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Original Article

Can the Use of *Eryngium caucasicum* Hydro-Alcoholic Extract, Along with Aerobic Exercise, Affect Blood Glucose, Lipid Factors, and Betatrophin Hormone Levels in Type 2 Diabetic Patients?

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Abstract

Background: *Eryngium caucasicum* (EC) is traditionally used for diabetes management. This study aimed to evaluate the combined effects of EC supplementation and aerobic exercise on blood glucose, lipid profile, and betatrophin levels in patients with type 2 diabetes mellitus (T2DM).

Methods: In this randomized controlled trial, 45 T2DM patients (mean age: 46.55 ± 7.58 years) were allocated to three groups: (1) Combined intervention group: aerobic exercise + *E. caucasicum* supplementation (200 mg/day); (2) Exercise-only group: aerobic exercise alone; and (3) Control group: no intervention. The 6-week aerobic protocol included five 45-minute sessions per week at moderate intensity. A total of 200 mg of EC per day (two 100-mg capsules) was taken, one in the morning and one in the evening after meals, for six weeks. Fasting blood glucose, triglycerides, betatrophin, HDL, LDL, and total cholesterol were measured before and after the intervention. Data were analyzed using ANCOVA.

Results: Compared with the control group, both intervention groups showed significant reductions in blood glucose and triglycerides, along with increased betatrophin levels ($P<0.05$). The exercise + EC group exhibited a more pronounced glucose reduction than the exercise-only group ($P<0.05$). HDL and LDL improved significantly only in the exercise + EC group ($P<0.05$), while total cholesterol remained unaffected.

Conclusion: The synergistic effect of aerobic exercise and *E. caucasicum* supplementation may offer a therapeutic strategy for improving metabolic parameters in patients with T2DM.

Keywords: Type 2 diabetes, Aerobic exercise, *Eryngium caucasicum*, Glucose, Lipid profile, Betatrophin

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Introduction

Diabetes mellitus is a widespread endocrine and metabolic disorder characterized by chronic hyperglycemia and dysregulated metabolism of carbohydrates, fats, and proteins (1-4). Insulin resistance and impaired beta-cell function are hallmarks of type 2 diabetes (T2D) (5). One potentially key hormone in this area, which has been recently identified, is betatrophin (also known as lipasin or angiopoietin-like protein 8). It is secreted by the liver and adipose tissue and is involved in the regulation of plasma triglyceride levels and glucose homeostasis (3, 6). According to previous research, elevated expression of the betatrophin gene is associated with increased beta-cell mass and improved glycemic control (3). Consequently, it has garnered significant attention for its potential in diabetes treatment (4). Yi et al demonstrated that overexpression of betatrophin in rodents led to an increase in beta-cell mass and improved glycemic control (7). Subsequent studies by Zhu et al, Ahnfelt-Rønne et al and Chen et al also support the role of betatrophin in promoting beta-cell proliferation (8-10). However, these studies were carried out on animal models; therefore, evidence from human studies remains limited to date. Given that serum betatrophin levels are related to glucose and lipid metabolism, it may represent a novel therapeutic target for insulin resistance, diabetes, and lipid disorders (6).

Medicinal plants and physical exercise can be used to improve glycemic control in patients with diabetes. They often have fewer side effects and are less expensive than conventional pharmaceuticals. *Eryngium* is a flowering perennial herbaceous plant belonging to the Apiaceae family (1). It is widely used as a medicinal agent to treat

inflammatory diseases and diabetes mellitus around the world (11). Its aerial parts and roots contain the principal medicinal constituents (12). Bioactive compounds found in Eryngium include terpenoids, saponins, flavonoids, coumarins, caffeine, beta-carotenes, polyacetylenes, and steroids (1, 11-13). Associated biological effects of these compounds include antidiabetic, anti-inflammatory, antioxidant, cytotoxic, anti-apoptotic, antibacterial, antifungal, and antimalarial properties. It is also used in traditional Iranian medicine for the treatment of diabetes mellitus (11). The antioxidant properties of this plant have been reported to help prevent cell damage due to oxidative stress; this may help repair damaged beta-cells and improve insulin secretion (14). Several studies have investigated the effect of *Eryngium* on blood glucose levels in diabetic patients. In a study by Norouzi and Valipour Chahardah Charic (2021), *Eryngium* extract was shown to reduce blood glucose levels and improve lipid profiles in diabetic male rats (1). In a study by Rabiee et al, *Eryngium* supplementation in combination with a program of incremental exercise was shown to reduce plasma glucose levels, insulin levels, the insulin resistance index, triglycerides, cholesterol, and acetoacetate in diabetic male participants (15). However, the effect of *Eryngium* on betatrophin levels has not been studied, and it is not known whether *Eryngium* may substitute betatrophin and thereby possibly promote beta-cell proliferation.

