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Euphorbia ammak leaf extract mitigates hyperglycemia in STZ-induced type 2 diabetic mouse model

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ABSTRACT

Euphorbia species have been employed to treat conditions such as cancer and headaches, exhibiting pharmacological properties that include antiviral, anticancer, antimicrobial, and antifungal effects. This research evaluates the ameliorative effects of different *Euphorbia ammak* extract (EAE) concentrations against hyperglycemia in the streptozotocin-induced type 2 diabetic mouse model. Thirty-six male mice were randomly allocated to six groups (n=6). The experiment consisted of six experimental groups: Group 1 was the normal control; Group 2 was the diabetic control; Group 3 was diabetic mice with a low dose of EAE treatment; Group 4 was diabetic mice with a high dose of EAE treatment; Group 5 was normal mice with a low dose of EAE treatment; and Group 6 was normal mice with a high dose of EAE treatment. EAE was administered via gavage for 21 days post-STZ injection. Blood samples were used for different biochemical tests, such as measurements of insulin levels and serum lipid profiles. Diabetic control mice showed significant increases in blood glucose, triglycerides (TGs), serum total cholesterol (TC), very-low-density lipoprotein cholesterol (VLDL-C), low-density lipoprotein cholesterol (LDL-C), and decreases in high-density lipoprotein cholesterol (HDL-C). Treatment with EAE significantly reduced fasting blood glucose, TGs, serum TC, VLDL, LDL-C. Meanwhile, EAE-treated groups approached normal levels for serum insulin and HDL-C. The results indicate that EAE oral administration may have amelioratory effects against deleterious hyperglycemic and hyperlipidemic manifestations of diabetes mellitus.

1. Introduction

Chronic hyperglycemia is a metabolic condition defined by inadequate secretion of insulin, diminished insulin action, or a combination of both, resulting in significant metabolic disturbances, particularly affecting adipose tissue, skeletal muscles, and the liver. Insulin, recognised as an anabolic hormone, is essential for metabolising carbohydrates, lipids, and proteins [1]. The manifestation of diabetes symptoms can differ widely depending on the type and duration of the condition. For instance, children diagnosed with Type 1 diabetes mellitus (T1DM) may exhibit symptoms such as increased appetite, excessive thirst (polydipsia), weight loss, and visual disturbances. In contrast, individuals having Type 2 diabetes mellitus (T2DM) may remain asymptomatic at the early stages [2]. Whenever left unmanaged, uncontrolled diabetes can lead to severe complications, including coma and, in rare instances, death due to ketoacidosis or hyperosmolar syndrome [1].

T2DM primarily stems from defective insulin secretion, where the production of insulin fails to meet the demands created by insulin resistance. The disposition index, which indicates the relationship between insulin sensitivity and secretion, is frequently low in T2DM patients, reflecting an inadequate capacity to enhance insulin production. This condition is characterised by a high proinsulin to insulin ratio and reduced insulin responses to stimuli [3, 4]. Over time, hyperglycemia exacerbates as β-cell function deteriorates, often remaining undetected for years before diagnosis [5].

The plasma lipid profile, which consists of triglycerides (TG), very-low-density lipoprotein cholesterol (VLDL-C), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and total cholesterol (TC), is a significant component of the pathophysiologic mechanisms of type 2 diabetes mellitus (T2DM) [6]. In an earlier report, Imran *et al.* [7] found that patients with diabetes have markedly elevated levels of TG, TC, VLDL-C, and LDL-C, but lower levels of HDL-C in comparison to healthy individuals. Elevated TC, mainly due to elevated LDL-C, is linked with atherosclerosis

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and CVD in patients with T2DM [8]. High TG levels correlate with insulin resistance and heightened CVD risk [9, 10]. Elevated VLDL-C, a precursor to LDL-C, also increases CVD risk, while low HDL-C levels contribute to dyslipidemia and elevated CVD risk in T2DM patients.

