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Full Length Article

Beyond traditional medicine: *Erythrophyleum suaveolens* (Guill. & Perr.) Brenan shows promising antidiabetic activity in experimentally induced type II diabetes

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ABSTRACT

This study aimed to investigate the antidiabetic activity of the methanolic extract of *Erythrophyleum suaveolens* stem bark (MEESS) in fructose-fed streptozotocin-induced diabetic Wistar rats. Diabetes was induced in rats by administering 10% fructose for two weeks, followed by an intraperitoneal (i.p.) injection of a low dose (40 mg/kg) of streptozotocin (STZ) to induce type 2 diabetes (T2D). The groups of experimental rats were categorized as follows: control, diabetic-control, diabetic metformin (100 mg/kg), diabetes + MEESS (150 mg/kg), and diabetes + MEESS (300 mg/kg). MEESS was administered to the two diabetic groups at doses of 150 and 300 mg/kg body weight. Following the conclusion of the experiment, blood samples (for serum collection) and liver tissues were collected for biochemical analysis. MEESS significantly ($p < 0.05$) attenuated STZ-induced elevations in blood glucose, alanine transaminase (ALT), aspartate transaminase (AST), triglyceride (TG), total cholesterol (TC), low-density lipoprotein (LDL), very-low density lipoprotein (VLDL), and malondialdehyde (MDA) levels and restored the levels of superoxide dismutase (SOD), catalase, reduced glutathione (GSH), and high-density lipoprotein (HDL), which were previously depleted by STZ. In diabetic rats, MEESS treatment led to increased hexokinase activity and decreased G6Pase activity. Additionally, MEESS upregulated the mRNA expression levels of nuclear factor erythroid 2-related factor 2 (Nrf2), NAD(P)H:quinone oxidoreductase-1 (NQO1), and peroxisome proliferator-activated receptor gamma (PPAR-γ = while downregulating kelch-like ECH-associated protein 1 (Keap1), protein tyrosine phosphatase 1B (PTP1B), and caspase-3 mRNA expression in the liver. MEESS regulates glucose homeostasis in diabetic rats while preventing redox imbalance.

1. Introduction

Diabetes mellitus (DM) is a condition characterized by insufficient insulin production by the beta cells of the pancreas, increased resistance, or both (Alanazi et al., 2024). This condition is also among the fastest-growing endocrine system disorders, with forecasts suggesting that it will impact over 700 million adults worldwide by 2045 (Wang et al., 2021). Diabetes is not just one disorder but rather a group of disorders related to hyperglycemia (Hossain et al., 2024). Diabetes has existed for centuries and has remained one of the most prevalent endocrine disorders worldwide. The first credible discussion that describes diabetes would have come from Aretaeus of Cappadocia in the

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2nd century. Much later, in the 1700s, Thomas Willis notably added the term "mellitus" to diabetes to explain the distinctive sweetness found in a urine sample (Sapra and Bhandari, 2025). Over the years, research on diabetes mellitus has been continuously carried out and is still ongoing in an effort to discover a permanent solution for the disease. In 2021, diabetes was responsible for a high number of deaths, resulting in approximately 6.7 million deaths, meaning that every 5 s, there was one death caused by diabetes (IDF Diabetes Atlas, 2022). Sun et al. (2022) reported that diabetes mellitus (DM) currently affects 537 million adults worldwide, with projections suggesting that this number could rise to 783 million by 2045. Various methodologies exist to explore the pathogenesis, complications, and environmental factors associated with DM (Mohammad et al., 2024; Elsharkawy et al., 2025).

Streptozotocin (STZ), an antibiotic derived from *Streptomyces achromogenes*, is frequently used to induce DM in animal models for the purpose of screening new antidiabetic drugs (Elsharkawy et al., 2025). Like single-target drugs, multitarget therapeutics for DM often fail. Therefore, network pharmacology is utilized to identify potential synergistic phytochemicals. Existing treatments, such as metformin and insulin, have notable limitations, including adverse side effects and cost considerations, increasing interest in natural alternatives (McInnes et al., 2023). Moreover, individuals with DM typically experience lower mental health and quality of life due to oxidative stress, which is associated with severe complications such as neuropathy, nephropathy, retinopathy, and cardiovascular disease (Elsharkawy et al., 2025). As hyperglycemia generates reactive oxygen species (ROS) that damage pancreatic β-cells and worsen insulin resistance, antioxidant-rich plants may help counteract these effects (Hussein et al., 2021; Elsharkawy et al., 2025).

Throughout history, herbal medicines have garnered increasing attention because of their availability, effectiveness, and safety profile, especially in terms of reduced side effects compared with those of chemically synthesized drugs (Mallik et al., 2024; Gouda et al., 2024). Importantly, promising antidiabetic agents with minimal adverse effects remain a challenge, as traditional medicines have been utilized as antidiabetic treatments for centuries, although few have been developed into pharmaceutical formulations. Several methods, either laboratory-made drugs or medicinal plants, have been applied for diabetes treatment. For many years, herbal remedies have long been employed to manage diverse health issues, including diabetes mellitus, because of the therapeutic importance of their phytochemicals.

Despite ongoing advancements in antidiabetic treatments, both natural and synthetic, diabetes and its related complications remain significant global health challenges. Historically, various indigenous medicinal plants have proven effective in managing diabetes. One key advantage of these botanical resources is their widespread availability and relatively low incidence of adverse effects (Satyanarayana et al., 2022). However, despite their potential as antidiabetic agents, plant-based therapies have not yet achieved the level of scientific investigation and acceptance necessary for widespread implementation. Nonetheless, current research increasingly suggests that appropriate dietary regulation, along with the careful inclusion of beneficial herbs, may help reduce the incidence of diabetes (Visen et al., 2022). *Erythrophyleum suaveolens*, often referred to as the ordeal tree, African rosewood, or sassy bark, is a species in the Fabaceae family that grows widely across tropical Africa. This plant has a long history of medicinal use, but it is highly toxic because it contains potent cardioactive alkaloids, such as erythrophleine and norcassamidine. Despite its toxic properties, *E. suaveolens* has garnered interest in pharmacological research because of its various phytochemical components, including alkaloids, saponins, flavonoids, tannins, procyanidins, and resveratrol. These compounds have shown anti-inflammatory, analgesic, antimicrobial, and wound-healing effects. Furthermore, traditional uses have suggested potential benefits as antimalarial, emetic, purgative, anthelmintic, and local anesthetics (Yusuf et al., 2022). However, its potential for managing diabetes has not been thoroughly researched in the current scientific literature. This study aimed to evaluate and confirm the effectiveness of *Erythrophyleum suaveolens* bark in diabetes management.

2. Methods

2.1. Plant materials and extraction

The stem bark of *Erythrophleum suaveolens* was obtained from Oluponna, Osun State, Nigeria. Our preserved samples are securely stored in the herbarium at Bowen University, specifically in the Department of Pure and Applied Biology, and are identified by voucher number BUH 020. The name of the plant *E. suaveolens* (Guill. & Perr.) Brenan was verified via the 'Medicinal Plant Names Services'.

2.2. Chemicals

The reagents and chemicals used were obtained from Glentham Life Sciences Ltd., Corsham, United Kingdom. Every chemical used was of analytical grade.

2.3. Preparation of the methanolic extract of Erythrophleum suaveolens (MEESS)

E. suaveolens stem bark was harvested by hand and washed before being left to air dry. Following air drying, the samples were ground, and extraction was carried out via maceration in accordance with previously published methods (Ojo et al., 2024a). A known mass (300 g) of the ground plant was placed in a beaker, and then 3000 mL of methanol was added to it. Its top was covered with aluminum foil, and the mixture was then left undisturbed at room temperature for four days to settle. The extracts were then collected using filter paper. After that, the solvent was dried at 40 °C in an oven to produce the methanolic extract of the plant.

