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Anti-Hyperglycemic Role of Hydroethanolic Extract of Foeniculum Vulgare Seed on Diabetic Wistar Albino Rats

Feven Tigstu Ayele[1*], Winner Kucha Dewelle[2], Maria Degef Teklemariam[3], Gnanasekaran Natesan[3], Yonas Bekuretsion Abraham[4], Gelila Woredebrhan Mesfin[5], Chala Bashea Hailu[6], Solomon Genet Gebre[3]

[1]Department of Biomedical, Dire Dawa University, Dire Dawa, Ethiopia.
[2]Department of Clinical Chemistry, Haramaya University, Harar, Ethiopia.
[3]Department of Biochemistry, Addis Ababa University, Addis Ababa, Ethiopia.
[4]Department of Pathology, Addis Ababa University, Addis Ababa, Ethiopia.
[5]Biomedical Department, Dilla University, Dilla, Ethiopia.
[6]National Clinical Chemistry Reference Laboratory, Ethiopian Public Health Institute, Addis Ababa, Ethiopia.

Abstract

Objective: Foeniculum vulgare has been suggested as a potential option for the management of hyperglycemia. This study aimed to evaluate the anti-hyperglycemic effects of the hydro-ethanolic extract of Foeniculum vulgare seeds (HEEFVS) in alloxan-induced diabetic rats.

Materials and Methods: Thirty-six male rats were randomly divided into six groups (I–VI). Diabetes was induced by intraperitoneal injection of alloxan (175 mg/kg) in groups II–VI. Groups I and II received distilled water; groups III, IV, and V were treated with HEEFVS at doses of 100, 200, and 400 mg/kg body weight/day, respectively; and group VI received glibenclamide (5 mg/kg body weight/day). Serum glucose, total cholesterol (TC), triglycerides (TG), aspartate transaminase (AST), alanine transaminase (ALT), and histological analysis of the liver were assessed.

Results: Administration of HEEFVS at 200 and 400 mg/kg significantly decreased ALT and AST activities ($P< 0.001$). Total cholesterol levels were significantly reduced ($P< 0.001$) at all tested doses (100, 200, and 400 mg/kg). Triglyceride levels showed a significant reduction ($P< 0.01$) only at the 400 mg/kg dose. During the second and third weeks, administration of 200 and 400 mg/kg markedly reduced glucose levels ($P< 0.001$). Complete regeneration of liver tissue was observed in the 400 mg/kg group, while partial restoration was seen in the 100 mg/kg and 200 mg/kg groups. DPPH radical scavenging and α-amylase inhibitory activities of HEEFVS demonstrated IC50 values of 146.6 µg/ml and 8.47 µg/ml, respectively. The LD50 of HEEFVS was greater than 3500 mg/kg.

Conclusion: HEEFVS exhibits strong hepato-protective, hypolipidemic and anti-hyperglycemic effects.

Keywords: Alloxan, Diabetes mellitus, Wistar albino rats, Foeniculum vulgare, Anti-hyperglycemic effect

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Corresponding Author:
Feven Tigstu Ayele, Department of Biochemistry, Dire Dawa University, Dire Dawa, Ethiopia.
Tel: (25) 1939182876
Email: tigistufeven24@gmail.com
Orcid ID: 0000-0009-3157-331X

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Introduction

Diabetes mellitus (DM) is a chronic condition that profoundly affects individuals, families, and societies worldwide. According to the 2021 International Diabetes Federation (IDF) report, DM affects 537 million adults, and this number is projected to rise to 643 million by 2030 and 783 million by 2045. In 2021, diabetes was responsible for approximately 6.7 million deaths (1). The prevalence of DM is rising rapidly in low- and middle-income countries (2). In Africa, about 24 million adults are living with DM, with an undiagnosed rate of 54% and 416,000 reported deaths in 2021 (1).

In Ethiopia, the prevalence of DM is increasing in both rural and urban areas. According to IDF, Ethiopia is among the top five African nations most affected by diabetes (3,4). Reports from referral hospitals in Ethiopia show that type 2 DM is a major cause of hospital admissions, often associated with complications at the time of presentation, leading to high mortality rates. This highlights the urgent need for increased awareness, better management, and access to both modern medications and traditional remedies for diabetes care (5).