On the other hand, the role of regular exercise in improving insulin sensitivity and metabolic parameters in patients with type 2 diabetes has been well established and has been demonstrated. Exercise also helps improve lipid profiles by increasing fat metabolism. Therefore, it is proposed that patients with diabetes may use exercise to improve their blood glucose control, lipid profiles, body weight, and blood pressure (16). Regarding appropriate exercise regimens for diabetics, the American Diabetes Association recommends that individuals with type 2 diabetes should complete at least 150 minutes of moderate-intensity aerobic exercise (50–70% of maximum heart rate) divided into at least three sessions per week (17). The effect of physical exercise on betatrophin levels has been investigated in several studies; however, the findings are inconsistent, with reports of increases, decreases, and no change in betatrophin concentration (3, 4, 6, 18, 19).

Despite substantial evidence supporting the antidiabetic effects of *Eryngium caucasicum* and exercise individually, their combined impact on betatrophin—a key regulator of β-cell proliferation and glucose homeostasis—remains unexplored in humans. Therefore, this study was designed to fill this critical gap.

Methods

The study used an applied, experimental design, using a pretest–posttest approach with three different groups: two intervention groups—one receiving aerobic exercise alone and the other combining aerobic exercise with *E. caucasicum* supplementation—and one control group. The target population consisted of male and female patients with type 2 diabetes aged 35 to 60 years, who actively sought treatment in specialized diabetes clinics. Recruitment took place at two specific locations: Tehran Diabetes Centre on Keshavarz Boulevard and the Specialized Diabetes Mellitus and Metabolic Diseases Clinic on Nejatollahi Street. The sample size was determined a priori using G*Power software, version 3.1 (20), with blood glucose levels designated as the primary outcome measure. The calculation was based on an effect size of 0.5 (Cohen's *d*), which was derived from prior studies investigating herbal interventions for T2DM (2). The parameters were set with a significance level (α) of 0.05 (two-tailed), a statistical power (1−β) of 0.8, and an F-test for ANOVA (between factors). This analysis indicated a minimum total sample size of 42 participants (14 per group). To mitigate the potential impact of attrition, a total of 45 participants (15 per group) were ultimately recruited. Following the initial call and screening process, 45 volunteer subjects were selected according to the study's eligibility criteria.

Inclusion criteria

were as follows: provision of informed consent; age between 35 and 60 years; a confirmed diagnosis of type 2 diabetes (T2DM); a fasting blood sugar (FBS) level ranging from 150 to 250 mg/dL; use of a stable regimen of metformin and sulfonylurea medications (e.g., Glibenclamide or Gliclazide) for glycemic control; adherence to a standardized diet plan provided by a study nutritionist; abstention from using any medicinal herbs other than the provided *Eryngium* supplement for the study's duration; and no engagement in a structured physical activity program during the three months preceding the study.

Exclusion criteria

comprised: any physical comorbidity—such as severe arthrosis or significant orthopedic issues—that would preclude safe participation in the aerobic exercise protocol; the presence of major concomitant diseases, including uncontrolled hypertension, cardiovascular disease, or thyroid disorders; failure to consume the prescribed *Eryngium* supplement; and absence from four or more exercise sessions within a single month.

After selecting eligible subjects, measurements of height, weight, blood sugar, lipid factors, and betatrophin were performed (pretest stage). Subsequently, to ensure unbiased allocation, participants were randomly assigned to three groups (n = 15 each) using a four-step Excel-based protocol: (1) Unique Identifier Assignment (Column A): Each participant received a sequential ID (1–45). (2) Random Number Generation (Column B): The formula = RANDBETWEEN (1,1000) assigned a unique integer (1–1000) to each ID, minimizing duplication risk.

(3) Ranking (Column C): IDs were ranked by random numbers (ascending) using = RANK (B1, B1: B45,1). (4) Group Allocation (Column D): Ranks 1–15: Aerobic exercise (9 men, 6 women); Ranks 16–30: Aerobic exercise + *Eryngium* (9 men, 6 women); Ranks 31–45: Control (7 men, 8 women). To prevent re-randomization upon reopening the file, the group assignments (Column D) were converted to static values via Copy → Paste Special → Values.

The control group was instructed to maintain their usual lifestyle and medication regimen throughout the study period without any intervention in the form of exercise or supplementation. It should be noted that a placebo was not administered in this study. In addition, the study was conducted as an open study, which means that both the participants and the research team were directly involved in the intervention and were aware of the group assignment. This lack of blinding was a natural consequence of the intervention-based nature of the study, as the participants in both active groups were necessarily aware of their training protocol. However, potential bias was reduced by blinding the assessor (e.g., laboratory technicians analyzing blood samples) and using standardized automated tests (e.g., ELISA, Abbott auto-analyzer) for all biochemical assays.

All measurements were performed at two times: once at the start of the treatment (before the intervention) and again 48 hours after the last treatment session (after the intervention). Height was measured with a wall-mounted stadiometer to the nearest 0.1 cm. Body weight was measured to a precision of 0.1 kg using a calibrated digital scale, and the volunteers were wearing lightweight clothing and no footwear for biochemical analysis. A 10 mL venous blood sample was taken from the brachial vein after a 12-hour fasting period. For the separation of the serum, the blood samples were centrifuged at 3000 rpm for 12 minutes in a Hettich centrifuge (Germany). Serum aliquots were immediately stored at −20°C to preserve the integrity of the analytes until batch analysis at the end of the study. Serum glucose was measured by ELISA using a Pars kit manufactured in Iran. The lipid profile was evaluated by means of an automatic analyzer (Abbott, Alcyon Model 300, USA), and Pars Azmun kits were used. Betatrophin levels were measured under the supervision of a laboratory expert using ELISA and a ZellBio betatrophin kit manufactured in Germany, with a detection range of 4 ng/mL and a sensitivity of 0.2 ng/mL. The research steps are shown in Figure 1.

