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Beneficial Hypoglycemic, Hypolipidemic Effects of Aerial Branches and Roots Extract *of Eryngium caeruleum* M. Bieb on Streptozotocin-Induced Diabetes Model in Rats

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Abstract

Eryngium caeruleum (Apiacea) is native to the northern forests of Iran. The anti-diabetic effect of other species of the genus *Eryngium* has already been reported in previous studies. In this study, the anti-diabetic effect of this extract and their effect on animal blood lipid factors was investigated. Hydroalcoholic extract was obtained from different parts of the plant, including roots, leaves, and aerial branches with fruits were prepared by maceration with 70% ethanol. Oral acute toxicity of the extracts was assayed in different doses of 2000, 4000, and 8000 mg/kg in rats. To induce diabetes in the studied animals, 60-70 mg/kg of streptozotocin (STZ) was injected intraperitoneally (IP). For the purpose of this study, 72 male Wistar rats were randomly divided into different groups of normal, diabetic, and positive controls (metformin 500 mg/kg) as well as 9 diabetic groups that orally received 200, 400, and 800 mg/kg of extracts. The effects of the treatment with extracts for a 14-day period were investigated on weight, blood glucose, and lipid profile. By comparing the control groups with the groups of hydroalcoholic extracts of *E. caeruleum* showed that the most effective sample on weight gain and also on reducing blood glucose was the group receiving 800 mg/kg of the aerial branches extract ($P < 0.01$ and $P < 0.001$, respectively) after 14 days. As well, the most effective sample on lowering the blood lipid factors was the hydroalcoholic extract of the root of *E. coareleum* with a dose of 200 mg/kg, which showed a significant effect on lowering total cholesterol in diabetic rats compared to the diabetic controls ($P < 0.05$). Hydroalcoholic extract of leaves with 200 mg/kg also showed a better effect on lowering the LDL and VLDL levels compared to the diabetic control group ($P < 0.001$). The results of pancreatic histology in the samples showed that the extracts of the aerial branch and root (800 mg/kg) had

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significant effects on the regeneration of the islets of Langerhans compared to the diabetic control group. In conclusion, *E. caeruleum* could significantly improve glycemic and lipid profiles in diabetic rats.

Keywords: *Eryngium*; Diabetes mellitus; Blood glucose; Streptozotocin (STZ); Rats

Introduction

Diabetes mellitus (DM) is a group consisting of metabolic disorders that have appearance similar to hyperglycemia. Epidemiological studies reported that DM can become an epidemic associated with metabolic and endocrine disorders worldwide [1]. The important issue is alarm increasing in type-2 diabetes mellitus (T2DM) among adults and children. Additionally, metabolic dysregulation with type-1 diabetes causes some secondary pathophysiological changes in many organs, which consequently impose a huge burden on the affected individuals and health systems [2].

Nowadays, due to the ineffectiveness of chemical drugs on controlling blood glucose and their subsequent side effects, one of the main goals of the effective diabetes treatment with minimal side effects is the need for systematic search in order to find natural resources, including herbs, as blood glucose lowering agents. Other benefits of using herbs to treat diseases are low side effects, low cost, high effectiveness, and availability. In recent years, the anti-T2DM properties of many herbs and natural compounds have been identified and many studies have been conducted to elucidate possible mechanisms in this regard [3].

Eryngium caeruleum M.Bieb. (Syn. *Eryngium caucasicum* Trautv.) is one of the herbs with many applications in the traditional Persian medicine (TPM), which recommended its roots usage besides the aerial parts of the herb. Researchers in the field of Persian medicine consider that E. *caeruleum* belongs to the genus *Eryngium*, which was also called “Qaracaane” in the book "Makhzan Al-Advieh.", as one of the sources of TPM. The genus *Eryngium* belongs to the Apiaceae family, and with 274 accepted species, it is considered as the largest genus of this family. The herbs of this genus have spread in all over the world, especially in Asia, Europe, America, Africa, and Australia [4].