Since ancient times, medicinal plants have played a vital role in promoting health and improving quality of life. Most traditional therapies rely on plant extracts or their active compounds. The World Health Organization (WHO) estimates that nearly three-quarters of the global population initially depends on traditional medicine for healthcare needs. The therapeutic value of plants lies in their bioactive components, which exert specific physiological effects on the human body (6).

Foeniculum vulgare (fennel) is a medicinal herb with reported hypoglycemic properties. It is a biennial or short-lived perennial herb that can grow up to 2 meters tall, with erect, branched stems, pinnately divided leaves, and terminal clusters of small yellow flowers. Its oval, ribbed seeds (5-10 mm long) are aromatic, initially bluish-green, and later turn greenish-brown (7). In Ethiopia, it is locally known as ensilal in Amharic. Beyond its hypoglycemic effects, fennel exhibits estrogenic, analgesic, anti-inflammatory, antioxidant, antibacterial, anticancer, anti-stress and anti-aging activities, largely attributed to its diverse phytochemical constituents (7-8).

Nutritionally, F. vulgare contains approximately 42.3% carbohydrates, 10.5% lipids, 9.5% proteins, 13.4% minerals, and 6.3% moisture. It is also a source of vitamin E, thiamine, riboflavin ,niacin, ascorbic acid, sodium, potassium, phosphorus, calcium, and iron (7). Ethiopian fennel, in particular, is rich in essential minerals such as Fe, Cu, Co, Zn, Ca, and Mg. Trace amounts of toxic elements like Cd are present, while Pb is undetectable (9).

The primary bioactive compound in fennel, trans-anethole, is believed to be responsible for its antidiabetic effects. Long-term use has been shown to reduce glycated hemoglobin, blood glucose, and lipid profiles (10). Researchers have therefore suggested fennel and its active components as potential therapeutic agents for diabetes management (11).

The aim of this study was to evaluate the anti-hyperglycemic and related effects of the hydro-ethanolic extract of Foeniculum vulgare seeds (HEEFVS) collected from Gara Muleta, Eastern Hararghe Zone, Oromia Region, Ethiopia, where its traditional use has not yet been scientifically validated. Specifically, we investigated the impact of daily oral administration of HEEFVS on blood glucose, total cholesterol (TC), triglycerides (TG), aspartate transaminase (AST), alanine transaminase (ALT), and liver histology in experimental diabetic Wistar albino rats.

Materials and methods

Study Design

An in vivo experimental study was performed on a Wistar albino rat model to evaluate the effects of HEEFVS on blood glucose, TC, TG, AST, ALT and liver tissue regeneration. Experiments and laboratory analyses were Laboratories of Addis Ababa University

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(AAU), as well as the Hematology and Clinical Chemistry Laboratories of the Ethiopian Public Health Institute. All chemicals used were of analytical grade and purchased from Sigma-Aldrich Chemical Co. The study was conducted over six months, from November 2019 to April 2020.

Sample size determination

Sample size was determined based on previously published studies using similar experimental designs (11). Six rats per group were deemed sufficient to detect meaningful differences while adhering to ethical considerations.

Eligibility criteria

Inclusion criteria: Healthy adult male Wistar albino rats 8-12 weeks old, weighing 180-220 g, free from visible illness or injury, and acclimatized for one month before the experiment.

Exclusion criteria

Rats showing signs of illness, injury, or abnormal behavior during acclimatization.

Experimental animals

A total of 36 male and 10 female Wistar albino rats (8-12 weeks, 180-220 g), obtained from the Department of Pharmacology, AAU, were used. Female rats were included only for the acute toxicity test. Rats were identified with coded markings on their tails and housed in labeled polypropylene cages (47× 34× 20 cm) with wire mesh tops and husk bedding (changed every three days). Each cage contained six male or five female rats. Animals were provided with rat pellets (Kality Animal Nutrition Production Ltd., Addis Ababa, Ethiopia) and water ad libitum. Housing conditions included proper ventilation, controlled temperature, and a standard 12 h light/dark cycle. All procedures were approved by the Department of Biochemistry, Addis Ababa University, and carried out in accordance with internationally accepted guidelines for animal handling and euthanasia.

Plant material and extraction procedure

Seeds of Foeniculum vulgare were collected on August 16, 2019, from Gara Muleta (Eastern Hararghe Zone, Oromia Region, Ethiopia; 9°4′60″N, 41°45′0″E; altitude 2057 m), approximately 335 km east of Addis Ababa. The site has a mean temperature of 16 °C and annual rainfall of 1270-1280 mm. The plant was authenticated as Foeniculum vulgare Miller and deposited at the National Herbarium, College of Natural Sciences, AAU (specimen number F-001).