Euphorbia is a diverse genus comprising nearly 2,000 species within the Euphorbiaceae family [11]. Historically, various Euphorbia species have been employed to treat conditions such as cancer and headaches, exhibiting pharmacological properties that include antiviral, anticancer, antimicrobial, and antifungal effects [12]. For instance, *Euphorbia peplus* has been utilised in Australian folk medicine, leading to the development of the drug Picato® [13]. Moreover, *Euphorbia hirta* has demonstrated a significant antidiabetic activity in various studies [14]. Bioactive molecules such as euphol, which have demonstrated cytotoxic effects against human cervical adenocarcinoma (HeLa) cells, have been identified as a consequence of a recent study on *Euphorbia ammak* leaves [15, 16]. To our knowledge, it is the first study to investigate the therapeutic impact of *Euphorbia ammak* extract (EAE) on hyperglycemia and hyperlipidaemia in an animal model of diabetes caused by STZ.

2. Materials and Methods

2.1. Plant Materials and Extraction

Euphorbia ammak leaves were collected from the Faifa Mountains, Jazan, Saudi Arabia (lat. 17°15′0″N, long. 43°6′0″E) and authenticated at Jazan University Herbarium (JAZUH). Air-dried pulverised leaves (200 g) were extracted using ethanol (96%, 2 L) for 24 hours at 37°C. Concentration of the filtrate was done using the filtrate kept at 4°C after being concentrated in a rotary evaporator set at 40°C.

2.2. Compounds

All reagents employed in this investigation were of high analytical purity, and STZ was sourced from MP Biomedicals, LLC, located in Lllkirch, France.

2.3. Diabetes model

Diabetes was produced in mice following a 16-hour fast. Fresh STZ was initially mixed with citrate buffer (pH 4.5) and administered intraperitoneally at a dosage of 60 mg/kg [17]. Furman.[18] reported that polydipsia, polyuria, and blood glucose levels above 150 mg/dL three days after STZ injection proved diabetes. On the fourth day after STZ injection, treatment began for three weeks. To avoid hypoglycemia-related deaths, a 0.200 M glucose solution was given 24–48 hours after STZ injection [19].

2.4. Experimental Methodology and Animals

The Institutional Animal Care and Use Committee at Fayoum University (FU-IACUC) granted consent for the current study under approval number AEC 2330-a. Thirty-six male mice (eight weeks old) weighing between 20 and 25 grams were purchased from the National Research Centre in Giza, Egypt. Standard settings (25°C, 6010% humidity, 12/12 h light/dark cycle) and unrestricted access to food and water were used to acclimatise them for a week. After a 16-hour fast, STZ (60 mg/kg in 0.1 M citrate buffer) was injected intraperitoneally (i.p.) to start diabetes. Day 4 after STZ injection marked the start of treatment, which lasted for 21 days. The mice were indiscriminately divided into six groups (n=6 each): Group 1: Control (citrate buffer, 1 ml/kg, i.p.). Group 2: Diabetic control (STZ only, i.p.). Group 3: STZ + Low-dose *E. ammak* extract (LEAE, 250 mg/kg/day, orally). Group 4: STZ + High-dose *E. ammak* extract (HEAE, 400 mg/kg/day, orally). Group 5: LEAE (250 mg/kg/day, orally). Group 6: HEAE (400 mg/kg/day, orally).

2.5. Blood collection

At the end of the research, blood samples were gathered for analysis. To separate the serum, the samples were centrifuged at 2000 g for 15 minutes at 4 °C after being incubated for 30 minutes at room temperature. To analyse the lipid profile, the samples were stored at -80 °C. Before dissection, the male mice were anaesthetised using a combination of xylazine and ketamine to minimise pain and distress.

2.6. Biochemical Assessments

2.6.1. Glucose Levels

A validated and widely used point-of-care instrument known for its accuracy and reliability, the Accu-Chek glucometer (Roche Diagnostics, Germany), was employed for the determination of blood glucose levels.