2.4. In vitro antioxidant studies

The ferric reducing power of MEESS was assessed via the method proposed by Pan et al. (2024). The DPPH radical scavenging capacity was evaluated following the procedure established by Pan et al. (2024). Hydroxyl radicals were quantified according to the methodology described by Karimi et al. (2020). Additionally, the iron chelating activity was measured via the protocol developed by Karimi et al. (2021).

2.5. Experimental animals

This study included twenty-five (25) male Wistar rats (*Rattus norvegicus*), each weighing between 130 and 160 g. The animals were housed in sanitized polypropylene cages with stainless steel mesh tops in a well-ventilated animal facility. The plants were maintained under standard environmental conditions, including a controlled temperature of 24 ± 2 °C, a relative humidity of 50 ± 5%, and a 12-hr light/dark cycle for 21 days under controlled conditions, and they received regular rat pellets and fresh water.

2.6. Animal grouping

After a stage of initial acclimatization, 25 male Wistar rats, which were randomly divided into five different study group categories ($n = 5$), were used for this study. These numbers are predicated upon set protocols for antidiabetic studies, which promote valid statistics correlated with the 'reduction' principle of animal ethics. This sample size is in line with the previously established protocols for STZ-induced diabetic models in Wistar rats, which have indicated that a sample size of $n = 5$ has sufficient statistical power to detect significant differences ($p < 0.05$) in biochemical and molecular parameters (Szkudelski, 2001; Abu, 2023). To establish baseline uniformity, the study rats were grouped

such that the initial mean body weight variance between group members was insignificant. This study adheres to the ARRIVE reporting guidelines on the use of animals. The following are the group assignments:

Control - This group consisted of normal animals that received standard feed and distilled water daily, and served as the vehicle control.

Diabetic Untreated - This group comprised diabetic animals (streptozotocin-induced) provided with only feed and distilled water daily, which acted as a baseline for untreated diabetic conditions.

Diabetic + metformin - Diabetic animals in this group were administered metformin at a dosage of 100 mg/kg body weight.

Diabetic +*E. suaveolens* (150 mg/kg) - This group received *E. suaveolens* at a concentration of 150 mg/kg body weight in addition to their diabetic condition.

Diabetic +*E. suaveolens* (300 mg/kg) - Diabetic animals in this group were treated with *E. suaveolens* at a relatively high dosage of 300 mg/kg body weight.

The doses of 150 mg/kg and 300 mg/kg were selected on the basis of previously published studies in similar experimental models, where these doses were reported to produce significant biological effects without observable toxicity (Ojo et al., 2024a).

2.7. Induction of diabetes

To induce type II diabetes mellitus in male rats, the methodology established by Ojo et al. (2017) was utilized. A total of twenty-five male Wistar rats, with an average weight of 135.54 ± 10.52 g, were subjected to a 12-h fasting period, during which they had access to only water. Before the administration of fructose and streptozotocin (STZ), fasting blood glucose levels were measured via a portable glucometer (Glucoplus Inc., Saint-Laurent, Quebec, Canada). Blood samples for these measurements were collected from the tail, following the previously described protocol. To induce insulin resistance, the rats were given 10% fructose solution ad libitum for two weeks. After this period, the rats received a single intraperitoneal injection of STZ at a dose of 40 mg/kg body weight, which was prepared by dissolving STZ in citrate buffer with a pH of 4.5. Fasting blood glucose levels were assessed again 72 h after STZ administration. The male rats were classified as having type 2 diabetes mellitus if their fasting blood glucose levels exceeded 250 mg/dL. Since this is a preclinical study, a clinical trial number is not relevant.

2.8. Animal sacrifice and sample collection

At the end of the 21-day treatment period, the rats were fasted overnight, and subsequently, sacrificed by being placed under anesthesia with ketamine (100 mg/kg b.w., i.m.), which was injected intramuscularly. The choice of ketamine is attributed to its rapid induction and lack of interference with blood glucose and carbohydrate metabolism, thereby preserving the various biochemical markers of interest. A syringe was used to extract blood samples (approximately 4–5 mL) from the right ventricle of the heart via cardiac puncture, which were subsequently placed in plain tubes. The blood samples were allowed to clot for 30 min at room temperature, followed by centrifugation at 3000 rpm for 5 min. The resulting serum was carefully labeled for subsequent biochemical analysis. Immediately following blood collection, the liver was dissected carefully, weighed, and homogenized in very cold phosphate buffer using a mortar and pestle. The homogenates were subsequently centrifuged at 5000 rpm for 10 min. The resulting supernatant was then collected and stored at −20 °C until further biochemical analysis.

2.9. Determination of biochemical parameters

To reduce the bias of the experimental results, the evaluation of the outcomes was carried out in a blinded manner, and the researchers who performed the biochemical analyses were not aware of the treatment groups until the data analysis step. Serum fasting blood glucose levels were determined via methods previously described by Ajiboye et al. (2018). Other biochemical parameters were assessed in the liver tissue homogenate according to their respective standard protocols: catalase activity, as described by Aebi (1984); superoxide dismutase (SOD) activity, as described by Misra and Fridovich (1972); reduced glutathione (GSH) levels, as described by Beutler et al. (1963); and malondialdehyde (MDA) levels, as described by Varshney and Kale (1990). Additionally, serum total cholesterol (TC) and triglyceride levels were measured following the methodology established by Friedewald et al. (1972), whereas serum low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) levels were quantified via the approach described by Jacobs et al. (1990).

2.10. Gene expression study

2.10.1. Isolation of total RNA

RNA was extracted from liver tissue samples at 4 °C via TRIzol reagent and the Quick-RNA MiniPrep Kit from Zymo Research (catalog No: R2050-1-50, Lot No: ZRC186885). To remove DNA contamination, the samples were treated with DNase I from New England Biolabs (catalog no. M0303S). The RNA was precipitated from the supernatant by adding an equal volume of isopropanol from Burgoyne Urbidges & Co. (Catalog No: 67-63-0). The resulting RNA pellet was washed twice with 70% ethanol, prepared by mixing 70 mL of absolute ethanol from BDH Analytical Chemicals (Catalog No: 10107-7Y) with 30 mL of nuclease-free water from Inqaba Biotec (Lot No: 0596C320, Code: E476-500 ML). After the pellets were allowed to air dry for 5 min, they were reconstituted in RNA buffer (pH 6.4) containing 1 mM sodium citrate.

2.10.2. cDNA conversion

One microgram of DNA-free RNA was converted into complementary DNA (cDNA) via the ProtoScript II First-Strand cDNA Synthesis Kit from New England Biolabs. The total reaction volume was 20 µL and contained the following components: 2 µL of N9 random primer mixture, 2 µL of 10X M-MuLV buffer, 1 µL of M-MuLV reverse transcriptase (200 U/microliter), 2 µL of 10 mM dNTP, 0.2 µL of RNase inhibitor (40 U/microliter), and 10.8 µL of nuclease-free water. The thermal cycling conditions for this reaction, as outlined by Ojo et al. (2022a) and Elekofehinti et al. (2020), included an initial incubation at 65 °C for 5 min, followed by a 1-h incubation at 42 °C, and a final step at 80 °C for 5 min.

