profile. This study evaluated the comparative effects of hydroethanol and acetone fractions of *Simarouba glauca* leaves on hematopoietic functioning in L-NAME/streptozotocin-induced hypertensive-diabetic male Wistar rats.

MATERIALS AND METHODS

Chemicals and Reagents

All chemicals and reagents employed in this study were of analytical grade and obtained from British Drug House (BDH, England) and Sigma-Aldrich (USA).

Plant Material and Authentication

Fresh leaves of *Simarouba glauca* were collected from Cercobela Farms®, Ubiaja, Esan Southeast Local Government Area, Edo State, Nigeria. Botanical identification was performed at the Department of Plant Biology and Biotechnology, University of Benin, and a voucher specimen (UBHS382) was deposited in the institutional herbarium. The leaves were air-dried at room temperature (25–30°C) for 7–10 days, pulverized using a mechanical grinder, sieved to obtain a uniform powder, and stored in airtight containers before extraction.

Preparation of Extracts

Hydroethanolic Extract (HE)

Hydroethanolic extraction was carried out by maceration using 80% ethanol (v/v). Powdered plant material (500 g) was immersed in 500–1000 mL of solvent (5:1–10:1, v/w) in a sealed glass vessel and kept at room temperature for 3–7 days with intermittent agitation. The mixture was filtered through Whatman No. 1 filter paper, and the filtrate was concentrated using a rotary evaporator (Buchi, Germany). The concentrate was freeze-dried and stored at −4°C until use.

Extraction yield (%) was calculated as:

Yield (%) = (Weight of dried extract × 100) / Weight of powdered material

Acetone Extract (AE)

Powdered *S. glauca* leaves (500 g) were subjected to maceration using analytical-grade acetone. The plant material was placed in a clean, dry glass Erlenmeyer flask and extracted with 500–1000 mL of acetone (solvent-to-sample ratio 5:1–10:1, v/w), ensuring complete submersion. The procedure followed the same steps described for the hydroethanolic extraction. All steps were carried out in a well-ventilated fume hood using appropriate personal protective equipment, in accordance with laboratory safety guidelines for flammable solvents.

Experimental Animals

Male Wistar rats (180–200 g) were obtained from the Animal House, Department of Biochemistry, University of Benin. Animals were housed under standard laboratory conditions (25°C, 55–65% humidity, 12 h light/dark cycle) with free access to commercial pellet feed and water. All experimental procedures conformed to the National Research Council (US) Institute for Laboratory Animal Research (Guide for the Care and Use of Laboratory Animals, Washington (DC):1996). Ethical approval was granted by the Institutional Animal Ethics Committee, Faculty of Pharmacy, University of Benin (Ref. EC/FP/021/11).

Acute Toxicity Assessment

Acute oral toxicity of the HE and AE was evaluated following the method of Lorke (1983). Thirty-six rats were used in a two-phase procedure.

Phase 1: Animals were allocated into three groups (n = 3) and administered 10, 100, and 1000 mg/kg of HE. Behavioural signs and mortality were monitored during the first hour and over 24 h.

Phase 2: In the absence of mortality, three additional rats received 1500, 2500, and 5000 mg/kg of HE.

Observations continued for 24 h and for an additional 48 h to detect delayed toxicity.

The same procedure was applied to determine the acute toxicity profile of the AE fraction.

Experimental Design and Treatment

After a two-week acclimatization period, twenty-four rats were randomly divided into four groups (n = 6):

- Group I: Normal Control (NND) Normotensive, non-diabetic rats were administered distilled water only.
- Group II: Hypertensive/Diabetic Control (HD) Induced with L-NAME and streptozotocin (STZ) without treatment.(Disease Control).
- Group III: HD + HE (25 mg/kg) (HDHE) Hypertensive and diabetic rats were treated daily with the hydroethanolic fraction of *Simarouba glauca* leaves.
- Group IV: HD + AE (25 mg/kg) (HDAE) Hypertensive and diabetic rats were treated daily with the acetone fraction of *S. glauca* leaves.