2.6.2. Serum Insulin Levels

Insulin levels were assessed in sera using the Rat Insulin ELISA Kit (Crystal Chem, Catalog #90010), which employs a sandwich enzyme immunoassay. The assay was conducted following the manufacturer's protocol, having a dynamic range of 0.039–10 ng/mL and a sensitivity of 39 pg/mL. Briefly, 5 µL of serum was diluted with 95 µL of diluent, incubated overnight at 4°C, followed by sequential addition of conjugate and substrate solutions. Optical density was measured at 450/630 nm.

2.6.3. Lipid profile parameters

Serum TC and TGs levels were assessed utilising methodologies outlined by [20- 22], employing reagent kits from Biodiagnostic, Egypt. LDL-C and HDL-C were assessed utilising methodologies established [23- 26], with reagent kits sourced from SPINREACT, Spain. VLDL-C was calculated utilising the Friedewald equation [23], predicated on serum TG levels.

2.7. Statistical analysis

The study employed GraphPad Prism software (version 110) for statistical analysis. One-way analysis of variance (ANOVA) followed by Duncan's multiple range test was used to evaluate group differences. Results are presented as means ± standard error, and differences between groups were considered statistically significant at $P < 0.05$.

3. Results

3.1. Effect of EAE on glucose level

Table 1 reveals fasting glucose levels in various groups of mice across five distinct time points. The normal control group displayed stable glucose levels, starting at 84.25 ± 3.6 mg/dL on day 0 and reaching 75.78 ± 1.7 mg/dL by the 3rd week. Conversely, the STZ group experienced a substantial increase in glucose levels from 86.54 ± 2.6 mg/dL on day 0 to 197 ± 2.6 mg/dL by the 3rd week. Diabetic mice treated with LEAE and HEAE exhibited a progressive reduction in glucose levels. The STZ+LEAE group decreased from 186.7 ± 4.2 mg/dL at day 3 post-STZ to 107.15 ± 4.5 mg/dL by the 3rd week, while the STZ+HEAE group showed a decline from 188.4 ± 5 mg/dL at day 3 post-STZ to 127 ± 3.6 mg/dL by the 3rd week. Normal mice treated with low-dose (LEAE) and high-dose (HEAE) EAE exhibited minimal decreases in glucose levels, with LEAE group glucose levels ranging from 83.53 ± 4.

Table 1: Fasting blood sugar concentrations (mg/dL) in different groups

	Day zero	3-days post STZ	1st Week	2nd Week	3rd Week
Normal Control	84.25 ± 1.5^{a}	73.52 ± 1.2^{a}	74.66 ± 0.7^{a}	74.92 ± 0.7^{a}	75.78 ± 0.7^{a}
STZ	86.54 ± 1.1^{a}	185.45 ± 1.6^{b}	190.15 ± 0.7^{b}	191.15 ± 0.9^{b}	197 ± 1.1^{b}
STZ+LEAE	87.97 ± 0.8^{a}	186.7 ± 1.7^{b}	136.7 ± 10^{c}	120.25 ± 14^{c}	107.15 ± 19^{c}
STZ+HEAE	86.9 ± 0.9^{a}	188.4 ± 2^{b}	165.3 ± 4.6^{d}	149.1 ± 8.2^{d}	127 ± 15^{c}
LEAE	83.53 ± 1.7^{a}	89 ± 3.8^{a}	87.32 ± 3^{a}	85.17 ± 2.7^{a}	82.6 ± 1.8^{a}
HEAE	85.65 ± 1.5^{a}	88.97 ± 3.8^{a}	87.03 ± 3^{a}	84.45 ± 2.5^{a}	81.93 ± 1.7^{a}

Levels of glucose were measured in various animal cohorts and are expressed as mean ± SE (n=6). Results inside each column sharing the same superscript are not statistically significant; $P < 0.05$.