The seeds were shade-dried for one week, ground into coarse powder, and soaked in 1000 mL of 80% ethanol (v/v) for 24 h with agitation. The mixture was filtered through Whatman No. 2 filter paper, and the filtrate was concentrated at 45 °C in a water bath. The residue was dried under reduced pressure and subsequently freeze-dried at 4 °C using a lyophilizer. The resulting extract was labeled and stored in a desiccator until use.

Experimental procedure

Daily quality control, equipment calibration, and maintenance were ensured. All tests were performed using standard operating procedures by trained professionals, with quality control materials included.

Phytochemical analysis

Qualitative phytochemical screening of HEEFVS was performed to detect tannins, terpenoids, phenols (13), saponins (14), flavonoids and glycosides (15) and alkaloids (16).

Extract preparation for administration

Extract doses of 100, 200, and 400 mg/kg body weight/day were freshly prepared in water. For the diabetic control group, glibenclamide (5 mg/kg) was prepared in water. Extracts were administered orally by gavage daily.

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In vitro antioxidant activity (DPPH Assay)

Both qualitative and quantitative assays were performed using 1,1-diphenyl-2-picrylhydrazyl (DPPH). The qualitative assay followed Soler-Rivas et al. (17), while quantitative assessment followed Wickramaratne et al. (18) with minor modifications. Absorbance was measured at 517 nm, and IC50 values were determined as the concentration required to scavenge 50% of DPPH radicals.

In vitro α-amylase inhibition

The α-amylase inhibitory activity of HEEFVS was assessed using 3,5-dinitrosalicylic acid following Wickramaratne et al. (18), with minor modifications. Absorbance was measured at 540 nm. IC50 values were determined as the concentration required to inhibit 50% of α-amylase activity.

Acute toxicity test

Ten female rats were used. Five rats received 2000 mg/kg HEEFVS orally and observed for 14 days. If no toxicity was observed, the remaining five rats were given 3500 mg/kg.

Induction of diabetes

After overnight fasting, rats received a single intraperitoneal injection of alloxan monohydrate (175 mg/kg) dissolved in saline (20). To prevent initial hypoglycemia, 10% glucose solution was provided for 24 h. After 48 h, fasting blood sugar (FBS) was measured; rats with FBS> 200 mg/dL were considered diabetic (22). Rats with extreme hyperglycemia (>400 mg/dL) were excluded to reduce mortality risk. Treatment was initiated on the fifth day (23).

Experimental groups

Rats were randomly allocated into six groups (n= 6 each):

Group I: Normal control (distilled water)

Group II: Diabetic control (distilled water)

Groups III–V: Diabetic+ HEEFVS (100, 200, and 400 mg/kg/day)

Group VI: Diabetic+ glibenclamide (5 mg/kg/day).

Sample collection and biochemical analysis

At the end of the experiment, blood samples (1.5 mL) were collected by cardiac puncture under diethyl ether anesthesia. Serum was separated and stored at –20 °C. Fasting blood glucose was measured using SensoCard Plus Glucose Meter (77 Elektronika, Hungary). TC, TG, ALT, and AST were analyzed using a COBAS 6000 Clinical Chemistry Analyzer (Roche Diagnostics, Germany). Measurements were taken at baseline, and on days 7, 14, and 21.

Histopathological analysis

Following blood collection, rats were sacrificed by cervical dislocation. Livers were excised, rinsed in saline, fixed in 10% formalin, processed, and stained. Histological sections were examined under a binocular microscope by an experienced pathologist.

Statistical analysis

Data were analyzed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). Results were expressed as mean ± SD. Normality and homogeneity of variance were tested with Shapiro-Wilk and Levene's tests, respectively. One-way ANOVA followed by Tukey's post hoc test was used for group comparisons. Statistical significance was set at $P< 0.05$.

Ethical considerations

The study was approved by the Research and Ethical Review Committee of the Department of Biochemistry, School of Medicine, College of Health Sciences, Addis Ababa University (Meeting No: DRERC 08/18, Protocol No: 05/18). All procedures adhered to internationally accepted guidelines for the care and use of laboratory animals.