2.10.3. PCR amplification and agarose gel electrophoresis

For gene expression analysis, the liver tissue samples were immediately snap-frozen with liquid nitrogen after excision and stored at −80 °C to maintain integrity. For the amplification of our target gene through polymerase chain reaction (PCR), we acquired primers from Inqaba Biotec located in Hatfield, South Africa, and OneTaq 2X Master Mix from New England Biolabs. The PCR mixture had a total volume of 25 µl, which included cDNA, specific forward and reverse primers, and OneTaq Quick-Load 2X Master Mix (NEB, Cat: M0486S). The thermal cycling protocol commenced with an initial denaturation step at 95 °C for 5 min. This was followed by 30 cycles that included 30 s each for denaturation, annealing, and extension, with the extension phase occurring at 72 °C for 60 s. The cycling program included a final extension step at 72 °C for 10 min. The PCR products were analyzed via electrophoresis on a 1.0% agarose gel (Cleaver Scientific Limited: Lot: 14170811), which was prepared with Tris-Borate-EDTA buffer (pH 8.4). The reagents used in this portion of the experiment were obtained from RGT (China, Lot: 20170605) and JHD Chemicals (China, Lot: 20141117). Band intensities were quantified via ImageJ software (see Table S1), following the methodologies established by Ojo et al. (2022a) and Olumegbon et al. (2022). The GAPDH gene served as an internal control to normalize the expression levels of the genes of interest. This method was chosen on the basis of its known stability and expression

under different physiological conditions, including diabetic and high-fructose conditions, where it is not affected by any metabolic changes (Bakhashab et al., 2014). This ensures that any changes observed in Nrf2, Keap1, and Caspase-3 expression are not due to any internal control effects. The uncropped gel images are shown in (Supplementary Fig. 1).

2.11. Statistical analysis

The results are presented as the mean ± standard error of the mean (SEM) for each group, with a sample size of n = 5. Statistical analysis was performed via one-way analysis of variance (ANOVA). A Duncan multiple range post hoc test (DMRT) was subsequently applied for comparisons where the p-value was less than 0.05. All the statistical computations were carried out via GraphPad version 8.0 software (GraphPad Software, Inc., San Diego, California, USA).

3. Results

3.1. In vitro studies of Erythrophyleum suaveolens

Fig. 1 shows that *E. suaveolens* stem bark methanolic extracts displayed a concentration-dependent reduction in DPPH radical scavenging activity at relatively high concentrations. Ascorbic acid, however, followed the opposite trend, whereby its ability to scavenge DPPH radicals was elevated at higher concentrations. The reducing power of the *E. suaveolens* methanolic extract was concentration-dependent. The free radical quenching property of the extract could be the cause of its reducing power. Compared with ascorbic acid, methanolic extracts of *E. suaveolens* stem bark inhibited hydroxyl radical activity in a dose-dependent manner. Fig. 1 shows that the chelating activity of the methanolic extracts of *E. suaveolens* stem bark decreased with increasing concentrations from 20 to 30 mg/ml.

3.2. Effects of Erythrophyleum suaveolens on biochemical parameters in streptozotocin-induced diabetic rats

3.2.1. Fasting blood glucose

Fig. 2 depicts the influence of oral administration of the methanolic extract of *Erythrophylem suaveolens* on fasting blood glucose levels in streptozotocin-induced type II diabetic rats. Notably, within 48 h after STZ injection, male Wistar rats developed fasting blood sugar levels above 250 mg/dL. A significant reduction in fasting blood glucose content was subsequently observed after MEESS treatment.

3.3. Body weight and organ body weight

Owing to the administration of STZ, the experimental animals presented a noticeable decrease in body weight (Fig. 3). The body weights of the rats changed after they were treated with MEESS at doses ranging from 150 to 300 body weights (Fig. 3), and the changes were dose dependent.

3.4. Hepatic lipid peroxidation level of diabetic rats treated with the methanolic extract of E. suaveolens

As presented in Table 1, the administration of metformin and the methanolic stem bark extract of *E. suaveolens* to diabetic rats resulted in a decrease in lipid peroxidation.

3.5. Hepatic antioxidant activity of diabetic rats treated with the methanolic extract of E. suaveolens

As shown in Table 1, the levels of superoxide dismutase (SOD), catalase (CAT), and glutathione (GSH) increased in the treated animals, indicating a notable difference compared with those in the untreated diabetic controls.

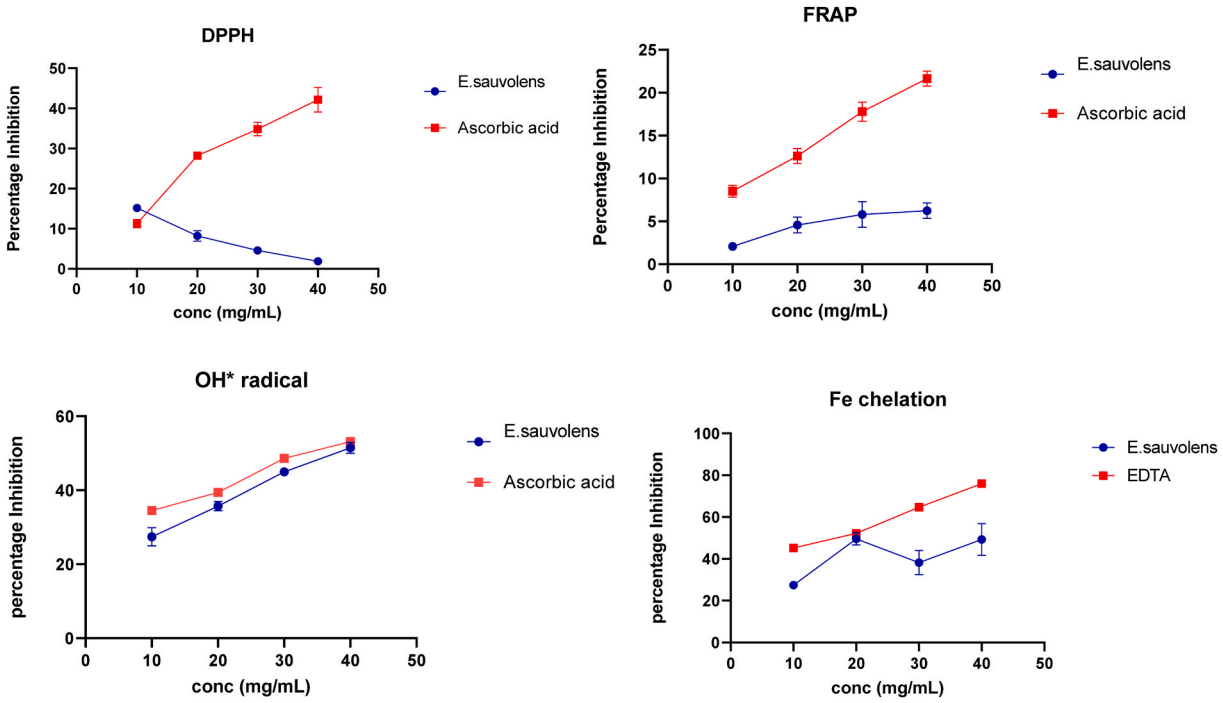

Fig. 1. In vitro radical scavenging ability the methanolic extract of *E. suaveolens*. a) Ferric reducing antioxidant properties (FRAP), b) 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging ability, c) hydroxyl radical scavenging ability (OH), and d) Iron-chelation (Fe) Legend: Values represent the means ± SDs of triplicates measurements.