3.2. Effect of EAE on insulin level

Measurements of insulin levels between the various groups of animals were taken and are presented graphically in Figure 1 as mean ± SE. The normal control group had an insulin level of 2.53 ± 0.18. On the other hand, STZ injection led to a remarkable decline in insulin levels to 0.9 ± 0.2 compared to group 1 ($P < 0.01$). Treatment with the low dose of EAE increased insulin concentration in the STZ+LEAE group to 1.33 ± 0.12 compared to the STZ group, but lower than normal control animals. Meanwhile, the higher dose of EAE caused a significant increase in insulin to a value of 2.3 ± 0.23 in the STZ+HEAE group relative to the STZ group ($P < 0.01$), where values almost matched those in the normal control mice. The LEAE and HEAE groups showed insulin levels of 2.43 ± 0.15 and 2.27 ± 0.33, respectively, without significant differences compared to group 1.

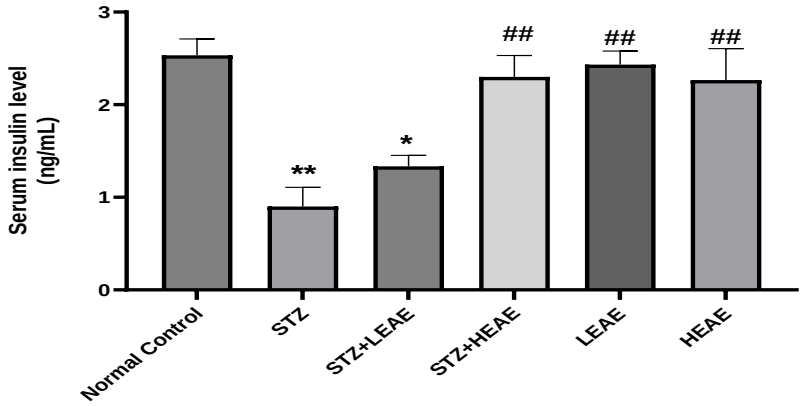

Fig. 1: Distribution of insulin levels across animal groups, post-STZ induction and treatment with EAE. Insulin levels across the different groups were quantified and reported as mean ± SE (n=6). *$P < 0.05$, **$P < 0.01$ relative to the normal control group; ##$P < 0.01$ relative to the STZ group.

3.3. Effect of EAE on serum lipid profile parameters

3.3.1. Serum cholesterol

Figure 2 presents the serum cholesterol levels across different groups of mice. The normal control had a mean of 102.3 ± 0.85 mg/dL. The STZ-induced diabetic group exhibited a notable elevation, with a mean of 178.8 ± 6.77 mg/dL in comparison to the control group ($P < 0.0001$).

Treatment with low-dose EAE (STZ+LEAE) resulted in a cholesterol level of 166.8 ± 3.33 mg/dL, not markedly different from the STZ group, and elevated compared to the normal control (P < 0.0001). Conversely, high-dose EAE (STZ+HEAE) resulted in a cholesterol level of 148.5 ± 4.13 mg/dL in diabetic mice, significantly lower than the STZ group (P < 0.001) but still higher than group 1 (P < 0.0001). Normal mice treated with low-dose (LEAE) and high-dose (HEAE) extracts had cholesterol levels of 100 ± 0.91 mg/dL and 97.25 ± 1.11 mg/dL, respectively, showing no remarkable difference from the normal control group.