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Results

Animal selection and grouping

A total of 42 rats received alloxan monohydrate. Five rats with fasting blood glucose (FBG) levels> 400 mg/dL were excluded to minimize acute mortality risk and to standardize the severity of hyperglycemia across groups. Four additional rats were excluded due to illness or abnormal behavior. Thus, 33 rats (78%) with FBG levels between 200-400 mg/dL were considered diabetic. From these, 30 rats were randomly allocated into five experimental groups (n= 6 per group).

Acute toxicity test

Oral administration of HEEFVS at doses of 2000 and 3500 mg/kg produced no observable signs of toxicity or mortality during the 14 day monitoring period, indicating that the median lethal dose (LD50 of HEEFVS) is greater than 3500 mg/kg.

Phytochemical screening

Qualitative phytochemical analysis of HEEFVS revealed the presence of alkaloids, flavonoids, glycosides, phenols, saponins , tannins, and terpenoids.

Antioxidant activity- qualitative assessment

The DPPH assay demonstrated dose-dependent antioxidant activity of HEEFVS on TLC plates. Yellow spots, indicative of free radical scavenging, appeared against the purple DPPH background. The diameter of the color change increased with extract concentrations from 250 to 750 mg/100 mL, confirming a concentration-dependent antioxidant effect.

Distilled water had no effect on DPPH coloration (Figure 1).

Antioxidant activity- quantitative assessment

In the quantitative DPPH assay, HEEFVS exhibited strong free radical scavenging activity. Absorbance decreased in a concentration-dependent manner, and the IC50 value of HEEFVS was determined to be 146.6 µg/mL, compared with vitamin C (positive control), which showed a lower IC50, indicating higher potency.

Quantitative assay for measurement of antioxidant activity of HEEFVS

For the quantitative assay, the absorbance of each concentration of HEEFVs and L-ascorbic acid (standard) at 50, 100, 150, 200, and 250 µg/ml was measured using a spectrophotometer (UV-1600PC, VWR International, LLC, Radnor, PA, USA) was used to measure at 517 nm. Absorbance and concentration values were entered into Microsoft Excel, and a plot of concentration versus percentage of inhibition was generated for both HEEFVS and L-ascorbic acid. Inhibitory concentration (IC_{50}) was calculated from the slope of the graph.

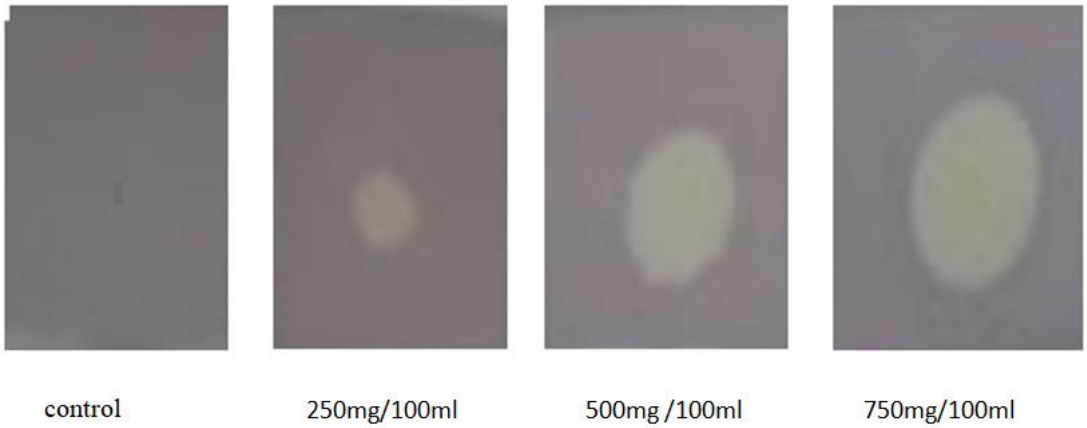


Figure 1. Qualitative antioxidant activity of hydroethanolic extract of *Foeniculum Vulgare* seed by TLC plate using 0.1 mM DPPH

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DPPH radical scavenging activities of HEEFVS and L-ascorbic acid showed IC_{50} of 146.6µg/ml (95% CI: 137.1- 156.1 µg/ml) and 97.06 µg/ml respectively, indicating that the IC_{50} value for HEEFVS was significantly higher than that of L-ascorbic acid ($P< 0.05$), implying a lower antioxidant capacity of HEEFVS compared to the standard.