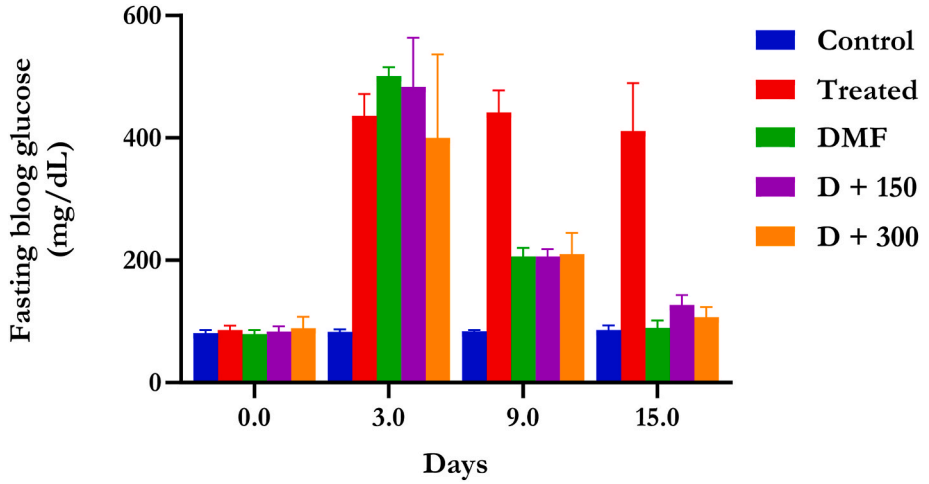

Fig. 2. Impact of orally administered *Erythrophyleum suaveolens* methanolic extract on fasting blood glucose concentrations. Legend: The values are presented as the means ± SEMs (n = 5). DMF: diabetic metformin group; D + 150 ES mg/kg: diabetic animals treated with 150 mg/kg E. *suaveolens*; D + 300 ES mg/kg: diabetic animals treated with 300 mg/kg E. *suaveolens*.

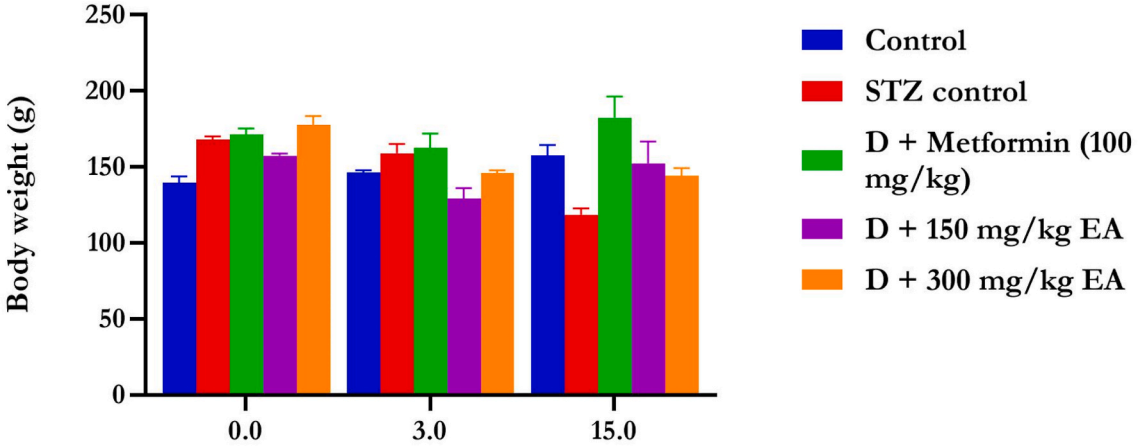

Fig. 3. Impact of orally administered *Erythrophyleum suaveolens* methanolic extract on the body weight of streptozotocin-induced diabetic rats.Legend: The data are expressed as the means ± SEMs of days 0, 3, 15, and 21.

Table 1
Effects of orally administered MEESS on liver antioxidant markers in streptozotocin-induced diabetic rats.

Parameters			
Groups	Malondialdehyde (nmol/l)	Superoxide dismutase (U/mg protein)	Reduced glutathione (g/mg protein)
Control	2.04 ± 0.84 [a]	2.22 ± 0.14[a]	93.47 ± 3.03 [a]
Diabetic Untreated	3.63 ± 0.00 [b]	1.20 ± 0.04 [b]	66.54 ± 0.92 [b]
Diabetics + Metformin	1.15 ± 0.00 [a]	2.19 ± 0.18 [a]	89.8 ± 14.06 [a]
Diabetics + MEESS (150 mg/kg)	1.53 ± 0.68 [a]	2.50 ± 0.22 [a]	79.32 ± 13.33 [c]
Diabetics + MEESS (300 mg/kg)	1.31 ± 0.30 [a]	2.00 ± 0.15 [a]	109.19 ± 9.56 [a,d]

The values are given as the means ± SEMs (n = 5). [a-b] Values in a single column for a single particular parameter signify that values are significantly different ($P < 0.05$) from one other. a indicates a significant difference at $p < 0.05$ compared with the normal control; b indicates a significant difference at $p < 0.05$ compared with the diabetic control.
*__MEESS:__ Methanolic extract of *E. suaveolens* leaves.

3.6. Hepatic biomarkers in diabetic rats treated with the methanolic extract of Erythrophleum suaveolens

Table 2 clearly shows that diabetic rats presented elevated serum levels of aspartate aminotransferase (AST), alanine transaminase (ALT), and alkaline phosphatase (ALP). In contrast, diabetic rats that received MEESS and metformin treatment presented significantly lower levels of these hepatic function indicators (AST, ALT, and ALP) than did their untreated diabetic counterparts.

3.7. Serum lipid profile and atherogenic index of diabetic rats treated with a methanolic extract of E. suaveolens stem bark

Table 3 presents a summary of the lipid profiles, which include total cholesterol (TC), triglyceride (TG), low-density lipoprotein (LDL), very low-density lipoprotein (VLDL), the atherogenic index (AI), and the coronary artery index (CRI), in untreated diabetic rats. The untreated subjects presented increased levels of these markers along with a decrease in high-density lipoprotein (HDL) levels. In contrast, diabetic rats that received treatment with metformin and the methanolic extract of *E. suaveolens* (MEESS) presented significantly elevated HDL levels compared with those in the untreated group. Additionally, combined treatment with metformin and MEESS resulted in a significant decrease

Table 2
Streptozotocin-induced diabetic rat liver function parameters following oral dosing of the methanolic extract of *Erythrophyleum suaveolens* stem bark.

Parameters			
Groups	Aspartate aminotransferase (IU/L)	Alanine aminotransferase (U/L)	Alkaline phosphatase (U/L)
Control	40.29 ± 3.97 [a]	21.66 ± 2.31[a]	14.30 ± 1.59 [a]
Diabetic Untreated	64.18 ± 5.89 [b]	37.29 ± 1.63 [b]	25.52 ± 2.35 [b]
Diabetics + Metformin	31.57 ± 5.64 [a]	25.19 ± 2.29 [a]	19.30 ± 3.27 [a]
Diabetics + MEESS (150 mg/kg)	31.12 ± 6.07 [a]	29.45 ± 3.04 [a]	15.95 ± 0.52 [a]
Diabetics + MEESS (300 mg/kg)	37.48 ± 0.45 [a]	18.21 ± 6.49 [a,c]	17.16 ± 0.34 [a]

The results are presented as the means ± SEMs (n = 5). [a-b]Values within a column for a particular parameter represent values that are significantly different (P < 0.05) from one another. a indicates a significant difference at p < 0.05 compared with the normal control; b indicates a significant difference at p < 0.05 compared with the diabetic control.
*__MEESS:__ Methanolic extract of *E. suaveolens* leaves.

in lipid profile parameters measured among diabetic rats.

3.8. Hepatic carbohydrate-metabolizing enzyme activities in diabetic rats

Table 4 presents the differences in hexokinase and glucose-6-phosphatase activity between the control group and the diabetic animals. Notably, compared with control rats, diabetic rats induced with STZ presented a decrease in hexokinase activity and an increase in glucose-6-phosphatase activity. On the other hand, treatment with MEESS and metformin resulted in an increase in hexokinase activity and a decrease in glucose-6-phosphatase activity in diabetic rats. The changes in enzyme activity were more pronounced in the rats that received MEESS treatment.