How to take Eryngium hydroalcoholic extract

The dose was determined based on similar studies. Subjects in the add-on group consumed 200 mg of *Eryngium* hydroalcoholic extract daily (two 100-mg capsules) in two doses, morning and evening, after meals (15). The supplementation period lasted for six weeks. Supplement capsules were distributed weekly to the participants. Participants completed five supervised exercise sessions a week in a gym. During each session, the researchers verbally confirmed capsule intake with each participant. On non-training days, follow-up was conducted via social media platforms to confirm the ingestion of capsules. This multimodal approach (personal confirmation + digital follow-up) ensured that the supplementation protocols were rigorously followed throughout the intervention period.

How to implement an aerobic exercise protocol

The American College of Sports Medicine and the American Diabetes Association recommended that people with diabetes take part in at least 150 minutes of aerobic exercise a week and at least two sessions of resistance training a week, even if they are not currently physically active. They also recommend moderate-intensity exercise to avoid hypoglycemia (21). Subjects in both intervention groups completed aerobic exercise in the evening (6:00 p.m.) at a moderate intensity of 50–75% of maximum heart rate (HRmax) for five sessions per week, each of 45 minutes, for six weeks in a gym under the supervision of an experienced trainer. The maximum heart rate was calculated using the formula 220 − age. The exercise consisted of a 10-minute warm-up (walking and stretching), 25 minutes of running, and a 10-minute moderate-intensity aerobic activity followed by a 10-minute cool-down (Table 1). All precautions for diabetics in exercise were observed to avoid the risk of hypoglycemia (22).

Adherence to the exercise protocol was ensured by having all sessions supervised by qualified trainers, electronically recording attendance, and monitoring heart rate throughout the sessions. The Borg Rating of Perceived Exertion (RPE) scale was utilized in this study. Furthermore, any participant who attended fewer than

Table 1. Aerobic exercise protocol (21, 23)

Exercise	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
warm-up (min)	10	10	10	10	10	10
main workout (min	10	10	20	25	25	25
cool-down (min)	10	10	10	10	10	10
Total (min)	30	30	40	45	45	45
Intensity (maximum heart rate)	50%	55-60%	55-60%	60-70%	60-75%	60-75%

four sessions in each week was excluded from the analysis.

Statistical analysis

The descriptive and inferential statistical methods were used in this study. Descriptive statistics were used to obtain means and standard deviations of study variables and for the production of tables and graphs. In the inferential statistics section, the Shapiro-Wilk test was used to determine the normality of the data. One-way ANOVA was used to evaluate group homogeneity. Analysis of Covariance (ANCOVA) was used to compare the three groups, and a Bonferroni post-hoc test was used to determine the differences between the groups. Statistical calculations were performed using SPSS version 21 at a significance level of 0.05.

Results

Data are presented as mean ± standard deviation. One-way ANOVA was used to assess homogeneity between groups. No significant differences were observed in any baseline variables (all $P > 0.05$), confirming balanced group allocation (Table 2).

Also, the Shapiro–Wilk test confirmed normality for all variables. ANCOVA was used to control pretest

Table 2. Baseline characteristics of participants across study groups (Mean ± SD)

Groups	Control (7 men & 8 women)	Aerobic Exercise (9 men & 6 women)	Exercise+ Eryngium (9 men & 6women)	*P* value
Age (years)	45.93±7.63	46.67±7.59	47.07±7.54	0.918
Height (m)	1.67±0.07	1.68±0.08	1.71±0.09	0.342
Weight (kg)	73.20±8.82	76.13±9.83	79±8.59	0.229
BMI (kg/m2)	26.35±2.92	27.13±3.86	27.10±2.83	0.758
SBP (mmHg)	113.33±16.76	126.33±19.04	114.33±15.34	0.080
DBP (mmHg)	73.01±12.36	80.33±15.06	73.87±12.44	0.850

BMI = Body mass index, SBP = Systolic blood pressure, DBP = Diastolic blood pressure.