HEEFVS's in vitro α-amylase inhibitory activity

The plot of percent α-amylase inhibition analysis was used to generate IC50 values as a function of the extract concentration. HEEFVS exhibited IC_{50} value of 8.47 µg/ml (95% CI: 7.21- 9.73 µg/ml) and acarbose (standard positive control) showed IC_{50} values of 1.71µg/mL. Statistical analysis demonstrated that the IC_{50} of HEEFVS was significantly greater than that of acarbose ($P< 0.05$), indicating that HEEFVS exhibits lower α-amylase inhibitory potency compared to acarbose.

Effects of HEEFVS on biochemical parameters

There was a significant increase in serum ALT and AST activity in diabetic controls compared to healthy controls. Compared to diabetic controls, treatment with HEEFVS for 21 days at doses of 200 mg/kg and 400 mg/kg significantly ($P< 0.001$) reduced serum ALT and AST activities in diabetic rats. For the same treatment duration, the effect was equivalent to that of glibenclamide at a dose of 5 mg/kg body weight.

Serum TC and TG levels in diabetic controls were considerably higher than those in normal controls ($P< 0.001$, $P< 0.01$), respectively. Compared to the diabetic controls, serum TC was considerably lower ($P< 0.001$) with HEEFVS therapy at all doses. A comparable outcome was also observed in the glibenclamide-treated groups. Serum TG showed a statistically significant reduction ($P< 0.01$) only at the dose of 400 mg/kg body weight HEEFVS treatment compared to the diabetic controls.

Table 1 shows the effect of HEEFVS on the blood levels of ALT, AST, TC, and TG in Wistar albino rats treated for 21 days with alloxan to induce diabetes.

Effect of HEEFVS on diabetic rats' fasting blood sugar (FBS) levels

Significant changes in FBS levels ($P< 0.05$) were observed throughout the experiment in healthy controls receiving distilled water. Substantial hyperglycemia was observed in all rats administered alloxan compared to untreated controls throughout the duration of the study. Compared to the first week of treatment and the FBS levels in diabetic controls, the FBS levels in diabetic rats treated with 200 mg/kg and 400 mg/kg HEEFVS and 5 mg/kg glibenclamide dramatically decreased ($P< 0.001$) in the second and third weeks of treatment. In diabetic rats given 400 mg/kg HEEFVS, mean blood glucose levels decreased more steadily and statistically significantly ($P< 0.001$) from 352 mg/dl on day 0 to 189.1 mg/dl, comparable to rats given glibenclamide, whose FBS decreased from 350.8 mg/dl to 188.8 mg/dl after 21 days of treatment. HEEFVS reduces blood sugar levels in a dose-dependent manner. Table 2 shows the effect of HEEFVS on FBS levels in diabetic rats at days 0, 7, 14, and 21.

Effect of HEEFVS on diabetic rats' body weight

The alloxan-injected diabetic groups exhibited a reduction in body weight, in contrast to the standard controls ($P< 0.05$). The ultimate body weight in both HEEFVS-receiving and standard treatment groups exhibited an increase compared with the diabetic control group's body weight; however, the difference was not statistically significant ($P> 0.05$). The effects of HEEFVS on the body weight of alloxan induced diabetic rats are presented in Table 3.

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Table 1. Effect of HEEFVS on the serum levels of AST, ALT, TG and TC in rats with alloxan-induced diabetes

Variable	Aspartate transaminase (U/L)	Alanine transaminase (U/L)	Triglyceride (mg/dl)	Total cholesterol (mg/dl)
Group I	188.5 (±14.6) $P< 0.001^{b}$	68.2 (±5.6) $P < 0.001^{b}$	48.3 (±5.2) $P< 0.01^{b}$	49.3 (±3.0) $P< 0.001^{b}$
Group II	437.8 (±45) $P < 0.001^{a}$	202.9 (±18.25) $P< 0.001^{a}$	66.1 (±8.9) $P< 0.01^{a}$	84.0 (±6.6) $P< 0.001^{a}$
Group III	312.2 (±16.4) $P< 0.001^{a,b}$	162.9 (±17.9) $P< 0.001^{a,b}$	59.2 (±6.8)	57.4 (±7.5) $P< 0.001^{b}$
Group IV	239.1 (±26.4) $P< 0.001^{b}$	84.4 (±11.7) $P< 0.001^{b}$	58.7 (±8.6)	55.5 (±8.01) $P< 0.001^{b}$
Group V	231.01 (±18.1) $P< 0.001^{b}$	75.4 (±9.5) $P < 0.001^{b}$	50.2 (±8. 2) $P< 0.01^{b}$	49.6 (±6.7) $P< 0.001^{b}$
Group VI	192.3 (±16.8) $P< 0.001^{b}$	70.31 (±5.62) $P< 0.001^{b}$	54.7 (±4.8)	51.1 (±2.8) $P< 0.001^{b}$