3.9. Modulation of the Keap1/Nrf2, PPAR-γ, and PTP1B signaling pathways by Erythrophylem suaveolens methanolic extract

Compared with nondiabetic control rats, diabetic control rats presented significantly lower liver Nrf2 expression following STZ-induced diabetes (p < 0.05), as indicated in Fig. 4A. Compared with the diabetic control group, the metformin and MEESS treatment groups presented significantly greater Nrf2 gene expression in their livers (p < 0.05). The expression of the cellular stress sensor Keap1 is shown in Fig. 4B. In diabetic control mice, we observed notable upregulation of Keap1 mRNA. Metformin and MEESS treatment, however, caused diabetic rats to overexpress Keap1 in their livers. The expression of PPAR-γ, which is essential for maintaining stable glucose levels, is shown in Fig. 4C. The findings demonstrated that PPARγ gene expression was noticeably lower in diabetic control rats than in nondiabetic control rats (p < 0.05). However, when metformin and MEESS were administered, this gene was overexpressed. Fig. 4D shows the PTP1B expression levels in the diabetic rats' livers. Compared with diabetic control rats, nondiabetic control rats presented noticeably reduced PTP1B gene expression (p < 0.05). Interestingly, compared with the diabetic control group, the metformin and MEESS therapy groups presented a decrease in PTP1B expression (p < 0.05).

3.10. Impact of the methanolic extract of Erythrophylem suaveolens on NQO1

As depicted in Fig. 5, hepatic NQO1 mRNA levels were significantly

Table 4
Hepatic carbohydrate-metabolizing enzymes in diabetic rats.

Treatment groups	Glucose-6-phosphatase (μ mole phosphate liberated/min/mg protein)	Hexokinase (μ mole glucose-6-phosphate formed/min/mg protein)
Control	48.77 ± 2.24[a]	2.37 ± 0.23[a]
Diabetic Untreated	94.22 ± 1.12[b]	0.95 ± 0.02[b]
Diabetics + Metformin	44.79 ± 1.10 [a]	2.73 ± 0.24[a]
Diabetics + MEESS (150 mg/kg)	54.40 ± 4.53 [a]	2.41 ± 0.08[a]
Diabetics + MEESS (300 mg/kg)	45.13 ± 1.82 [a]	2.31 ± 0.00[a]

Legends: The values are given as the means ± SEMs (n = 5). [a-c]Values in a column with different letters for the same parameter are significantly different (P < 0.05) from one other. a indicates a significant difference at p < 0.05 compared with the normal control; b indicates a significant difference at p < 0.05 compared with the diabetic control.
*__MEESS:__ Methanolic extract of *E. suaveolens* stem bark.

Table 3
Lipid profiling of diabetic rats following oral administration of MEESS.

Parameters							
Groups	Total cholesterol (mmol/l)	High-density lipoprotein (mmol/l)	Triglycerides (mmol/l)	Very low-density lipoprotein (mmol/l)	Low density lipoprotein (mmol/l)	AI	CRI
Control	14.13 ± 0.12[a]	16.30 ± 0.90 [a]	7.69 ± 0.19 [a]	1.54 ± 0.02[a]	7.69 ± 0.11 [a]	0.15 ± 0.06[a]	0.87 ± 0.05 [a]
Diabetic Untreated	19.83 ± 1.97[b]	12.81 ± 0.75[b]	11.25 ± 1.15[b]	2.25 ± 0.23 [b]	11.25 ± 1.15 [b]	0.30 ± 0.08[b]	1.69 ± 0.19 [b]
Diabetics + Metformin	14.87 ± 0.13[a]	16.49 ± 0.12[a]	7.49 ± 0.28 [a]	1.50 ± 0.06 [a]	7.50 ± 0.28 [a]	0.11 ± 0.00[a]	0.90 ± 0.00 [a]
Diabetics + MEESS (150 mg/kg)	13.69 ± 0.59[a]	15.57 ± 0.69[a]	6.30 ± 0.50 [a]	1.26 ± 0.10 [a]	6.29 ± 0.50 [a]	0.14 ± 0.07[b]	0.88 ± 0.05 [a]
Diabetics + MEESS (300 mg/kg)	13.60 ± 0.90[b]	15.07 ± 1.39[a]	6.36 ± 0.57 [a]	1.27 ± 0.11[a]	4.97 ± 1.96 [a,c]	0.02 ± 0.15[b]	1.07 ± 0.30 [a]

The values are given as the means ± SEMs (n = 5). [a-b]Values within one column for one parameter are significantly different (P < 0.05). a indicates a significant difference at p < 0.05 compared with the normal control; b indicates a significant difference at p < 0.05 compared with the diabetic control.
Legends.
AI (atherogenic index): This index is derived from the ratio of the difference between total cholesterol and high-density lipoprotein-cholesterol to high-density lipoprotein-cholesterol [(TC - HDL-c)/HDL-c].
CRI (coronary risk index): Calculated as the ratio of total cholesterol (in mg/dl) to high-density lipoprotein-cholesterol (in mg/dl) [TC (mg/dl)/HDL-c (mg/dl)].
MEESS: Methanolic extract of *E. suaveolens* leaves.