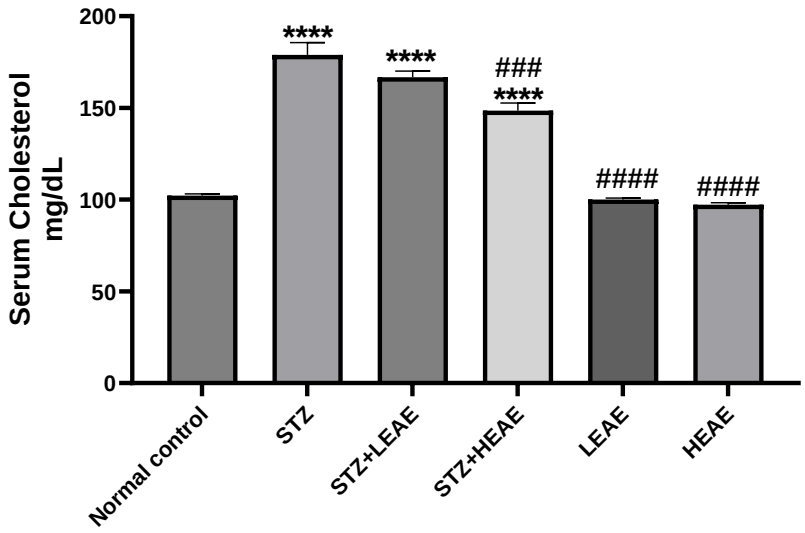

Fig. 2: The mean serum cholesterol levels in normal control, diabetic, and EAE-treated animals in mg/dL. Serum cholesterol concentrations were evaluated across all groups and are shown as mean ± SE. **** *P* < 0.0001 in comparison to the control group; ### *P* < 0.001, #### P < 0.0001 in comparison to the diabetes control group.

3.3.2. Serum TGs

Serum TGs levels across all animal groups (mean ± SE) are shown in Figure 3. The control group had a TGs level of 71.74 ± 4.35. The STZ group displayed significantly higher TGs levels of 145.5 ± 9.22 (*P* < 0.0001). In the STZ+LEAE and STZ+HEAE groups, TGs levels were 105.8 ± 7.05 and 96.32 ± 6.85, respectively, significantly lower than group 2 (P < 0.01 and P < 0.001, respectively). Only STZ+LEAE showed a substantial difference (*P* < 0.05) relative to the control cohort. LEAE and HEAE groups had TGs levels of 70.63 ± 4.74 and 69.75 ± 4.94, respectively, with no significant change compared to normal mice.

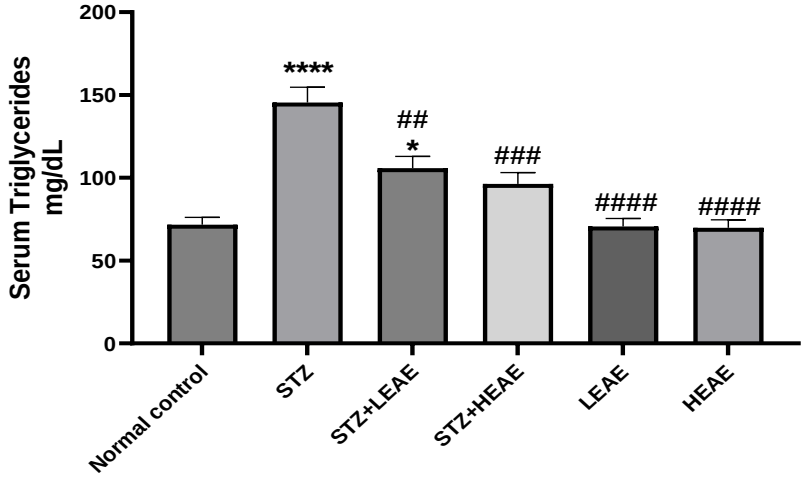

Fig. 3: Serum triglycerides (TGs) concentration levels in normal and diabetic control, EAE-treated diabetic mice, and EAE-treated normal groups in mg/dL. Serum TGs levels are reported as mean ± standard error (n=6). *P < 0.05, ****P < 0.0001 compared to the normal control group; ##P < 0.01, ###P < 0.001, ####P < 0.0001 compared to the STZ group.

3.3.3. LDLC levels

The LDL-C levels across all animal groups (mean ± SE) are shown in Figure 4. The normal control group had an LDL-C level of 44 ± 2.67. The STZ group exhibited significantly higher LDL-C levels of 80.88 ± 6 (P < 0.0001). In the STZ+LEAE and STZ+HEAE groups, LDL-C levels were 43.77 ± 1.87 and

59.07 ± 4.21, respectively, significantly lower than the STZ group (P < 0.05). Only the LEAE group showed a significant difference from the normal control group (P < 0.05). The LEAE and HEAE groups had LDL-C levels of 43.32 ± 2.91 and 42.78 ± 3.03, respectively, similar to the normal control group.