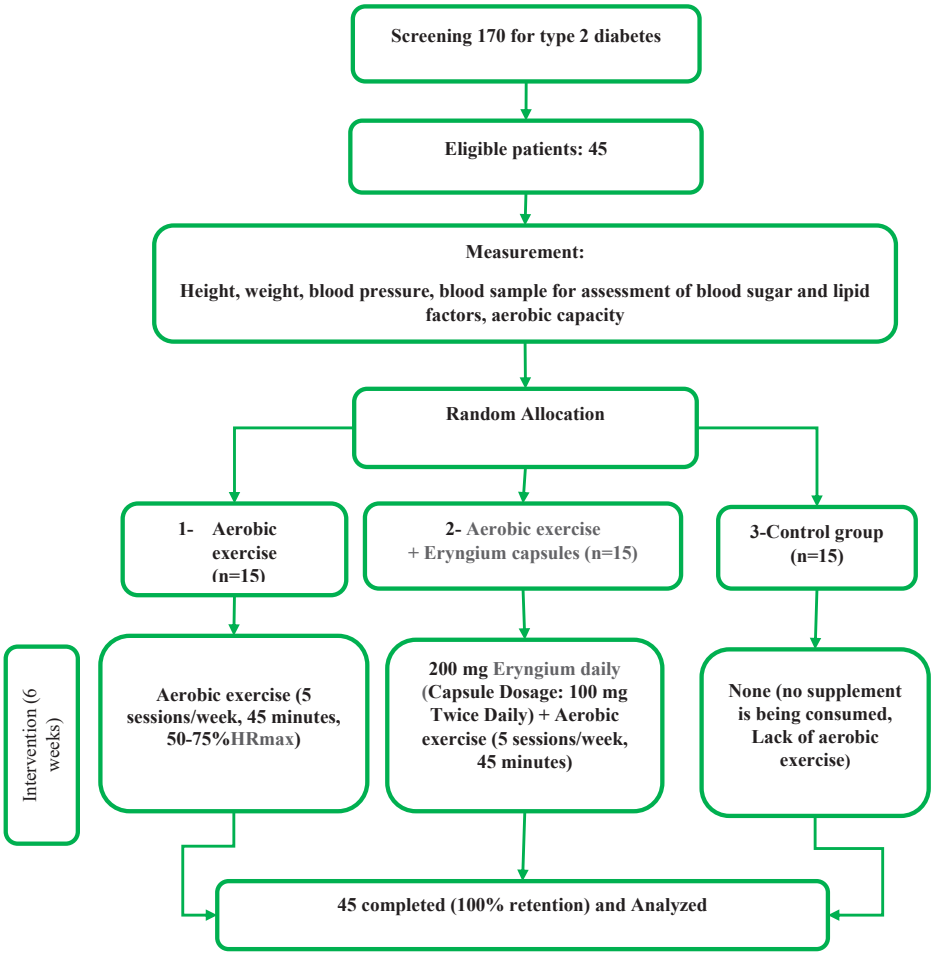

Figure 1. Research process

effects due to the small sample size. Assumptions ($r < 0.8$, normal residuals, homogeneity of variance) were met. For significant pretests ($P < 0.05$), adjusted posttest means are reported (between-group comparisons only).

Table 3 shows the pretest and posttest results of the research variables in the three groups. As shown in the table, in the two intervention groups, blood glucose decreased, betatrophin increased, and lipid factors improved.

Analysis of covariance (ANCOVA; Table 3) and Bonferroni post-hoc tests (Figure 2, A) revealed a significant difference in fasting blood glucose among groups ($P < 0.001$). The Exercise + *Eryngium* group showed the largest reduction in the serum FBS (from 190.40 ± 40.68 mg/dL to 131.53 ± 29.29 mg/dL, Δ = −58.87 ± 11.39 mg/dL), significantly lower than both the Exercise-only group (144.73 ± 32.35 mg/dL, $P = 0.035$) and the control group (175.93 ± 39.47 mg/dL, $P < 0.001$). The Exercise-only group also outperformed the control group ($P < 0.001$; Δ = −35.67 ± 6.22 mg/dL vs. control Δ = + 4.20 ± 1.66 mg/dL).

There was a significant difference in serum betatrophin levels among the three test groups ($P < 0.001$) (Table 3, Figure 2, B). The Exercise + *Eryngium* group achieved the highest posttest levels (699.87 ± 58.01 pg/mL, Δ = + 76.47 ± 7.70 pg/mL), followed by the Exercise-only group (681.07 ± 64.63 pg/mL, Δ = + 50.34 ± 2.19 pg/mL), both surpassing the control group (591.53 ± 60.59 pg/mL, Δ = −33.34 ± 3.55 pg/mL; $P < 0.001$ for both comparisons).

There was no significant difference in total serum cholesterol (TC) between groups ($P = 0.47$) (Figure 3, C). Serum triglyceride (TG) levels showed a significant decrease in the Exercise + *Eryngium* group (from 187.07 ± 43.44 mg/dL to 131.67 ± 34.93 mg/dL, Δ = −55.40 ± 8.51 mg/dL, $P < 0.001$ vs. control group) and the Exercise-only group (Δ = −45.20 ± 5.74 mg/dL, $P = 0.003$ vs. control group) (Figure 3, D). Serum HDL showed a significant

Table 3. Descriptive statistics related to the tests of the three research groups and their comparative results