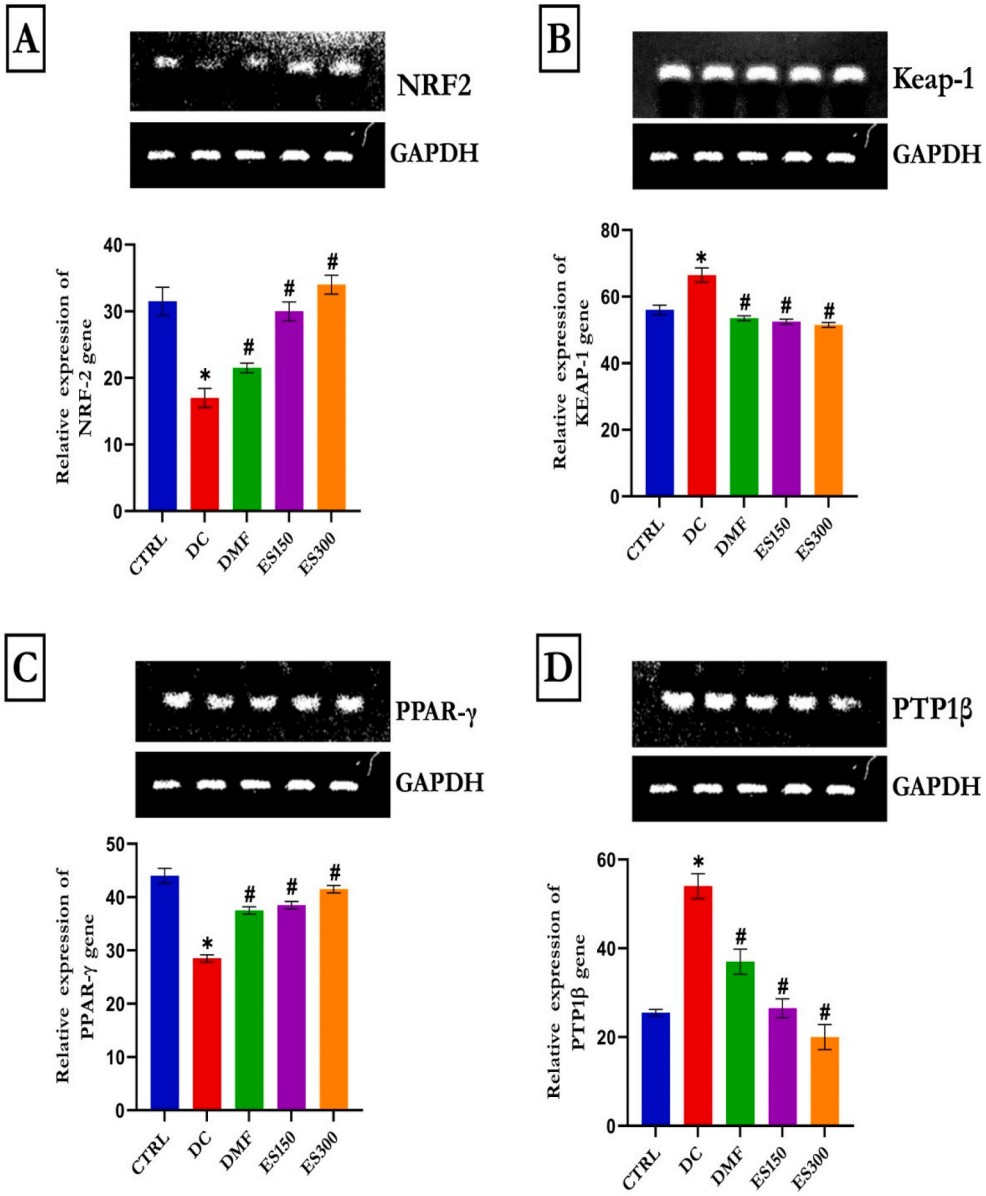

Fig. 4. Influence of *E. suaveolens* on hepatic gene expression in diabetic rats. Panels display the relative expression of (A) Nrf2, (B) Keap1, (C) PPAR-γ, and (D) PTP1B. All the data are presented as the means ± SEMs for n = 5 animals per group. Statistical significance is denoted as *$p < 0.05$, indicating a significant difference in relation to control animals; #$p < 0.05$, indicating a significant difference with respect to diabetic control animals. GAPDH served as the loading control for normalization of gene expression.

Legends.
CTRL: Control group.
DC: Diabetic group (untreated diabetic).
DMF: Diabetic + metformin.
ES150: Diabetic +*E. suaveolens* stem bark at 150 mg/kg.
ES300: Diabetic +*E. suaveolens* stem bark at 300 mg/kg.

($p < 0.05$) decreased in diabetic rats. Conversely, treatment with metformin or MEESS notably ($p < 0.05$) increased NQO1 expression in the livers of diabetic animals.

3.11. *Influence of Erythrophyleum suaveolens on Caspase-3*

Fig. 6 shows a significant increase ($p < 0.05$) in caspase-3 levels in diabetic rats, indicative of increased apoptotic cell damage within the hepatic tissue. Notably, both the metformin and MEESS treatments substantially downregulated ($p < 0.05$) this increases in caspase-3 expression.

4. Discussion

Free radical production is strongly correlated with the onset of type II diabetes and its consequences; however, these reactions can be neutralized by the action of antioxidants (Volpe et al., 2018). To ascertain the antioxidant ability of MEESS in neutralizing reactive oxygen species, several *in vitro* parameters were measured. *The in vitro* parameters identified by MEESS were 1,1-diphenyl-2-picryl-hydrazyl (DPPH) scavenging activity, ferric reducing antioxidant power (FRAP), and hydroxyl scavenging radical capacity. The results revealed that MEESS has antioxidant activities that are dependent on the increase in the concentration of MEESS, with the exception of DPPH, which has the

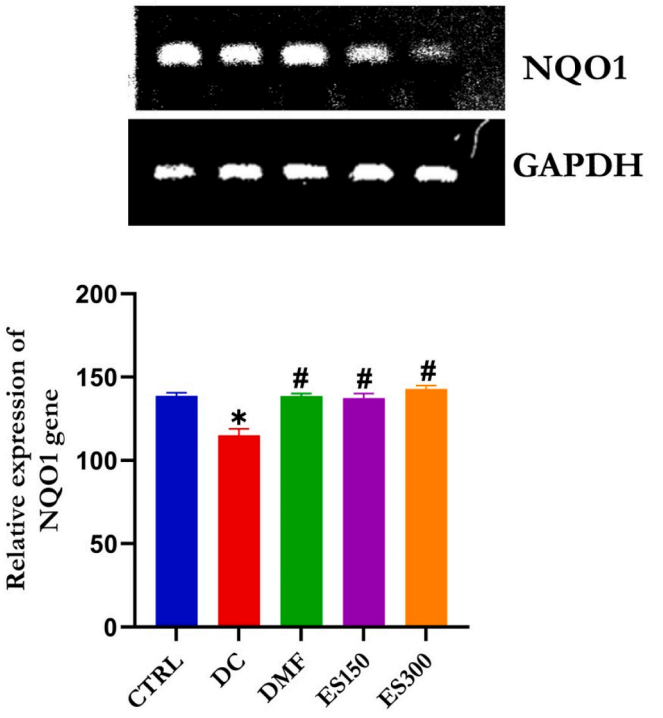

Fig. 5. Effects of *Erythrophyleum suaveolens* on NQO1 gene expression in the livers of diabetic rats.
All the data are presented as the means ± SEMs for n = 5 animals per group. Statistical significance is denoted as *p < 0.05, indicating a significant difference in relation to control animals; #p < 0.05, indicating a significant difference with respect to diabetic control animals. GAPDH served as the loading control for normalization of gene expression.
Legends.
CTRL: Control group.
DC: Diabetic group (untreated diabetic).
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opposite effect. The bioactive substances in plants provide MEESS with the capacity to scavenge free radicals. Our study is in agreement with previously published data (Bamidele, 2020).

The global increase in how often diabetes mellitus occurs has led to extensive research on the management of this endocrine disorder. Although there is currently no effective treatment for diabetes mellitus, diabetes mellitus can be treated with insulin, oral antidiabetic medications, or dietary changes (Kifle et al., 2022). Herbal plants possess potent antidiabetic properties with minimal side effects and are less paternalistic than typical allopathic medicines (Satyanarayana et al., 2022).

Fasting blood glucose serves as a diagnostic marker for type II diabetes mellitus (Wilson and Islam, 2012). Metformin, a widely used antidiabetic drug, enhances glucose and fatty acid processing (Yakubu et al., 2016; Ojo et al., 2022b). Our observations revealed elevated blood glucose levels 48 h after STZ induction, likely due to the selective cytotoxicity of STZ toward β-cells (Wilson and Islam, 2012). Interestingly, both MEESS (a methanolic extract of *Erythrophyleum suaveolens* stem bark) and metformin led to decreased serum glucose levels in diabetic animals. This reduction suggests that the medicinal properties of MEESS may involve secondary metabolites reported to have these properties. Furthermore, MEESS-induced glucose lowering may be linked to increased glucose uptake, which is supported by increased glycolysis (as evidenced by increased liver hexokinase activity) (Yakubu et al., 2016; Ojo et al., 2022b). This study revealed that MEESS has the ability to regulate blood glucose to some extent (Pratiwi et al., 2021).

Oxidative stress arises when the equilibrium between oxidant production and antioxidant defense mechanisms is disrupted (Singh et al., 2022). This imbalance is recognized as a prevalent pathophysiological factor in diabetes-related conditions, including retinopathy, nephropathy, cardiovascular alterations, and central nervous system disorders such as epileptic seizures (Panigrahy et al., 2017). Table 3 shows the liver antioxidant markers of streptozotocin-induced type II diabetic rats following oral treatment with the methanolic extract of the stem bark of *Erythrophylem suaveolens*. This finding indicates that the antioxidant activity present in MEESS is strong enough to inhibit free radicals. The level of MDA, a product of lipid peroxidation, was elevated in diabetic rats in the control group. However, after MEESS was administered orally, a different outcome was observed, as the MDA levels returned to a close range to those of Wistar rats in the control group. The antioxidative potential of *E. suaveolens* was demonstrated by the reduced levels of GSH in the liver of diabetic rats and its recovery in animals treated with metformin and MEESS (Ojo et al., 2024b). GSH levels in diabetic rats may decrease because hepatocytes frequently use GSH to reduce the generation of lipid peroxides after STZ treatment. The level of GSH drastically increased in diabetic rats after treatment with MEESS and metformin. Reports suggest that traditional plants exhibit potent antidiabetic properties, which ultimately results in decreased GSH conjugation (Ojo et al., 2024b). SOD and CAT are two main enzymes that neutralize free radicals, such as superoxide anions and hydrogen peroxide. SOD converts superoxide anions to hydrogen peroxides and water, and CAT then takes over by catalyzing the production of hydrogen peroxides, protecting liver tissues from hydroxyl radicals. After the induction of type II diabetes, we noted a decrease in SOD and CAT activities in the liver, probably due to the overproduction of free radicals in the hepatocytes of diabetic Wistar rats (Ojo et al., 2024b). After the oral administration of MEESS, there was a discernible increase in the activities of SOD and CAT in the liver, which was the reverse of the anticipated reaction. The phytochemical components of MEESS may have the ability to counteract oxidative stress-related damage, which could explain the increase in SOD and CAT activity in the liver (Chen et al., 2021; Bhatti et al., 2022).