Different parts of the genus *Eryngium* has been used for the treatment of various diseases such as diarrhea and gastrointestinal problems, bladder and kidney disorders, kidney stones, tumors, infections, skin diseases, anemia, sexually transmitted diseases, women's reproductive problems such as infertility, menstrual cramps, eliminating and facilitating labor problems, postpartum abdominal pain, vaginal infections, various inflammatory diseases, colds, flu, fever, asthma, cough, sinusitis, rheumatism, hypertension, eye disorders, poisoning, liver disease, diabetes, malaria, and snake bites in traditional medicines from various ethnic groups and various countries in all parts of the world, including

Asia, Europe, and Central and South America from ancient times to the present day. These herbs also have some properties, including fitness enhancing, pain relief, constipation treatment, wound healing, anthelmintic, analgesic, anti-malarial and antibacterial, diuretic, appetizing, sedative, and sexual stimulating properties in ethnobotanical treatments performed in different countries [5].

Several pharmacological studies have also proven the effects of herbs of different species of this genus on bacteria and fungi, malaria, leishmaniasis and worms, venom, and bite of snakes and scorpions, as well as analgesic and anti-inflammatory, anti-diabetic, anti-seizure, anti-hypoxic, anti-cancer, anti-mutagenicity, cytotoxic effects, renal protective effects, anti-hemolytic activity, antioxidant activity, skin effects, and the increased skin permeability, food preservation effect, and their high nutritional values [6,7].

In the present study, considering the anti-diabetic effects of different species of *Eryngium* genus, the anti-diabetic effects of its different parts, including roots, leaves, and fruiting branches of *Eryngium caereleum* in streptozotocin-induced diabetic rats were investigated.

Methods

Plant material

E. caeruleum samples were collected from Gilan province, north of Iran. As well, its species and genus were identified in the herbarium of the Faculty of Pharmacy, Tehran University of Medical Sciences with the voucher number THE-6610. Thereafter, different parts of this herb, including its roots, leaves, and aerial parts (fruiting branches), were dried at the ambient temperature away from light and moisture.

Hydroalcoholic Extraction

The extraction process was performed on 300 g of dried powder of the studied samples via 70% ethanol using maceration method for 3 days (72 h). Accordingly, this process was repeated three times and the extracts were then concentrated using a rotary evaporator.

Animal studies

At this stage, the experiment was performed on male Wistar rats weighing between 250 and 300 g. These rats were purchased from the Faculty of Pharmacy, Tehran University of Medical Sciences. Thereafter, the animals were placed in their cages in a temperature-controlled environment (24 ± 1 ° C), with 12:12 light–dark (LD) cycle. The animals were then fed with standard food and water. Afterward, they were placed in the laboratory for one week prior to the experiment in order to be accustomed to the experimental conditions. In the current study, all the experimental protocols were approved by the Research Ethics Committee of the Faculty of Science, University of Tehran (IR.TUMS.TIPS.REC.1398.112).

Oral acute toxicity

Acute oral toxicity was assessed by gavage in ten groups, each one consisting of three rats, including three different doses of extracts (2000, 4000, 8000 mg/kg), as well as the normal saline

as the control group. Subsequently, animal mortality, and behavioral and nutritional symptoms were evaluated for 24-72 h.

Induction of diabetes

After the time of 24 h fasting in rats, intraperitoneal (IP) streptozotocin (STZ) (Sigma, USA) at a dose of 60-70 mg/kg was used. Accordingly, STZ was dissolved in 0.05 mol/L cold sodium citrate buffer at pH 4.5 proximately before use. After 72 h, hyperglycaemia was defined using a glucometer (Glucotrend, Germany) in the blood samples obtained from the tail veins of the study rats. Finally, only those animals with non-fasting blood glucose levels higher than 200 mg/dL were selected and then studied in this research.

Experimental design

The rats were randomly divided into the following 12 groups, each one consisting of 6 rats: 1. Normal control (normal saline 5 ml/kg, n = 6); 2. Diabetic control (normal saline 5 ml/kg, n = 6); 3. Diabetic + metformin 500 mg/kg, (n = 6); 4, 5, and 6. Diabetic + hydroalcoholic extract of *E. caeruleum* (HEC) root (RE) (200, 400, 800 mg/kg, respectively, n = 6); 7, 8, and 9. Diabetic + hydroalcoholic extract of *E. caeruleum* (HEC) leave (LE) (200, 400, and 800 mg/kg, respectively, n = 6); and 10, 11, and 12. Diabetic + hydroalcoholic extract of *E. caeruleum* aerial part (AE) (200, 400, and 800 mg/kg, respectively, n = 6).