All administrations were by oral gavage for 28 consecutive days.

Induction of Hypertension

Hypertension was induced by administering NG-nitro-L-arginine methyl ester (L-NAME, 40 mg/kg) in drinking

water for four weeks. Systolic blood pressure (SBP) was monitored weekly using a non-invasive tail-cuff system (CODA, Kent Scientific, USA). Rats with SBP ≥ 140 mmHg were classified as hypertensive.

Induction of Diabetes

Diabetes mellitus was induced after an overnight fast by a single intraperitoneal injection of streptozotocin (50 mg/kg) prepared in cold 0.1 M citrate buffer (pH 4.5). Fasting blood glucose was measured after 72 h using an ACCU-CHEK Advantage II glucometer (Roche, Germany). Animals with fasting glucose ≥ 200 mg/dL were considered diabetic. Blood glucose was monitored weekly throughout the 28-day treatment period.

Haematological Analysis

Following the 28-day treatment period, animals were fasted overnight and euthanized under light anesthesia. Blood samples were collected via cardiac puncture into EDTA-coated tubes for haematological assessment. The evaluated parameters included white blood cell count (WBC), lymphocyte percentage (LYM), absolute lymphocyte count (LYM#), mid-sized cell percentage (MID), absolute mid-sized cell count (MID#), granulocyte percentage (GRAN), absolute granulocyte count (GRAN#), red blood cell count (RBC), haemoglobin concentration (Hb), hematocrit (HCT), mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), red cell distribution width–standard deviation (RDW-SD), red cell distribution width–coefficient of variation (RDW-CV), platelet count (PLT), mean platelet volume (MPV), plateletcrit (PCT), and platelet distribution width (PDW). All analyses were performed using an automated haematology analyzer (Sysmex KX-21N, Japan) following the manufacturer's standardized operating procedures. Quality control calibration of the analyzer was performed before sample analysis. Abnormal readings or flagged samples were re-evaluated to ensure accuracy and repeatability.

Statistical Analysis

Data were expressed as mean ± standard deviation (SD). Statistical analyses were performed using GraphPad Prism version 8.0 (GraphPad Software, USA). Differences among groups were assessed using one-way analysis of variance (ANOVA) followed by Tukey's post hoc test for multiple comparisons. A p-value ≤ 0.05 was considered statistically significant. All analyses adhered to recommended statistical guidelines for pre-clinical pharmacological studies.

RESULTS AND DISCUSSION

Acute Toxicity Test of HE and AE 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 HE

Dose (mg/kg body weight) of HE	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 AE

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 presents the fasting blood glucose levels and body weight changes across all experimental groups. The hypertensive/diabetic control group exhibited significantly elevated fasting blood glucose (462.4 ± 221.9 mg/dL) relative to the normotensive control group (89.00 ± 5.72 mg/dL). Treatment with *S. glauca* extracts produced notable anti-diabetic effects, with the acetone fraction demonstrating superior glucose-lowering activity (270.99 ± 129.97 mg/dL) compared to the hydroethanolic fraction (386.85 ± 193.03 mg/dL). Additionally, the hypertensive/diabetic control group experienced significant body weight loss (78.45 ± 6.51 g) relative to normotensive controls (117.73 ± 0.76 g), whereas both extract treatments effectively mitigated weight reduction, indicating protective effects against diabetes-induced cachexia.