Values are mean ± SD; n= 6 for each group; [a] compared with normal control, [b] compared with diabetic control, HEEFVS: hydroethanolic extract of Foeniculum vulgare seed

Table 2. Effects of HEEFVS on alloxan- induced diabetic rats' fasting blood sugar levels

Variable	Group I	Group II	Group III	Group IV	Group V	Group VI
0 day	95.1 (±3.86) $P < 0.001^{b}$	354.0 (±53.3) $P< 0.001^{a}$	354.5 (±52.2) $P< 0.001^{a}$	351.6 (±49.5) $P< 0.001^{a}$	352 (± 50.6) $P< 0.001^{a}$	350.8 (±43.5) $P< 0.001^{a}$
7th day	96.5 (±3.2) $P< 0.001^{b}$	361.8 (±48.8) $P< 0.001^{a}$	332.3 (±56.2) $P< 0.001^{a}$	334.8 (±53.9) $P< 0.001^{a}$	317.8 (±60.1) $P< 0.001^{a}$	298.6 (±40.4) $P< 0.001^{a}$
14th day	93.5 (±5.2) $P< 0.001^{b}$	372 (± 63.7) $P< 0.001^{a}$	302.7 (±58.3) $P< 0.001^{a}$	252.2 ± (48.2) $P< 0.001^{a,b}$, $P< 0.01^{c}$	226.3 (±19.3) $P< 0.001^{a,b,c}$	248.1 (±28.1) $P< 0.001^{a,b}$
21st day	91.3 (±5.5) $P< 0.001^{b}$	399.3 (±64.9) $P< 0.001^{a}$	271.6 (±37.9) $P< 0.001^{a,b}$	228.3 (±43.5) $P< 0.001^{a,b,c}$	189.1 (±23) $P< 0.001^{b,c}$, $P< 0.01^{a}$	188.8 (±11.5) $P< 0.001^{b}$, $P< 0.01^{a,c}$

Values are the mean ± SD; n= 6 for each group. [a] compared with normal control, [b] compared with diabetic control, [c] compared with the initial level of fasting blood sugar (0 days) of the rats in the respective group, HEEFVS: hydroethanolic extract of Foeniculum vulgare seed

Table 3. Effect of HEEFVS on the body weight of rats with diabetes brought on by alloxan

Groups	Body weight (gram)	
Variable	**0 day**	**21st day**
Group I	214.9 (±20.1)	237.6 (±13.1)
Group II	215.0 (±20.8)	183.9 (±13.4) $P< 0.05^{a}$
Group III	216.8 (±14.4)	186.5 (±8.9) $P< 0.05^{a}$
Group IV	215.4 (±22.9)	186.5 (±28.8) $P< 0.05^{a}$
Group V	217.3 (±24.8)	190.25 (±20.3) $P< 0.05^{a}$
Group VI	212.7 (±17.0)	193.5 (±11.2) $P< 0.05^{a}$

Values are mean ± SD (n= 6) a, compared to healthy controls, b $P< 0.05$
Compared with the diabetic controls, HEEFVS: hydroethanolic extract of Foeniculum vulgare seed

Liver histopathological observation in alloxan-induced versus HEEFVS treated rats

Normal liver tissues exhibited obvious central veins and normal hepatocyte morphology. Liver tissue from diabetic rats administered 175 mg/kg alloxan displayed fatty alterations, dilated sinusoids, and noticeable lymphocytic inflammation in the portal regions.

Diabetic rats administered HEEFVS exhibited complete rejuvenation at a dose of 400 mg/kg, with a certain amount of restoration seen in the 100 mg/kg-and 200 mg/kg-treated rats.