Owing to compromised liver membrane integrity, these enzymes may leave the cytosol and enter the bloodstream (Lozano-Paniagua et al., 2021). In this study, the activities of serum AST, ALT, and ALP in the groups treated with metformin at low and high doses of MEESS were monitored. After MEESS was orally administered to streptozotocin-induced diabetic rats, we observed improvements in liver function. This increased the activity of some enzymes upon the induction of type II diabetes via STZ, particularly in comparison with the diabetic untreated group. Leaching of these enzymes into the blood of diabetic rats could be responsible for the increase in serum AST, ALT, and ALP activity, which also highlights the adverse effects of STZ on the livers of the test animals (Ojo et al., 2024b).

Andonova et al. (2023) reported that streptozotocin-induced type 2 diabetes mellitus (T2DM) in fructose-fed rats is associated with elevated concentrations of triglycerides (TGs), total cholesterol (TC), low-density lipoprotein (LDL), and very low-density lipoprotein (VLDL) concurrently with reduced levels of high-density lipoprotein (HDL). It is evident from this experiment that the changes in the lipid profile are due to dyslipidemia. With the induction of type II diabetes, HDL-c levels are seen to decrease, possibly because of a deficiency of the enzyme lecithin cholesterol acyltransferase (Ojo and Yakubu, 2024). In the transportation of cholesterol, HDL-C prevents atherosclerosis complications, thereby preventing the oxidative damage caused by LDL-C. The concentrations of VLDL-C and HDL-C are inversely correlated, and a significant increase in LDL-C and VLDL-C can result in a decrease in HDL-C (Ojo and Yakubu, 2024). Hypertriglyceridemia was also detected in the serum of diabetic rats. The levels of total cholesterol and triglycerides are markers used for determining lipid metabolism in the liver. The administration of MEESS decreased the levels of TC, TG, and LDL-C while elevating the levels of HDL-C, which signifies that MEEL can not only increase lipid metabolism in the liver but also reverse dyslipidemia.

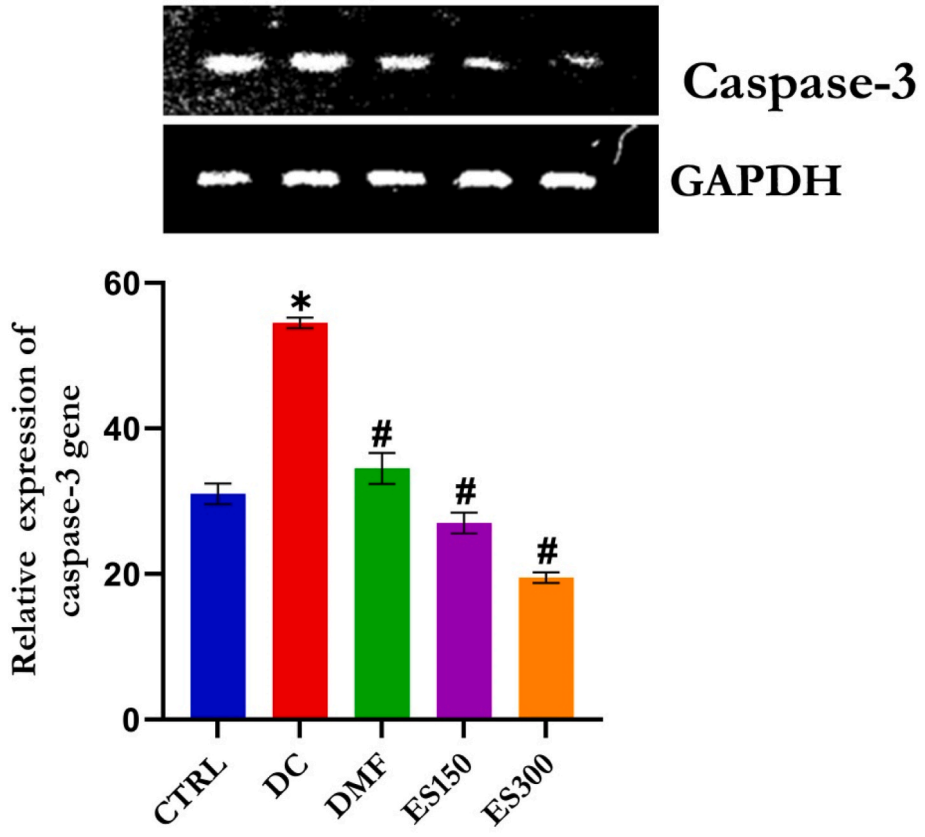

Fig. 6. Influence of Erythrophyleum suaveolens on the gene expression levels of caspase 3 in the liver of diabetic rats.
All the data are presented as the means ± SEMs for n = 5 animals per group. Statistical significance is denoted as *p < 0.05, indicating a significant difference in relation to control animals; #p < 0.05, indicating a significant difference with respect to diabetic control animals. GAPDH served as the loading control for normalization of gene expression.
Legends.
CTRL: Control group.
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The AI and CRI have been reported to be reliable indicators of atherosclerosis and predictors of CVD (Raaj et al., 2024). The amelioration of resistance to insulin could be associated with obvious decreases in the levels of AI and CRI in groups treated with metformin and MEESS (Ojuade et al., 2021).

These key carbohydrate-metabolizing enzymes were also examined in the current research. In the present study, significant decreases in the activity of hexokinase and increases in the activity of glucose-6-phosphatase were observed following the induction of type II diabetes mellitus in male Wistar rats with STZ. The reduction in the activity of hexokinase might be due to the oxidative damage induced by free radicals, which are also known to degrade protein and metabolize enzymes in liver tissues, a condition that may also be responsible for the increase in glucose-6-phosphatase activity (Abdella et al., 2024). This result was overturned in the metformin- and MEESS-treated groups. MEESS appears to stimulate glycolysis and inhibit gluconeogenesis in diabetes mellitus, as evidenced by the notable increases in hexokinase activity and decreases in glucose-6-phosphatase activity observed in STZ-induced diabetic rats. This restoration of hepatic enzyme activity following MEESS treatment in diabetic rats may be attributed to the antidiabetic properties of *E. suaveolens*.

The development of liver injury in diabetic patients is caused mostly by metabolic abnormalities and oxidative stress resulting from hyperglycemia (Ojo et al., 2024b). Therefore, our study examined how MEESS can act as an antioxidant in diabetes by influencing the Keap1/Nrf2/ARE antioxidant pathway. The Keap1/Nrf2 system is essential for cellular defense mechanisms during diabetes, as demonstrated by animal model studies (Yagishita et al., 2014; Elekofehinti et al., 2021). A significant reduction in Nrf2 expression was observed in the livers of diabetic rats, which is consistent with previous findings (Osorio et al., 2014; Wang et al., 2015; Elekofehinti et al., 2021). This decrease in Nrf2 activity under diabetic conditions highlights its potential role in the pathogenesis of diabetes-related complications. The specific mechanism responsible for the deregulation of Nrf2 in diabetes patients is not yet fully understood. Nevertheless, treatments that increase the production of Nrf2 mRNA could help reduce oxidative damage. In contrast, diabetic rats presented increased levels of Keap1, which is a negative regulator. This finding indicates a more pronounced interaction between Nrf2 and Keap1, resulting in reduced translocation of Nrf2 to the nucleus and therefore decreased activation of antioxidant genes (Padiya et al., 2014). The results of our investigation align with the conclusions of other studies conducted by Osorio et al. (2014), Wang et al. (2015), and Elekofehinti et al. (2021). The antioxidant effectiveness of MEESS was shown by the increased movement of Nrf2 into the cell nucleus and the reduced expression of Keap1 mRNA in diabetic rats caused by streptozotocin.