All the study animals were treated daily for a 2-week duration by oral gavage. Non-fasting blood glucose level and weight of the rats were measured at the baseline, at the end of the first, and at the end of the second week of this experiment. At the end of the study on the 15th day, heart blood samples were collected from the rats under deep anesthesia of xylazine (15 mg/kg) (Alfasan, Netherlands) as well as ketamine (80 mg/kg) (Alfasan, Netherlands). The obtained blood samples were centrifuged at 4000 revolutions per minute (RPM) for 10 min and then the separated serum was stored at -70°C until biochemical analysis [8]. Subsequently, Lipid profiles, including ventricular blood low density lipoprotein (LDL), high density lipoprotein (HDL), very-low-density lipoprotein (VLDL), and cholesterol lipid indices, were measured. Finally, the animal's abdomen was opened and the histology sample of rat pancreas was isolated from the five groups of normal and diabetic controls as well as 800 mg/kg groups of RE, AE and metformin for performing the pathology study.

Statistical analysis

All the obtained data were compared using SPSS software. Data were first analyzed for normal distribution and equal variance. One-way ANOVA and post hoc (Tukey's multiple comparisons test) tests were also used to determine the statistically significant differences among the groups. Finally, the data were expressed as mean±SEM and $P<0.05$ was considered as statistically significant.

Results

Acute toxicity test

Administration of doses of 2000, 4000, 8000 mg/kg of 70% hydroalcoholic extracts (RE, LE,

and AE) showed no death or change in the animals after 24 and 48 h. Based on these results, the LD50 is considered higher than 8 g / kg.

Body weight measurement

Figure 1 shows the effect of the repeated administration of RE, LE, and AE of *E. caeruleum* on body weight in diabetic rats. In both the first and second weeks of the treatment protocol, no significant difference was found between the diabetic control and normal control rats in terms of body weight. By analyzing the results, it was shown that root extract (RE) at a dose of 800 mg/kg led to a significant improvement in the weight of diabetic rats on the day 7 ($p < 0.05$). Additionally, at the end of the experiment (day 14), root extract at dose of 800 mg/kg led to a significant improvement in the weight of the diabetic rats in the RE ($P < 0.001$) and AE groups ($P < 0.01$), respectively.

Treatment with metformin at a dose of 500 mg/kg (as the standard anti-diabetic drug) led to a significant increase in the weight of the diabetic rats in the second week ($P < 0.05$).

Blood glucose assay

Figure 2 shows the effects of hydroalcoholic extract of *E. caeruleum* leaf, root, and aerial parts on the STZ-induced diabetic rats. STZ injection at a dose of 60 mg/kg significantly increased