Variables	Steps	Groups			F	*P*	η^2
		Control (Mean ± SD)	Exercise (Mean ± SD)	Exercise + *Eryngium* (Mean ± SD)			
FBS (mg/dL)	pre-test Post-test	171.73 ± 37.81 175.93 ± 39.47	180.40 ± 38.59 144.73 ± 32.35	190.40 ± 40.68 131.53 ± 29.29	28.45	0.001*	0.58
Betatrophin (pg/ml)	pre-test Post-test	624.87 ± 64.14 591.53 ± 60.59	630.73 ± 66.44 681.07 ± 64.63	623.40 ± 65.71 699.87 ± 58.01	28.88	0.001*	0.57
TC (mg/dL)	pre-test Post-test	183.20 ± 25.64 180.47 ± 27.32	174.27 ± 25.64 175.33 ± 22.63	178.93 ± 34.17 169.40 ± 27.20	0.77	0.47	0.04
TG (mg/dL)	pre-test Post-test	192.07 ± 46.66 200.07 ± 39.96	200.27 ± 40.80 155.07 ± 46.46	187.07 ± 43.44 131.67 ± 34.93	12.81	0.001*	0.39
HDL (mg/dL)	pre-test Post-test	44.73 ± 4.42 42.93 ± 4.98	44.93 ± 5.27 45.87 ± 5.91	45.13 ± 3.99 47.87 ± 7.94	3.61	0.036*	0.15
LDL (mg/dL)	pre-test Post-test	112.20 ± 14.73 114.47 ± 13.32	110.87 ± 17.54 106.47 ± 15.89	111.27 ± 11.98 101.07 ± 10.84	4.70	0.014*	0.19

*A significant difference between the three groups.

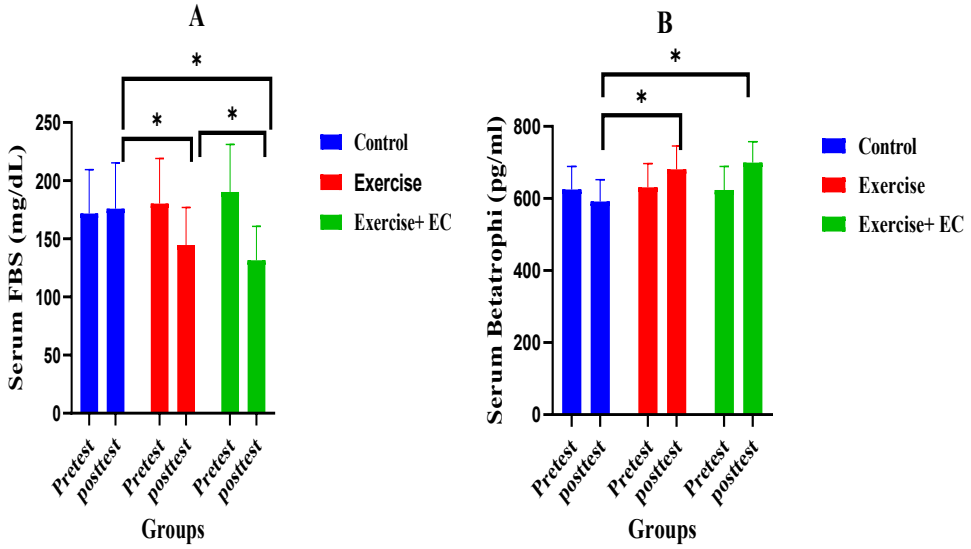

Figure 2. A: The results of the Bonferroni test for comparing means in three groups (control, aerobic exercise, aerobic exercise with *Eryngium* capsule) for fasting blood glucose (serum FBS). B: The results of the Bonferroni test for comparing means in three groups (control, aerobic exercise, aerobic exercise with *Eryngium* capsule) for serum Betatrophin.
Exercise + EC = Aerobic exercise + *Eryngium caucasicum*. * *Significant difference* ($P < 0.05$)

difference among the three test groups ($P<0.036$). The Exercise + *Eryngium* group showed increased HDL (from 45.13 ± 3.99 mg/dL to 47.87 ± 7.94 mg/dL, Δ = + 2.74 ± 3.95 mg/dL, $P=0.033$ vs. control) (Figure 4, E). Serum LDL showed a significant decrease in the Exercise + *Eryngium* group (from 111.27 ± 11.98 mg/dL to 101.07 ± 10.84 mg/dL, Δ = −10.20 ± 1.14 mg/dL, $P=0.012$ vs. control group) (Figure 4, F).

Discussion

In this study, blood glucose levels decreased significantly in both treatment groups compared with the control group. This finding supports existing literature that has shown the effectiveness of regular physical exercise in lowering blood glucose. Consequently, exercise is considered a cornerstone of diabetes mellitus management, especially for type 2 diabetes. Its proven benefits include improved physical performance, reduced adipose tissue, improved metabolic control, reduced risk of coronary heart disease, psychosocial benefits, reduced stress, and possible reduction or elimination of the need for hypoglycemic medicines in type 2 diabetes (4). The glucose-lowering effect of exercise is well documented in the literature. For example, Ghalavand et al showed that an 8-week regimen of continuous aerobic and circuit resistance training resulted in significant reductions in fasting blood glucose in men with type 2 diabetes (17). Similarly, Nezamdoust et al reported that twelve weeks of aerobic training resulted in a decrease in fasting glucose and an improvement in insulin sensitivity in female patients with the same disease (24). The beneficial effects of exercise on glucose metabolism and insulin sensitivity can be ascribed to several underlying physiological mechanisms. These include increased expression of glucose transporter type 4 (GLUT4), increased activity of insulin receptors, glycogen synthase, and protein kinase B (Akt), in addition to trans-regulation of key components of the insulin signaling cascade (19).