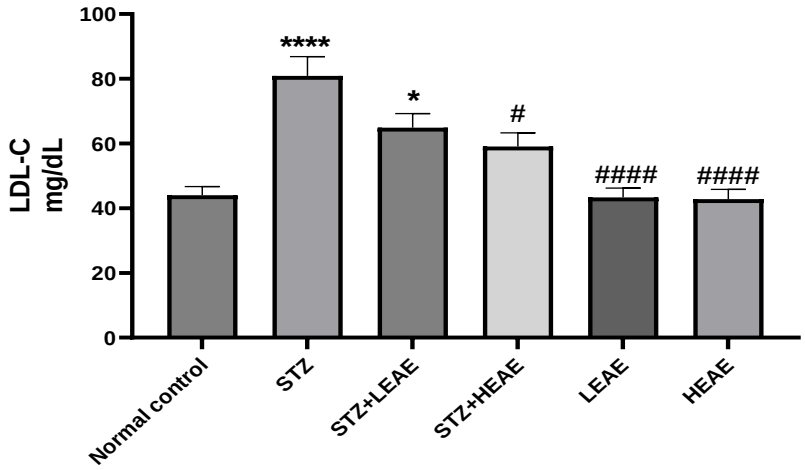

Fig. 4: LDL-C levels quantification in normal and diabetic control, EAE-administered diabetic mice, and EAE-administered normal mice in mg/dL. Serum LDL-C concentrations are expressed as mean ± SE (n=6). *P < 0.05, ****P < 0.0001 in comparison to normal mice, and #P < 0.05, ####P < 0.0001 in comparison to the diabetes control cohort.

3.3.4. HDL-C levels

HDL-C levels across all animal groups (mean ± SE) are presented in Figure 5. The normal control group had an HDL-C level of 24 ± 1.46. The STZ group showed a slightly lower HDL-C level of 21.53 ± 0.46. Treatment with low and high doses of EAE in the STZ+LEAE and STZ+HEAE groups resulted in HDL-C levels of 22.25 ± 0.23 and 24.83 ± 0.17 (P < 0.05), respectively, comparable to group 2. The LEAE and HEAE cohorts had HDL-C levels of 23.9 ± 0.64 and 23.88 ± 0.63, respectively.

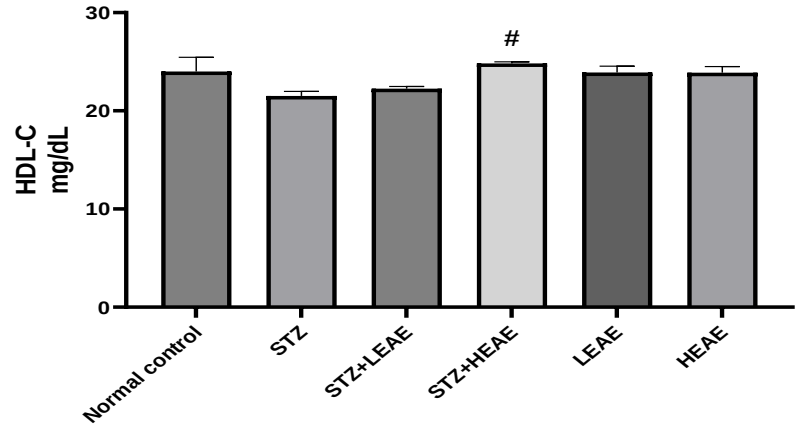

Fig. 5: HDL-C concentrations in normal and diabetic control, EAE-diabetic mice, and EAE-recipient healthy mice in mg/dL. Serum HDL-C levels are expressed as mean ± SE (n=6). #P < 0.05 compared to the diabetic group.