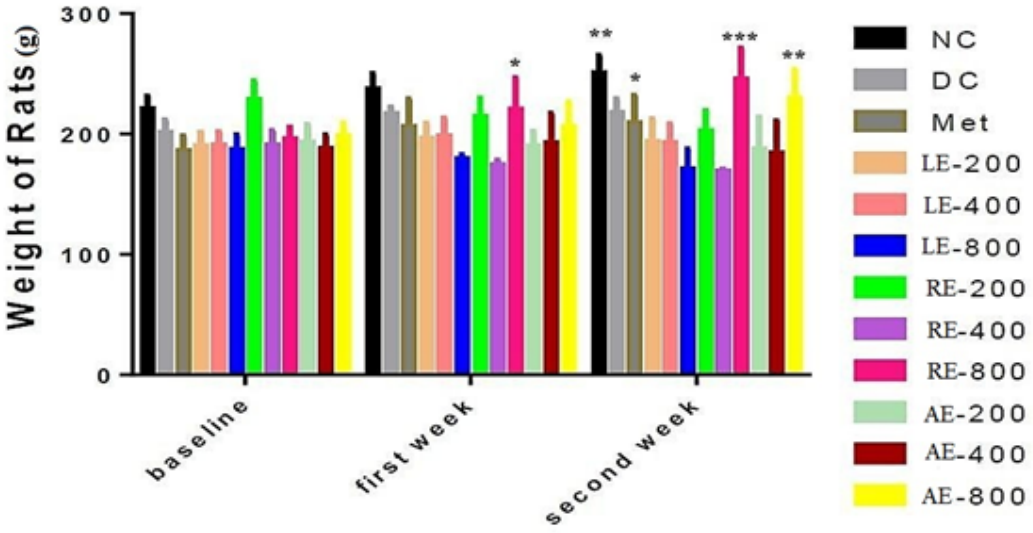

Figure 1: Effect of hydroalcoholic extract of *E. caeruleum* (EC) root (RE), leave (LE) and aerial part (AE) on body weight changes in rats with STZ-induced diabetes (mean ± SEM) (n = 6). Data expressed as means ± SEM. *** $P < 0.001$, ** $p < 0.01$, * $p < 0.05$ compared to DC. NC: Normal control; DC: Diabetic control; Met: metformin 500 mg/kg of animal weight; LE: Hydroalcoholic extract of EC leave; RE: Hydroalcoholic extract of EC root; AE: Hydroalcoholic extract of EC aerial part; weight of rats (gram)

blood glucose levels in rats in the diabetic control group compared to the normal control group ($P < 0.001$).

Notably, daily administration of hydroalcoholic extract of *E. caeruleum* AE at a dose of 800 mg/kg resulted in a significant hypoglycemic effect on days 7 ($P < 0.05$) and 14 of the experiment ($P < 0.001$). Moreover, daily administration of metformin at a dose of 500 mg/kg showed a significant hypoglycemic effect on diabetic rats

in the first and second weeks of this study ($P < 0.001$). As well, no significant difference was found between AE at a dose of 800 mg/kg with the metformin treatment in terms of the hypoglycemic effect in the first and second weeks ($P > 0.05$).

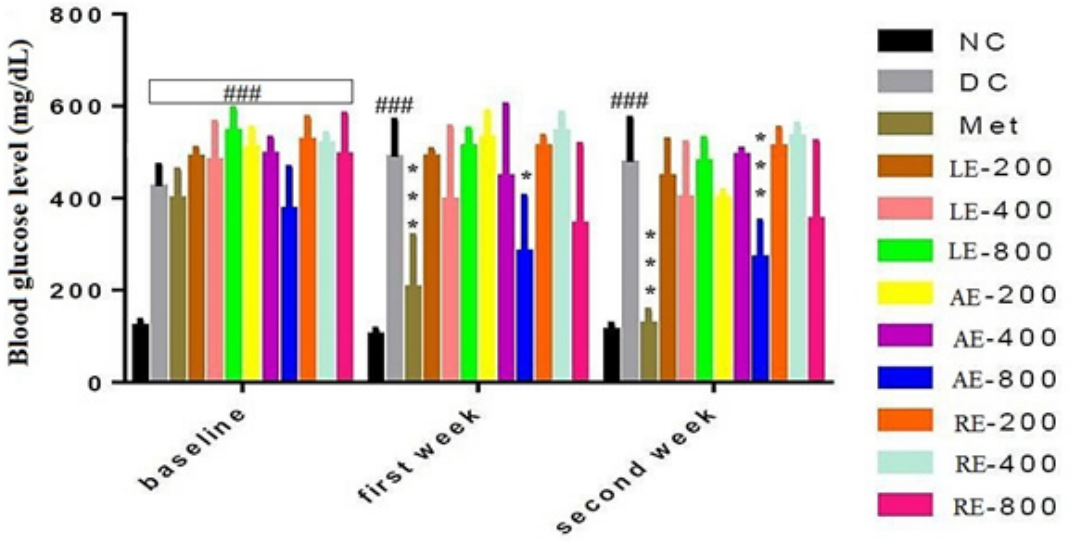

Figure 2. Effect of hydroalcoholic extract of E. = (EC) root (RE), leave (LE) and aerial part (AE) on blood glucose level in rats with STZ-induced diabetes (mean ± SEM) (n = 6). Data expressed as means ± SEM. *** $P < 0.001$, ** $p < 0.01$, * $p < 0.05$ compared to DC. ### $P < 0.001$ compared to NC. NC: Normal control; DC: Diabetic control; Met: metformin 500 mg/kg of animal weight; LE: Hydroalcoholic extract of EC leave; RE: Hydroalcoholic extract of EC root; AE: Hydroalcoholic extract of EC aerial pars.