In addition, the significant reduction in blood glucose observed in the *Eryngium*-supplemented aerobic exercise group compared to the aerobic exercise group alone may also be attributed to the plant's phytotherapeutic

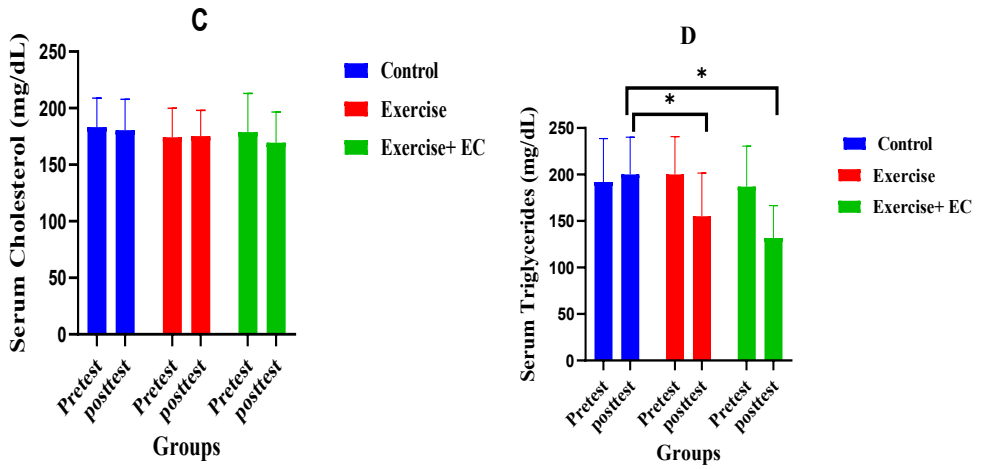

Figure 3. C: The results of the Bonferroni test for comparing means in three groups (control, aerobic exercise, aerobic exercise with *Eryngium* capsule) for the total serum cholesterol variable. D: The results of the Bonferroni test for comparing means in three groups (control, aerobic exercise, aerobic exercise with *Eryngium* capsule) for the total serum triglycerides variable.
** Significant difference* ($P<0.05$)

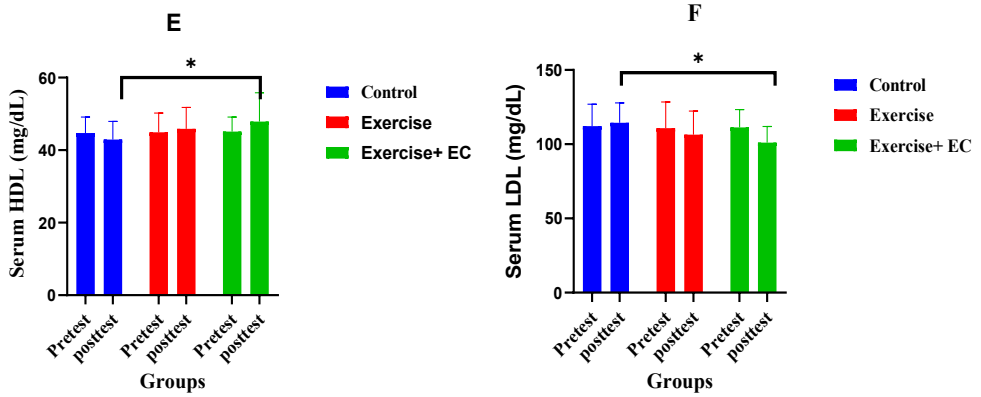

Figure 4. E: The results of the Bonferroni test for comparing means in three groups (control, aerobic exercise, aerobic exercise with *Eryngium* capsule) for the total serum HDL variable. F: The results of the Bonferroni test for comparing means in three groups (control, aerobic exercise, aerobic exercise with *Eryngium* capsule) for the total serum LDL variable.
** Significant difference* ($P<0.05$)