3.3.5. VLDL-C

The serum VLDL-C concentrations across different groups of mice (mean ± SE) are presented in Figure 6. The normal control group had a VLDL-C level of 14.39 ± 0.55 mg/dL. Diabetic mice induced with STZ showed a significant increase in VLDL-C levels, reaching 29.06 ± 1.16 mg/dL (P < 0.0001) compared to the normal cohort. Treatment with low-dose EAE significantly reduced VLDL-C levels to 14.12 ± 0.6 mg/dL (P < 0.0001), and high-dose EAE treatment also significantly reduced VLDL-C levels to 14.17 ± 0.66 mg/dL (P < 0.0001) relative to the diabetic group. Non-diabetic mice treated with low-dose EAE had a VLDL-C level of 21.42 ± 0.93 mg/dL, and those treated with high-dose EAE had a VLDL-C level of 19.04 ± 0.89 mg/Dl. Neither of them was significantly different from the healthy control group.

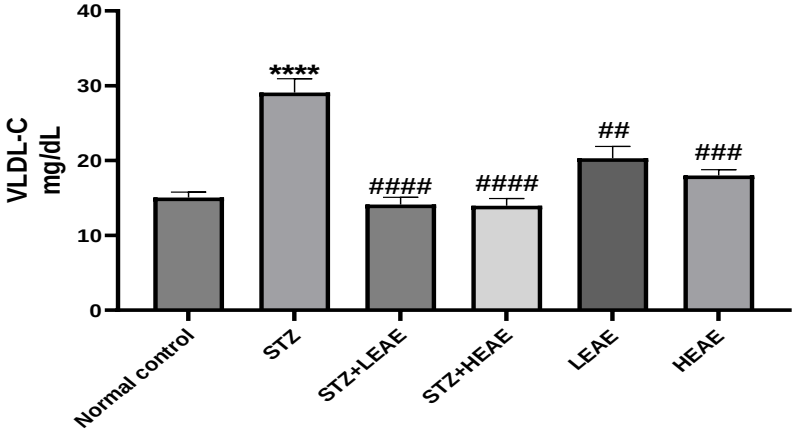

Fig. 6: VLDL-C concentrations in normal and diabetic control, EAE-treated diabetic mice, and EAE-treated healthy mice in mg/dL. The concentrations of serum LDL-cholesterol are given as mean ± SE (n=6). ##P < 0.01, ###P < 0.001, ####P < 0.0001 in comparison to the diabetic control group, and ****P < 0.0001 in comparison to the healthy control group.

4. Discussion

The current research explored the beneficial effects of EAE on STZ-induced T2DM in male mice. According to our findings, EAE significantly decreased the blood glucose levels of diabetic mice, indicating potent hypoglycemic and antidiabetic properties. Additionally, EAE improved insulin sensitivity and glucose tolerance. Furthermore, EAE positively influenced lipid profiles by reducing TGs, LDL-C, VLDL-C, and TC levels, while increasing HDL-C levels. We identified 41 bioactive compounds in the EAE (Unpublished). The most prominent components included o-Thymol, (E)-Phytol, n-Hexadecanoic acid, α-Linolenic acid, and Neophytadiene (Unpublished).

In our study, EAE-treated diabetic animals exhibited improved fasting blood glucose levels, dose-dependently. The hypoglycemic effects of EAE can be attributed to various key components, including caryophyllene, phytol, neophytadiene, stearic acid, and thymol. Al Kury et al. [27] documented that the daily intake of thymol, the primary constituent of EAE, over 35 days led to a significant lowering in blood glucose levels. Our findings regarding thymol's hypoglycemic properties align with previous research [28- 33]. Furthermore, studies have shown that caryophyllene [34], E-phytol [35], neophytadiene [36], and stearic acid [37] enhance glucose metabolism and insulin sensitivity. These compounds work synergistically, contributing to the hypoglycemic effects observed in EAE-treated diabetic animals.