Blood lipid profile assay

The effect of the hydroalcoholic extracts of *E. caeruleum* obtained from leaf, aerial part, and root on the lipid profile (TG, TC, LDL, and HDL) are shown in table 1. In this regard, the results showed no significant difference in terms of the total cholesterol (TC) level between the diabetic control group and normal control group. However, TC level was significantly higher in the metformin–treated group compared to the normal control ($P < 0.05$) and the diabetic control groups ($P < 0.01$).

The treatment with hydroalcoholic root extract (RE) at a dose of 200 mg/kg for a 2-week duration resulted in a significant reduction in TC level compared to the diabetic control group ($P < 0.05$). Although the TC level was lower in the other extract-treated groups than the diabetic control group, this difference was not statistically significant. Of note, there was no significant difference in terms of TC levels between other extract-treated groups and the normal control group. The results of investigating the effects of the extracts as well as metformin on the blood triglyceride (TG) level of the studied animals showed no significant difference between the TG levels in all the experiment groups and the normal control group after the two weeks of treatment. As it was found, the administration of extracts and metformin for 14 days led to no significant changes in HDL levels in the treatment groups compared to the control groups.

Additionally, the plasma LDL level in all the groups, except the LE group 200 mg/kg in the diabetic group (P <0.001), was not changed significantly. While the VLDL level showed a significant increase in both the metformin and LE groups (200 mg/kg) compared to the normal and diabetic controls (P < 0.001).

Table 1: Effects of *Eryngium caeroleum* hydroalcoholic extract on the lipid profile in the serum of streptozotocin induced diabetic rats (mean ± SEM, n = 6).

Treatment	Dose (mg/kg)	TC (mg/dl)	TG (mg/dl)	HDL (mg/dl)	LDL (mg/dl)	VLDL (mg/dl)
Normal control (NC)	Normal saline (5 mL/kg)	53.5±10.3	49.67±13.7	30.17±6.3	5.67±1.6	9.83±2.7
Dabetic control (DC)	Normal saline (5 mL/kg)	50.2±11.4	43.67±7.3	26.5±4.7	5.33±2.2	8.83±1.5
Metformin	500 mg/kg	73.2±6.8$^{\#,*}$	83.5±20.5*	39.67±4.5	8.67±1.4	19.83±3.4$^{\#\#\#,***}$
LE	200 mg/kg 400 800	57.2±5.6 48.3±12.0 53.0±6.3	77.0±52.1 46.67±10.1 42.33±14.1	31.17±7.2 32.83±8.5 26.83±5.8	11.67±1.5$^{\#\#\#,***}$ 7.67±3.3 6.17±1.2	24.83±10.2$^{\#\#\#,***}$ 10.0±2.4 11.17±3.1
AE	200 mg/kg 400 800	42.7±8.3 40.8±10.8 47.5±7.8	33.83±7.4 38.33±7.2 48.5±14.9	37.33±6.4 32.0±9.2 31.33±3.3	5.0±2.7 6.0±1.5 6.7±1.4	6.67±1.6 8.17±0 9.67±3.2
RE	200 mg/kg 400 800	29.5±14.1* 35.5±7.1 44.5±10.5	25.17±5.0 30.0±7.2 33.67±10.9	25.0±13.3 28.17±4.7 37.5±7.7	3.67±1.8 3.67±1.2 6.67±1.8	5.17±1.2 6.17±1.5 6.83±2.2

The one-way ANOVA and post hoc test were used to determine statistically significant differences between the groups. #P < 0.05, ###P < 0.001 significant compared with Normal control, *P < 0.05, ***P < 0.001 significant compared with Diabetic control. TC: Total cholesterol; TG: Triglyceride; HDL: High density lipoprotein; LDL: Low-density lipoprotein; VLDL: Very low density lipoprotein; LE: Leaf extract; AE: Aerial (fruiting) part extract; RE: Root extract.