properties. This finding is supported by existing literature demonstrating the antihyperglycemic effects of *Eryngium* species (1, 11, 12, 25, 26). For instance, Khani et al reported that the administration of a hydroalcoholic extract of *Eryngium* significantly reduced blood glucose and increased serum insulin levels in diabetic rats (26). Similarly, Ghadry et al and Afshari et al observed similar effects, with a marked increase in insulin secretion and a concurrent decrease in blood glucose levels in obese rat models after ingestion of *Eryngium* (12, 25). Researchers attribute *Eryngium*'s antidiabetic properties to its constituents. Compounds found in medicinal plants have powerful antioxidant properties. The most important antioxidant compounds in *Eryngium* are terpenes, saponins, flavonoids, tannins, phenols, and carotenoids. By reducing oxidative stress and inhibiting free radicals, they prevent damage to different components of the body, including cells in the pancreas. Finally, they may enhance the activity of insulin receptors, hepatocyte antioxidant enzymes, and enzymes involved in the metabolism of carbohydrates in liver tissue while minimizing lipid peroxidation. By improving pancreatic function, they increase insulin secretion and reduce the level of sugar in the blood (6, 11, 12, 14, 25, 27, 28). Other important constituents in *Eryngium* are octanoic acid and isoxazole. Octanoic acid has been shown to increase the expression of glucose oxidase and glucokinase and to stimulate glucose-induced insulin production in humans and rats (11). Isoxazole derivatives have recently been shown to reduce insulin resistance in HepG2 cells by increasing glucose uptake and are therefore classified as antidiabetic agents (29, 30). In some studies, *Eryngium* did not affect the level of glucose in the blood. In a study by Vaez et al, the consumption of the species *Eryngium caucasicum* did not affect blood glucose in diabetic mice (31). This contradicts the results of the present study. In a study by Shirazi et al , *Eryngium* extract also did not reduce blood glucose levels in type 2 diabetic rats but had a positive effect on reducing liver inflammation and protecting pancreatic cells from oxidative damage (14). The effect or lack of effect of *Eryngium* may be affected by different factors such as the type of plant, the dose administered, the duration of the study, and the diet of the patient. In this study, the dose of *Eryngium* capsules was appropriate based on previous studies. We have observed its effectiveness by regularly administering it and monitoring the patients' nutritional status by a researcher.

In this study, the cholesterol levels of patients in both treatment groups did not change. Triglyceride levels decreased significantly in both treatment groups compared with the control group. High-density lipoprotein (HDL) and low-density lipoprotein (LDL) levels in the exercise group and the *Eryngium* group showed significant changes compared with the control group, with increasing HDL and decreasing LDL. In a study by Ghalavand et al eight weeks of aerobic exercise with three training sessions per week did not affect triglycerides or total cholesterol, but it increased HDL and significantly reduced LDL (17). In this study, the patients' lipid factors were within the normal range at baseline and did not change significantly with aerobic exercise. In a study by Magalhães et al , combined training with various intensities did not affect total cholesterol or triglycerides in patients with type 2 diabetes; however, HDL and LDL improved (32). Asako et al showed that an aerobic exercise regimen in patients with diabetes led to significant improvements in blood glucose levels and fasting plasma lipid profiles (22). Similarly, Nasiri et al found that, in women with type 2 diabetes, an 8-week combination training program resulted in significant reductions in triglycerides, total cholesterol, and LDL concentrations, but no significant changes in HDL concentrations were observed (33). In the above-mentioned studies and in this study, only a subset of lipid parameters was observed to be significantly altered. This limited effect can be attributed to the baseline characteristics of the lipid profiles of the patients. The optimal reference ranges for lipid factors according to established clinical guidelines are total cholesterol < 200 mg/dL; triglycerides < 200 mg/dL; HDL 50–59 mg/dL in women and 40–50 mg/dL in men; and LDL < 100 mg/dL is desirable (borderline: 100-129, high: > 130) in diabetic patients. In studies where patients with diabetes had a baseline normal lipid profile, physical exercise had a smaller effect on diabetes scores (19). Other factors influencing lipid parameters include training intensity, training duration, number of training sessions per week, and changes in body weight (19, 33).

In this study, aerobic exercise alone produced significant effects on triglyceride levels only. Conversely, the combination of *Eryngium* supplementation and aerobic exercise resulted in significant changes in triglycerides, LDL, and HDL concentrations. This synergistic effect suggests that the observed wider lipid modification effect is likely attributable to the additional *Eryngium* intake. This finding is consistent with previous literature, where *Eryngium* has been associated with reductions in total cholesterol (11, 12, 26), triglycerides, and LDL (12, 26) in the diabetic population, as well as an increase in HDL (26) in diabetic patients. The results reported by Ghadery et al also showed that six weeks of *E. campestre* consumption in obese rats significantly reduced the levels of cholesterol, triglycerides, and LDL, but not HDL (25). Researchers have attributed dyslipidemia to specific compounds in *Eryngium*, such as flavonoids, tannins, saponins, phenols, and alkaloids (26, 34, 35). Increased insulin production may also be the cause of the improvement in lipid profile. Insulin deficiency is known to reduce lipoprotein lipase activity, resulting in hypertriglyceridemia and increased plasma levels of free fatty acids (36). The rate of improvement in lipid factors with *Eryngium* can be

attributed to the initial state of the lipids, the dose, and the duration of administration. In this study, although the lipid status of patients was already favorable at the start of the study, it was also affected by *Eryngium* use.