Table 3: Effects of treatments on FBS and body weight

Groups	FBS (mg/dL)	Body Weight (g)
Normotensive/ non-diabetic (+ve control)	89.00±5.717[a]	117.73± 0.76[c]
Hypertensive/ Diabetic (-ve control)	462.4 ± 221.9[c]	78.45 ± 6.51[a]
Hypertensive/ Diabetic +HE (25mg/kg)	386.85±193.03[bc]	91.5 ± 6.45[b]
Hypertensive/ Diabetic +AE (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 summarizes the systolic (SBP) and diastolic blood pressure (DBP) values across all experimental groups. The normotensive/non-diabetic control group exhibited normal blood pressure (SBP: 112.51 ± 5.35 mmHg; DBP: 76.36 ± 4.35 mmHg), whereas the hypertensive/diabetic control group showed marked elevations in both SBP (139.20 ± 19.54 mmHg) and DBP (91.37 ± 4.09 mmHg). Administration of *S. glauca* extracts produced significant antihypertensive effects, with the acetone fraction demonstrating slightly greater efficacy, reducing SBP to 127.99 ± 15.62 mmHg and DBP to 79.73 ± 3.49 mmHg, compared to the hydroethanolic fraction.

Table 4: Effects of treatments on systolic and diastolic blood pressure

Group	SBP (mmHg)	DBP (mmHg)
Normotensive/non-diabetic (+ve control)	112.51 ± 5.35[a]	76.36 ± 4.35[a]
Hypertensive/diabetic (-ve control)	139.20 ± 19.54[c]	91.37 ± 4.09[c]
Hypertensive/diabetic+ HE (25 mg/kg)	129.13 ± 10.04[b]	83.17 ± 5.13[b]
Hypertensive/diabetic +AE (25 mg/kg)	127.99 ± 15.62[b]	79.73 ± 3.49[ab]

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

Effect of treatment on white blood cell (WBC) and differential counts

Table 5 summarizes the white blood cell (WBC) and differential counts across the experimental groups. The hypertensive/diabetic (HD) group showed a significant elevation in total WBC, lymphocyte percentage (LYM%), and granulocyte percentage (GRAN%) compared with the normotensive/non-diabetic (NND) group ($p < 0.05$).

Treatment with the hydroethanolic fraction produced the highest WBC count and significantly increased MID% and GRAN% relative to the NND, HD, and acetone (HDAE) groups ($p < 0.05$), suggesting a more pronounced immune-modulatory response. In contrast, the acetone fraction (AE) normalized total WBC and maintained LYM%, MID%, and GRAN% values within the physiological range observed in the NND group.

Table 5. White blood cell (WBC) and differential cell counts across treatment groups.

Group	WBC (×10³/µL)	LYM(%)	MID(%)	GRAN(%)	LYM# (×10³/µL)	MID# (×10³/µL)	GRAN# (×10³/µL)
NND	7.03 ± 0.30	67.93± 4.99	12.2±1.55	18.2 ±3.08	4.28 ±0.64	1.78 ±0.65	1.78 ±0.69
HD	8.2 ± 0.40*	77.23±2.51*	12.4±1.65*	11.48±1.70 *	6.6 ±0.44	1.1 ± 0.51	1.07 ±0.06
HDHE	8.45± 0.77*	67.43 ± 9.09	13.4 ±1.00*	38.3± 10.14*	3.9 ±0.35	1.15 ±0.13	3.03±1.02*
HDAE	7.35 ± 0.35	63.7 ± 5.45	14.3 ±0.81*	24.25 ±3.89	4.85±0.07* *	1.37±0.55*	1.45 ±0.35

Values are expressed as mean ± SD (n=5). Asterisks (*) indicate significant differences ($p \leq 0.05$) and (**) indicates no significant difference ($p \geq 0.05$) between groups.

Effect of treatment on red blood cell (RBC) counts and related parameters across treatment groups.

Table 6 presents the red blood cell indices across the experimental groups. The hypertensive/diabetic (HD) group showed slight, non-significant increases in hemoglobin (HGB) and mean corpuscular volume (MCV) compared with the normotensive/non-diabetic (NND) group ($p > 0.05$). Treatment with Acetone 25 produced a significant elevation in red blood cell (RBC) count, HGB, and hematocrit (HCT) compared with the HD, NND, and HDHE groups ($p \leq 0.05$), indicating a superior erythropoietic response. Hydroethanol treatment enhanced MCV, mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC), maintaining values within the physiological range of the NND group.