Discussion

Diabetes was induced in the rats using alloxan monohydrate. However, animals of the same species show different levels of susceptibility to the toxic and diabetogenic effects of alloxan. A dose that induced severe hyperglycemia in one rat sometimes caused only mild or no effect in another, making consistent outcomes difficult to achieve. This property of alloxan has been well described by Misra and Aiman (21). Antioxidants play a vital role by scavenging free radicals ,inhibiting lipid peroxidation, and reducing oxidative stress . Plant-derived antioxidants are increasingly recognized as preventive and therapeutic agents. In our study, 80% HEEFVS demonstrated dose-dependent antioxidant

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activity, with an IC50 of 146.6 µg/mL, which is comparable to the standard ascorbic acid (IC50= 97µg/mL). The antioxidant effect is likely attributed to the presence of phenolic compounds such as flavonoids, as confirmed by phytochemical analysis. Previous studies have reported variability in antioxidant potential depending on plant parts, extraction solvents, and environmental factors (24-26).

Another important finding was the α-amylase inhibitory activity of HEEFVS, with an IC50 of 8.47 µg/mL compared to 1.71 µg/mL for acarbose. Similar but variable results were reported by Sayah et al., likely due to differences in cultivation conditions and extraction methods (25). This inhibitory action could contribute to reduced glucose absorption in the intestine.

We also observed that administration of 400 mg/kg HEEFVS significantly reduced glucose levels, consistent with earlier reports of the hypoglycemic effects of fennel extracts in streptozotocin**)** STZ)-induced diabetic models (26-28). The antihyperglycemic activity of HEEFVS may be mediated by alkaloids that inhibit α-glucosidase and α-amylase, as well as phenolic compounds and trans-anethole, which inhibits aldose reductase, a key enzyme in the polyol pathway (10,29).

Liver enzyme analysis and histopathological examination demonstrated that diabetes induced hepatic injury, evidenced by elevated ALT and AST levels, lymphocytic infiltration, fatty changes, and sinusoidal dilation. These findings are consistent with previous studies (30). Treatment with HEEFVS significantly reduced ALT and AST activities and improved histopathological alterations. Complete regeneration of liver tissue was observed only at the highest dose (400 mg/kg), while partial improvement was seen at lower doses. This difference may reflect a temporal gap between biochemical normalization and histological recovery. Similar hepatoprotective effects of fennel have been reported in carbon tetrachloride- and STZ-induced liver injury models (26,31).

Furthermore, HEEFVS demonstrated hypolipidemic effects .After 21 days of treatment, serum total cholesterol (TC) and triglyceride (TG) levels were significantly reduced in a dose-dependent manner, in agreement with earlier findings (10,31). Polyphenols in fennel may enhance insulin secretion, reduce lipid peroxidation, and inhibit hepatic hydroxymethylglutaryl-CoA reductase activity ,contributing to improved lipid metabolism (29).

Body weight loss is a characteristic feature of diabetes ,mainly due to muscle protein catabolism caused by impaired glucose utilization. In this study, diabetic rats exhibited significant weight reduction compared with healthy controls. Although HEEFVS and glibenclamide improved body mass in diabetic rats, the effect was not statistically significant. Previous studies, however, reported long-term administration of fennel leading to weight loss in obese models ,possibly due to trypsin inhibitors, cholecystokinin release, fat mobilization, and diuretic action (32).

Limitations

This study had some limitations. First, variations in the diabetogenic response to alloxan may have introduced heterogeneity in the results. Second, the study was conducted in animal models, and therefore the findings cannot be directly extrapolated to humans without further clinical investigation. Finally, the study did not quantify specific phytochemicals such as flavonoids and alkaloids, which could provide more precise insight into the mechanisms underlying the observed effects**.**

Conclusions

Our findings demonstrate that HEEFVS, particularly at 400 mg/kg, significantly reduced fasting blood glucose, triglycerides, total cholesterol, and liver enzyme (ALT and AST) activities, while restoring liver tissue architecture in alloxan-induced diabetic rats. These results suggest that HEEFVS possesses antihyperglycemic, hypolipidemic **,**and

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hepatoprotective properties. In addition, the extract exhibited antioxidant and α-amylase inhibitory activities and contained bioactive secondary metabolites that may underlie its therapeutic potential.

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None.

Conflict of Interest

The authors declare that there are no conflicts of interest.

Author contributions

F.T: developed the project, collected the samples, carried out the experiments, analyzed the data and wrote the manuscript; M.D, G.N, and S.G: participated in the research design and guidance, and supervised the work; Y.B, C.B, and G.W: performed the experiments. W.K: analyzed the data and wrote the manuscript. M.D, G.N, Y.B, and S.G: reviewed the manuscript and provided comments. All authors have read and approved the manuscript.

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