Maintaining an adequate level of insulin in the bloodstream is essential for homeostasis, as insulin regulates blood glucose levels to ensure cells receive the required energy while preventing diabetes and hypoglycemia. Proper insulin activity is critical for metabolic balance, cellular function, and preventing the complications of diabetes [38]. STZ is widely utilized to induce diabetes models in laboratory animals due to its specific toxicity to β-cells. STZ is taken up by these cells via GLUT2, causing DNA necrosis and damage, leading to a significant loss in functional β-cells [39]. This destruction results in a substantial decline in insulin production and secretion, culminating in a hyperglycemic condition, wherein the body can no longer effectively regulate blood glucose levels [40].

The extent of β-cell damage and resultant insulin deficiency is dose-dependent. High doses of STZ typically lead to T1DM with almost complete loss of insulin production, whereas lower doses can induce a state resembling T2DM with insulin resistance and partial loss of insulin production [41]. In addition, STZ enhances oxidative stress, causing further β-cell damage and insulin deficiency [40].

In the present research, EAE-treated groups exhibited increased insulin levels in a dose-responsive manner, with the highest dose proving the most effective. Thus, higher doses of EAE may offer significant therapeutic benefits in managing diabetes by improving insulin secretion and overall glycemic control. The biologically active components of EAE, such as terpenes, phenolic compounds, flavonoids, fatty acids, and coumarins, play a vital role in enhancing insulin secretion and improving glycemic control. Furthermore, several studies have stated that thymol can improve insulin secretion and insulin sensitivity in diabetic subjects [42-44]. Notably, phytol, which constitutes a significant portion of EAE, has been reported to possess antihyperglycemic effects and can augment insulin secretion and sensitivity in T2DM [35, 45, 46]. Elmazar et al. [47] demonstrated that phytol exerts antidiabetic and insulin-sensitising effects in STZ-induced diabetic rats. The conversion of phytol into phytanic acid involves oxidation to its aldehyde and further oxidation to phytanic acid [48]. The antidiabetic effects of phytol and phytanic acid are mediated through the activation of nuclear receptors and modulation of biochemical parameters. Phytanic acid binds to PPAR-γ, mimicking the binding mode of antidiabetic drugs like rosiglitazone, and also shows a high affinity for retinoid X receptor alpha (RXRα), enhancing PPAR-γ activity [47]. Hence, the availability of these compounds improves glucose homeostasis, lowers blood glucose levels, and enhances insulin sensitivity.

Furthermore, EAE treatment in diabetic mice decreased elevated levels of LDL, TGs, TC, and VLDL, while HDL levels were higher compared to the STZ-treated group. Lipid profiles, including LDL-C, and lipid ratios, such as the LDL-C/HDL-C, are indicators of glycemic status in T2DM patients. Higher lipid profile factors (TC, LDL-C) and higher lipid ratios (TC/HDL-C, TGs/HDL-C, LDL-C/HDL-C ratio), along with lower HDL-C, are typically found in groups with poor glycemic control [49]. The reductions in cholesterol and TG concentrations observed in this study due to EAE administration may help prevent the onset and development of diabetic complications and improve lipid metabolism. This advantage has been previously linked to the reduction of cholesterol and TG levels in animals [50]. A possible mechanism for regulating the lipid profile in diabetic mice treated with EAE could be the antioxidant activity of the extract's biologically active constituents, which delay lipid peroxidation (LPO) by scavenging free radicals [51].

5. Conclusions

This study proved the hypoglycemic and antidiabetic properties of EAE by significantly lowering blood glucose levels, improving insulin sensitivity, enhancing glucose tolerance, and modulating lipid metabolism in diabetic mice. These beneficial effects can be attributed to the antioxidant properties of its phytochemical components, which mitigate lipid peroxidation and oxidative stress. Evaluating EAE's clinical potential in human subjects and future research on elucidating the precise molecular mechanisms underlying the antidiabetic effects are highly recommended. Evaluating EAE's clinical potential in human subjects.

Author Contributions

MSE, SMF, AMA, and MSM suggested the research point of the study and designed the experimental protocol. MSE, SMF, AMA, DSA, and MSM were involved in the implementation of the overall study, performed the statistical analyses of the study, researched the data, and wrote the manuscript. All authors contributed to the critical revision of the manuscript.

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.

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