Table 6: Red blood cell (RBC) counts and related parameters across treatment groups**.**

Group	RBC (×10⁶/µL)	HGB (g/dL)	HCT (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)
N\ND	6.44 ±0.56	13.18±0.613	38.55 ±2.03	62.22 ±1.05	21.38 ±0.69	34.36±0.611
H\D	6.35±0.68**	13.4 ±0.43**	38.98±1.14**	64.05±2.46**	22.14±1.22**	34.26±1.06**
HE	6.53 ±0.38	14.08 ±0.41	42.7 ±3.12	65.46±1.70**	22.2 ±0.64**	33.96 ±0.26*
AE	7.09 ±0.67*	15.27 ±1.32*	44.77 ±4.70*	63.1 ±2.35	21.47 ±0.378	34.77 ±0.95

Values are expressed as mean ± SD (n=5). Asterisks (*) indicate significant differences (p≤ 0.05) and (**) indicates no significant difference (p ≥ 0.05) between groups.

Effect of HE and AE of *S. glauca* on platelet and coagulation parameters across treatment groups.

Table 7 summarizes the platelet and coagulation parameters across the experimental groups. The hypertensive/diabetic (HD) group showed non-significant increases in platelet count (PLT) and platelet distribution width (PDW) compared with the normotensive/non-diabetic (NND) group ($p > 0.05$). Acetone (AE) treatment produced a significant elevation in PLT and plateletcrit (PCT) compared with the HD, NND, and HDHE groups ($p \leq 0.05$), indicating enhanced thrombopoietic activity. While hydroethanol (HE) treatment resulted in platelet indices similar to those observed in the Acetone (HDAE) group, a statistically significant difference in PDW was noted ($p \leq 0.05$). Additionally, hydroethanol (HE) treatment resulted in significant increases in RDW-SD and RDW-CV relative to the HD, NND, and HDAE groups ($p \leq 0.05$).

Table 7: Platelet and coagulation parameters across treatment groups**.**

Group	RDW-SD (fL)	RDW-CV (%)	PLT (×10³/µL)	MPV (fL)	PCT (%)	PDW (fL)
NND	36.76 ±1.80	16.76 ±0.55	284 ±48.68	7.34±0.23	0.22±0.02	8.22 ±0.72
HD	38.9 ±1.79	16.98 ±0.46	318±34.88**	7.18±0.19	0.20±0.05	8.42±0.65**
HDHE	40.18±0.94*	17.66±0.29*	343±38.12*	7.5 ±0.63	0.24±0.05*	9.36 ±0.84*
HDAE	37.0 ±3.26	16.73 ±1.04	405±103.23*	7.4 ±0.2	0.28±0.12*	7.8 ±0.17

Values are expressed as mean ± SD (n=5). Asterisks (*) indicate significant differences (p≤ 0.05) and (**) indicates no significant difference (p ≥ 0.05) between groups.

The present study compared the modulatory effects of hydroethanolic (HE) and acetone (AE) leaf extracts of *Simarouba glauca* in a rat model of comorbid hypertension and diabetes induced by L-NAME and STZ. Both fractions exhibited significant corrective effects on haematological disturbances and metabolic dysregulation; however, the AE fraction consistently demonstrated superior activity across most parameters.

Acute oral toxicity testing revealed no mortality or overt clinical signs at doses up to 5000 mg/kg for either fraction, indicating a favourable safety profile under acute exposure conditions (OECD, 2008). While these results suggest the absence of highly toxic constituents at the administered doses, chronic toxicity and long-term safety evaluations remain necessary.