Histopathological analysis

As shown in figure 3, in the diabetic control rats, size and β cells in the islets of Langerhans have significantly reduced, some islet's were found to have degraded. On the other hand, the metformin-treated diabetic group with normal cells showed a change in the size of the islets. Apoptotic changes were also seen in the form of a small picnotic nucleus and a deeply acidophilic cytoplasm. In addition, the diabetic group treated with aerial AE (800 mg/kg) showed the regenerated pancreatic islet cells as well as the reduced pancreatitis. Furthermore, the diabetic rat group treated with RE (800 mg/kg) showed the regenerated pancreatic islet cells as well as the reduced pancreatitis. In this study, histological and biochemical evaluations showed the possibility of regenerating the islets using both AE and RE (800 mg/kg) of *E. caeruleum.*

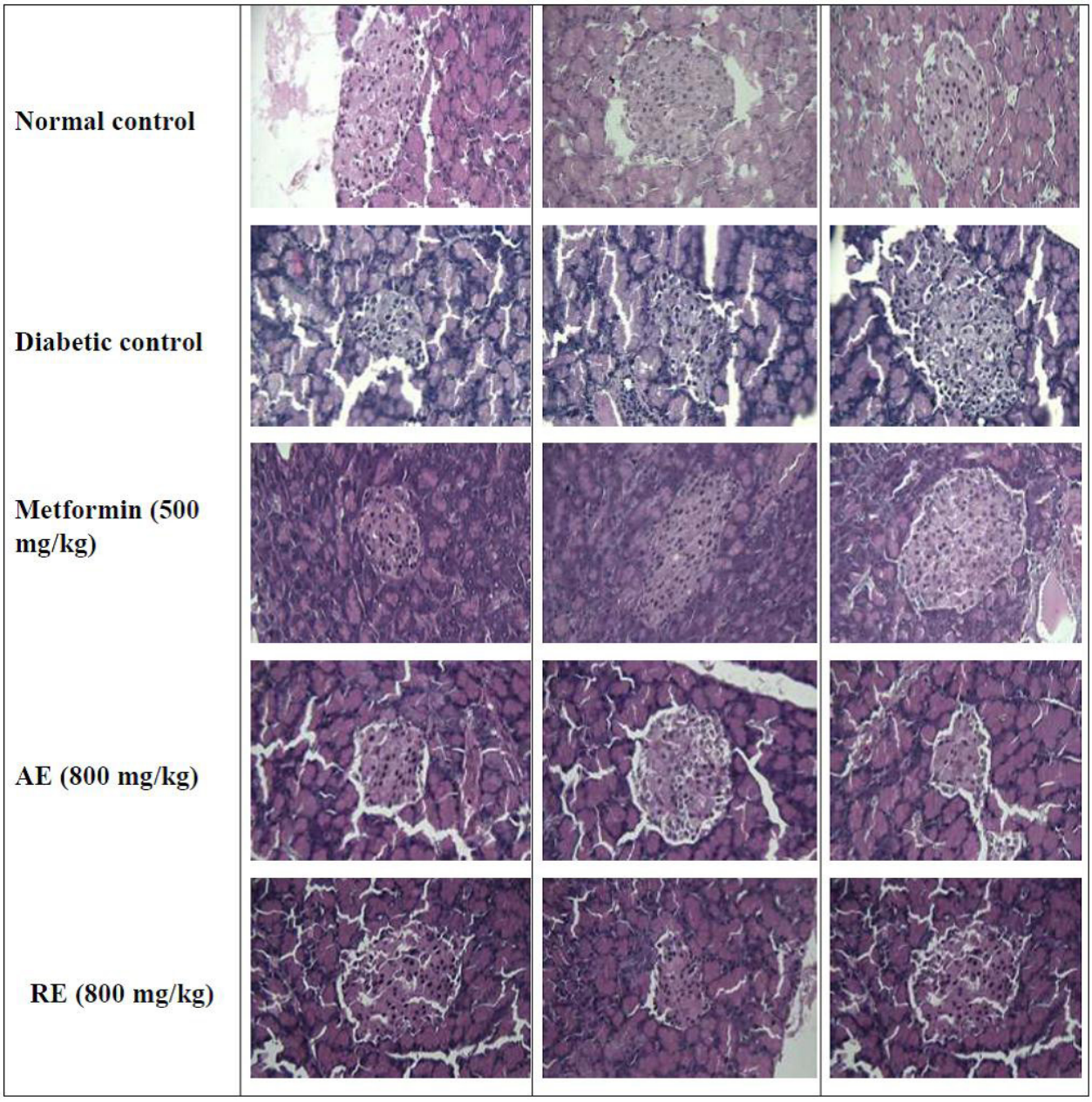

Figure 3: Pancreas histopathology. Control rats shows endocrine glands with normal histological features of islets of Langerhans. Pancreatic acini are normal in the exocrine part with pyramidal cells and represents basal basophils and apical acidophilic cytoplasm (H&E, x200). Diabetic rats: The islets of Langerhans have been significantly reduced in size and in terms of β cells, some of the islet cells have been shown to be destroyed by the cytoplasm (H&E, x200, 400). Metformin 500 mg/kg: The metformin-treated diabetic group with regular cells shows a change in the size of the islets. Apoptotic changes are seen in the form of a small picnotic nucleus and a deeply acidophilic cytoplasm (H&E, x200, 400) .AE (800 mg/kg) sample: A diabetic group treated with aerial part extract showed regenerated pancreatic islet cells and reduced pancreatitis (H&E, x200).RE (800 mg/kg): A diabetic rat group was treated with root extract and showed regenerated pancreatic islet cells and reduced pancreatitis (H&E, x400).

Discussion and Conclusion

Considering the confirmed anti-diabetic effects of different species of *Eryngium*, the hydroalcoholic extract of *E. caereleum* was evaluated for the anti-diabetic effects of its different parts, including roots (RE), leaves (LE), and fruiting branches (AE) in the STZ-induced diabetic rats. According to the data obtained from weight measurements in the current study, RE and AE at the dose of 800 mg/kg led to a significant increase in rat's weight as about 2% and 25% after 14 days of treatment, respectively, compared to the diabetic control group. Additionally, daily treatment with AE (800 mg/kg) significantly reduced the blood glucose level on days 7 and 14 of the experiment. Thus, no significant difference was observed with the metformin group. The results of the pancreatic histology also showed that the AE and RE (800 mg/kg) had significant effects on controlling blood glucose level compared to the diabetic control group, which may possibly be due to the regeneration of the islets of Langerhans.