In this study, significant increases in betatrophin were observed in both treatment groups compared with the control group, but no significant difference between the two treatment groups was observed. The effect of exercise on betatrophin has been investigated in several studies, but the effect of *Eryngium* on betatrophin has not been investigated in any of the studies. In several studies, combined exercise (aerobic and strength training) in obese patients reduced elevated betatrophin levels (6, 18, 19). However, in another study, betatrophin levels in obese subjects were not altered after combined training (18). These findings contrast with those of this study. Most of the existing literature confirms that weight gain, obesity, and increased blood lipid levels are associated with betatrophin elevations. By contrast, weight loss leads to a decrease in the level of this substance (6, 19). Researchers described exercise as a form of calorie restriction, which reduced the levels of betatrophin in obese patients as they lost weight (6). In this study, subjects were moderately overweight, with a body mass index (BMI) of 26–27. They differed in body weight from those in the above studies who were obese, which may explain the difference in the study results. In a study by Salehi et al, eight weeks of high-intensity endurance and interval training significantly increased lipasin (betatrophin) gene expression in the livers of type 2 diabetic rats in the training group compared with the control group. Moreover, a negative correlation between lipasin gene expression and the insulin resistance index was observed (4). This is in line with the results from the present study. In a study by Sadeghiupour et al four weeks of endurance training increased betatrophin levels in diabetic rats, although this was not statistically significant (3). They reported that rats in the diabetic group weighed less than rats in the healthy control group due to insulin induction and that their betatrophin levels were lower than those of healthy rats at baseline. Physical exercise in diabetic rats was able to improve the decrease in betatrophin levels. Exercise actually helps to balance betatrophin levels. Other factors affecting betatrophin include insulin and insulin resistance. Lu et al highlighted the negative correlation between betatrophin and insulin resistance and explained that betatrophin levels are affected by relative insulin levels and that insulin stimulates the secretion of betatrophin by activating the PI3K–Akt signaling pathway, in which case insulin resistance is an inhibitor of this pathway (37). Insulin status and insulin resistance were not examined in this study; however, a significant reduction in blood glucose was observed. This decrease was attributed to improved function and increased insulin levels, which ultimately resulted in increases in betatrophin. In the above-mentioned studies, the effect of exercise on betatrophin varied among different individuals (healthy, obese, diabetic), with increases, decreases, or no changes in betatrophin levels being observed. The effect of training on betatrophin is influenced by several factors, including baseline betatrophin levels and the health status of the subjects (whether they are healthy, diabetic, overweight, etc.), body composition, insulin resistance, and training protocol (intensity, duration, and volume of training). One factor is the type of equipment used (38). In fact, exercise seems to have reduced betatrophin levels in studies with a high baseline and increased them in studies with a low baseline. In this study, three diabetic groups and no healthy group were enrolled, and initial betatrophin levels were not compared with those in healthy subjects. As beta-cell proliferation is stimulated, betatrophin may be beneficial in people with diabetes. However, excessive expression of betatrophin may lead to increased blood triglycerides, which are harmful to the body. As a result, its equilibrium is beneficial, whereas both its increase and decrease are detrimental. We have seen a lot of fluctuation in people with diabetes. Physical activity has been shown to help stabilize these changes. When comparing the two treatment groups, betatrophin levels were higher in the group receiving both *Eryngium* and exercise compared to the group receiving only exercise, but the difference was not statistically significant, indicating that *Eryngium* did not affect betatrophin levels. To our knowledge, no research in this field has been carried out. If the duration of *Eryngium* use were prolonged, the effects of *Eryngium* on glucose and insulin resistance might also affect betatrophin.

This study has several limitations. The duration of the intervention was short. It is recognized that the 6-week intervention period may not fully capture the long-term effects of aerobic exercise and supplementation with *Eryngium caucasicum*. Future studies with longer follow-up periods (e.g., 12 weeks or more) are warranted to assess the durability of the results. The sample size was moderate (n = 15 for each group). Although our study was sufficiently robust to detect significant differences, a larger sample size would have increased the generalizability of the findings, especially across different demographic groups. Another limitation of our study was the lack of blinding (no placebo use and participants' awareness of group assignment). Due to the nature of the exercise intervention, full blinding was not practicable. Future studies could consider using a placebo-controlled design to further minimize bias. Additionally, some variables, such as insulin, were not measured in this study. The inclusion of measures of insulin sensitivity or insulin levels would provide more insight. This limitation is now explicitly mentioned, and we recommend that such measurements be included in future work as well.

The clinical results of this study suggest that combining

aerobic exercise with *Eryngium caucasicum* may provide an additional approach to the management of type 2 diabetes, especially to improve glycemic control (reduction in fasting glucose) and lipid profiles (increased HDL, decreased LDL). The observed increase in betatrophin, a potential regulator of beta-cell proliferation, also suggests promising therapeutic avenues, although further research is needed to confirm its mechanistic role.

Conclusion

According to this study, aerobic exercise alone and in combination with hydroalcoholic *Eryngium* extract reduced blood glucose and triglycerides, while increasing betatrophin, compared with the control group. In the *Eryngium* aerobic training group, HDL increased and LDL decreased significantly. Total cholesterol was not influenced by the intervention variables. Only the glucose variable was significant when comparing the two treatment groups, suggesting that both *Eryngium* and aerobic exercise were effective. Therefore, it is recommended that patients with diabetes use aerobic exercise in combination with *Eryngium*, which has fewer side effects than synthetic medicines, to improve glycemic control.

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Competing Interests

The authors declared that there is no conflict of interest.

Ethical Approval

All ethical principles were observed for the subjects. Ethics Committee of Qazvin University of Medical Sciences: IR.QUMS.REC.1401.104 and clinical trial code: IRCT20211116053081N1.

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