Progressive body-weight loss is a hallmark of untreated L-NAME/STZ-induced cardio-metabolic dysfunction, reflecting impaired nutrient utilization and catabolic dominance (Corremans *et al*., 2021; Ojeaburu and Osagie-Eweka, 2025). Body-weight changes are recognized as indicators of systemic metabolic integrity. As reported previously, weight loss is commonly associated with impaired appetite or disruptions in carbohydrate, protein, and lipid metabolism (Tiiro *et a*l., 2021; Farhana *et al*., 2023; Ojeaburu and Osagie-Eweka, 2025). Treatment with either fraction attenuated this loss, with the AE fraction affording significantly greater weight preservation than the HE fraction, implying superior restoration of anabolic processes and energy homeostasis (ADA, 2020).

The AE fraction also achieved more effective glycaemic control, lowering fasting blood glucose to a greater extent than the HE fractions. This observation is in harmony with the findings of Rahman *et al*. (2022). This superior hypoglycaemic activity likely reflects higher concentrations of quassinoids and flavonoids that enhance peripheral glucose uptake and protect pancreatic β-cell function. (NoorShahida *et al*.,2009; Al-Ishaq *et al*., 2019)

Both fractions significantly lowered systolic blood pressure, confirming antihypertensive potential (Kumar *et al*., 2024; Ojeaburu and Osagie-Eweka, 2025). The marginally greater reduction observed with the AE fraction may be mediated through nitric oxide-dependent vasodilation, antioxidant activity, and improvement of endothelial function—mechanisms previously ascribed to phenolic and triterpenoid constituents enriched in acetone extracts (Kumar *et al*., 2023).

Comorbid hypertension and diabetes exert profound deleterious effects on haematopoiesis via oxidative stress, chronic inflammation, and advanced glycation end-product accumulation (Leite *et al*., 2020; Osagie-Eweka *et al*., 2023). Both fractions ameliorated these disturbances, albeit with lineage-specific differences that underscore the influence of solvent polarity on phytochemical composition.

Regarding leucocyte parameters, both fractions increased total white blood cell counts toward normal values without provoking leukocytosis. The HE fractions elicited more pronounced elevations in monocyte and granulocyte percentages, consistent with immunostimulatory properties frequently reported for hydroalcoholic extracts (Essiet *et al*., 2016; Njagi, 2021). In contrast, the AE fraction produced a more balanced response, which may be advantageous in chronic inflammatory states (Mehvish *et al*., 2024).

Both fractions supported erythropoiesis, but the AE fraction yielded significantly higher red blood cell counts, haemoglobin concentrations, and haematocrit values, likely mediated by membrane-stabilising flavonoids and haematopoietic stimulation (Umar *et al*., 2022; Hingu *et al*., 2023; Osagie-Eweka *et al*., 2023). Improvements in platelet count and plateletcrit were most pronounced with the AE fraction, whereas the HE fraction maintained platelet indices closer to disease-control levels—an effect that may protect against hypercoagulability in the hypertensive–diabetic milieu (Aboyade *et al*., 2010; Sailo *et al*., 2018; Rosidah *et al*., 2021).

Collectively, these findings demonstrate that *S. glauca* leaf extracts offer important dual benefits in haematological protection and glycaemic regulation in hypertensive-diabetic pathology. Importantly, extraction solvent polarity emerged as a key determinant of phytochemical yield and bioactivity, consistent with earlier research emphasizing solvent-dependent variations in therapeutic potential (Patel *et al*., 2024).

CONCLUSION

The hydroethanolic and acetone leaf extracts of *Simarouba glauca* both exhibited significant therapeutic potential in a rat model of comorbid hypertension and diabetes, improving body-weight maintenance, glycaemic control, blood pressure, and multiple haematological parameters. The acetone fraction consistently demonstrated greater efficacy, particularly in restoring glucose homeostasis, stimulating erythropoiesis, and modulating platelet production. These findings underscore the importance of solvent selection in optimizing the phytochemical profile and biological activity of plant-derived preparations. *Simarouba glauca* emerges as a promising candidate for the development of multifunctional phytotherapeutics targeting cardio-metabolic disorders. Further studies elucidating underlying molecular mechanisms, establishing chronic safety profiles, and evaluating clinical efficacy are warranted.

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