In a study by Afshari *et al.,* the hypoglycemic and lipid-lowering effects of the leaf extract of *E. caeruleum* on streptozotocin-nicotinamide induced type 2 diabetes in male rats were investigated. In this study, it was observed that the extract at doses of 200 and 300 mg/kg significantly reduced the fasting blood sugar level compared to the control group. Moreover, this improved serum insulin levels. LDL levels were also decreased significantly by administrating a dose of 300 mg/kg [9]. In our study, a random blood glucose measurement was performed, in which the animal's blood glucose was found to be better controlled than the other groups using a dose of 800 extracts of the fruiting branch (AE) of this plant.

In another study conducted by Abdul Sadiq *et al.,* the chloroform fraction obtained from the methanolic extract of the aerial parts of *E. caeruleum* showed a better effect compared to the other fractions by applying α-glucosidase inhibition test. Correspondingly, this fraction in the diabetic mice by passing 24 h from the intraperitoneal injection of different doses showed a significant reducing effect compared to the control group. In this study, blood sugar levels were measured in different hours after the first injection of the extract [10].

Many studies have been previously conducted on hypoglycemia in animal models using various extracts of *Eryngium* species. As well, the hypoglycemic activity of the aqueous branch extract of *Eryngium creticum* has been tested in the STZ-induced diabetic rats. The results indicate that this extract could significantly reduce the blood glucose concentration [11].

A study performed on diabetic rats in 2012 showed that blood glucose, creatinine, uric acid, and TC levels have elevated in diabetic rats treated by ethanolic extract of *E. carlinae.* Accordingly, the results showed that the herb extract could significantly reduce TG, uric acid, and TC levels. This herb can also be effective on lowering blood lipids in patients with cardiovascular diseases and even in patients with diabetes mellitus [12].

Norouzi and Valipour (2021) in their study investigated the effects of *E. campestre* extract on blood sugar levels and blood lipid indices

in diabetic male rats. Their results showed that the treatment with different doses of *E. campestre* extract for two weeks significantly reduced blood sugar ($p < 0.001$), triglyceride ($p < 0.001$), and VLDL ($p < 0.001$) levels; however, LDL level was significantly increased ($p < 0.001$). In addition, *E. campestre* extract significantly increased total cholesterol ($p < 0.05$) at 100 mg/kg dose and HDL at both 100 mg/kg ($p < 0.05$) and 200 ($p < 0.001$) doses [13].