Under normal physiological conditions, Nrf2 resides in the cytoplasm, where it is complexed with Keap1. This interaction prevents Nrf2

translocation to the nucleus, thereby inhibiting its binding to the antioxidant response element (ARE) and the subsequent transcriptional activation of antioxidant genes such as NQO1 and HO-1 (Li et al., 2014). In contrast, our investigation revealed a significant reduction in NQO1 mRNA levels, coupled with notable increases in both Keap1 mRNA and Nrf2 protein levels in the livers of diabetic rats. Nonetheless, the coadministration of MEESS and metformin in diabetic rats successfully suppressed the expression of these genes, thus protecting the liver from oxidative injury on the basis of their antioxidant activities (Ojo et al., 2024b).

In streptozotocin (STZ)-induced diabetic rats, notable increases in protein tyrosine phosphatase 1B (PTP1B) levels were observed. PTP1B is recognized as a pivotal phosphatase within the insulin signaling cascade that directly dephosphorylates insulin receptors (IRs) and insulin receptor substrate 1 (IRS-1), thereby negatively regulating insulin signaling. The resulting impairment in insulin action contributes to the characteristic hyperglycemia observed in diabetes (Kołodziej-Sobczak et al., 2024). Our findings demonstrated a significant reduction in blood glucose levels following the administration of MEESS. Furthermore, RT–PCR analysis revealed significant downregulation of PTP1B expression in diabetic rats treated with MEESS. Such a reduction in PTP1B is anticipated to increase insulin sensitivity and improve glucose-stimulated insulin secretion, consequently leading to a substantial decrease in blood glucose concentrations.

Peroxisome proliferator-activated receptor gamma (PPARγ) plays a crucial role in regulating lipid and carbohydrate metabolism, and its expression or activity is typically diminished in diabetic tissues (Małodobra-Mazur et al., 2024). Diabetic rats that received MEESS or metformin presented notable increases in PPARγ levels in their liver tissue. These findings indicate that PPARγ is essential for the physiological changes observed in diabetic liver tissues.

Our work revealed that rats with STZ-induced diabetes presented increased expression of the liver caspase-3 gene. These findings support the findings of prior studies suggesting that STZ effectively triggers apoptosis by activating caspase-3. The initiation of diabetes is commonly attributed to apoptosis, which is considered a key causative mechanism for diabetes mellitus (Lu et al., 2024). The cysteine protease caspase-3 is a crucial regulator of apoptosis that has been extensively researched and shown to be increased under diabetic conditions (Mustafa et al., 2024). Our findings revealed a relationship between STZ-induced diabetes and the expression of caspase-3. Compared with control rats, MEESS-treated rats presented notable decreases in caspase-3 activity in their liver cells. These findings suggest that MEESS helps protect against diabetic liver damage by inhibiting caspase-3.

Although the results of the present study provide important information regarding the regulation of the Nrf2/Keap1 signaling pathway by MEESS, several limitations should be noted. In particular, the expression of genes was analyzed by semiquantitative RT–PCR and densitometric analysis. Although this approach can clearly show the orientation of changes in mRNA expression levels, it is not as sensitive as real-time quantitative PCR (RT–qPCR). Future studies using RT–qPCR would be helpful to offer even more accurate information regarding these molecular markers. Furthermore, despite the promising findings of this study, certain limitations should be acknowledged. First, comprehensive phytochemical characterization of the extract (including quantification of total phenolics, flavonoids, or chromatographic fingerprinting) was not performed. As a result, the specific bioactive constituents responsible for the observed effects could not be identified or correlated directly with the biological outcomes. Future studies incorporating detailed phytochemical profiling will be important for establishing a clearer relationship between chemical composition and pharmacological activity.

Second, although no overt signs of toxicity were observed during the experimental period, detailed toxicological evaluation including assessment of renal function markers and histopathological analysis was not conducted. This is particularly relevant given that *E. suaveolens* is reported to contain bioactive alkaloids with potentially toxic properties. Therefore, further investigations are warranted to comprehensively evaluate the safety profile of the extract through biochemical and histological analyses. Addressing these aspects in future studies will strengthen the mechanistic understanding and safety validation of the extract.

5. Conclusion

This study investigated the effects of the methanolic extract of *Erythrophleum suaveolens* stem bark (MEESS) on metabolic disturbances, oxidative stress, and key molecular pathways associated with diabetes in an experimental rat model. The findings demonstrated that MEESS significantly improved hyperglycemia, dyslipidemia, and oxidative stress. In addition, MEESS modulated critical signaling pathways, including Keap1/Nrf2, PPAR-γ, and PTP1B, and enhanced the expression of antioxidant enzymes such as NQO1 while reducing apoptotic activity, as evidenced by decreased caspase-3 levels. These results highlight the extract's multifaceted antidiabetic, antihyperlipidemic, antioxidative, and anti-apoptotic properties, suggesting its potential as a promising therapeutic agent for diabetes mellitus.

However, this study has certain limitations. The findings are based on an animal model and may not fully translate to humans. Furthermore, although key molecular pathways were assessed, detailed mechanistic interactions were not fully elucidated, and histopathological analysis was not performed to confirm tissue-level effects. Future studies should focus on comprehensive mechanistic investigations, including pathway-specific interventions, long-term safety evaluations, histological assessments, and clinical studies to validate the therapeutic potential of MEESS in humans.

CRediT authorship contribution statement

Oluwafemi Adeleke Ojo: Writing – review & editing, Validation, Supervision, Methodology, Data curation, Conceptualization. **Pearl Ifunanya Nwafor-Ezeh:** Writing – original draft, Validation, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation. **Adebola Busola Ojo:** Writing – review & editing, Writing – original draft, Visualization, Resources, Methodology, Data curation. **Damilare Emmanuel Rotimi:** Writing – original draft, Visualization, Software, Methodology. **Akingbolabo Daniel Ogunlakin:** Visualization, Resources, Methodology. **Clinton Ayodeji Akanbi:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Methodology. **Peter Tolulope Adeyemi:** Visualization, Methodology, Investigation, Formal analysis. **Olorunfemi Raphael Molehin:** Writing – review & editing, Visualization, Validation, Project administration.

Consent to publish

Not applicable.

Ethics approval and consent to participate

The experimental protocols received approval from the Department of Biochemistry, Bowen University Animal Ethics Committee (BUAC/BCH/2023/0004A). All animal procedures adhered to the guidelines outlined in NIH publication #85-23 (revised 1985) from the United States, and reporting was conducted in accordance with the ARRIVE guidelines.

Data statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Clinical trial numbers

Not applicable.

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None received.

Declaration of competing interest

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

Abbreviations

ARE	Antioxidant responsive element
CAT	catalase
DM	Diabetes mellitus
G6 Pase	glucose-6-phosphatase
GSH	reduced glutathione
Keap-1	Kelch-like ECH-associated protein 1
MDA	malondialdehyde
MEESS	methanolic extract of *Erythrophyleum suaveolens* stem
MET	Metformin

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.kjs.2026.100594.

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