Rehman et al. (2017) showed that two new flavonol glycosides obtained from the aerial parts of *E. caeruleum* represented an inhibitory effect on the aldose reductases (ALR1 and ALR2) and glucosidases (α and β) enzymes under *in vitro* condition. It was also found that these two flavonoids had stronger effects on inhibiting ALR1, rather than ALR2 [14].

Dehghan et al. (2016) reported that methanolic, hexane, and ethyl acetate extracts derived from the aerial parts of *E. caeruleum* by inhibiting the α-amylase and α-glucosidase enzymes showed anti-diabetic effects. In this regard, the highest inhibitory effect was found to be related to methanolic extract, followed by ethyl acetate and hexane extracts, respectively [15].

Another study showed that the oral administration of aqueous extract of *E. creticum* aerial parts could reduce blood glucose levels in rats with normal blood glucose (20%) and also in streptozocin-induced diabetic rats (64.2%). Moreover, a study reported that the aqueous extract of this herb has a strong hypoglycemic effect on rats under starch diet [16]. Besides, some laboratory studies have previously shown that the methanolic extract of *E. creticum* has an inhibitory effect on hormone-sensitive lipase (HSL) activity. Considering the fact that high levels of fatty acids and triglycerides play important roles in the development of type 2 diabetes and insulin resistance, so this enzyme plays key roles in both fat metabolism and energy homeostasis in mammals [17]. Furthermore, in a previous study conducted on rats with normal blood glucose as well as diabetic rats, the oral administration of a single dose of *E. foetidum* leaf extract showed no significant effect on lowering blood glucose levels [18]. The results of the present study show that aerial part (fruiting) (AE) and root extracts at the dose of 800 mg/kg could have a significant effect on weight control in diabetic rats. Moreover, AE (800 mg/kg) indicated a significant hypoglycemic effect. According to this result, it can be concluded that the administration of hydroalcoholic extract of *E. caeroleum* aerial parts could be effective on lowering blood glucose in STZ-induced diabetes. Additionally, none of the extract doses had a significant effect on reducing LDL and VLDL, except the leaf extract at dose of 200 mg; however, this requires further studies to be confirmed. Histological results showed that the treatment with AE and RE (800 mg/kg) had significant effects on the regeneration of pancreatic cells in this group in comparison with the diabetic control group.

Considering the presence of some effective compounds such as flavonoids, triterpenes, and saponins in different parts of this medicinal plant [5], so its beneficial hypoglycemic effects can be attributed to various mechanisms, including the inhibition of alpha and beta-gluco-

sidase enzymes as well as antioxidants effects, and playing a role in the regeneration of pancreatic cells.

The results of the present study can be used as a starting point for further usages of different parts of this herb in the preparation of food products as well as the production of herbal medicinal supplements in the future.

Conflict of Interest

None.

Acknowledgment

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References

[1] Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. PLoS medicine 2006;3:e442.

[2] Kasper DLFA, Hauser S, Longo D. Harrison's Principles of Internal Medicine. 19th ed. McGraw-Hill Companies. New York 2015.

[3] Xu L, Li Y, Dai Y, Peng J. Natural products for the treatment of type 2 diabetes mellitus: Pharmacology and mechanisms. Pharmacol Res 2018;130:451-465.

[4] Ghajarieh Sepanlou M, Salami F, Mirabzadeh Ardakani M, Sadati Lamardi SN, Sadrai S et al. The proximate, mineral and amino acid composition of spring, autumn leaves and roots of *Eryngium caeruleum* M. Bieb. RJP 2019;6:1-7.

[5] Sepanlou MG, Ardakani MM, Hajimahmoodi M, Sadrai S, Amin GR et al. Ethnobotanical and traditional uses, phytochemical constituents and biological activities of Eryngium species growing in Iran. TMR 2019;4:148.

[6] Wang P, Su Z, Yuan W, Deng G, Li S. Phytochemical constituents and pharmacological activities of *Eryngium* L.(Apiaceae). Pharm Crops 2012;3:99.

[7] Kikowska M, Dworacka M, Kędziora I, Thiem B. *Eryngium creticum*-ethnopharmacology, phytochemistry and pharmacological activity. A review. Revista Brasileira de Farmacognosia 2016;26:392-399.

[8] Majidi Z, Sadati Lamardi SN, Mohajjel-Nayebi A, Vatankhah AM, Asnaashari S et al. Effects of *Heracleum persicum* hydroalcoholic extract on insulin, serum anti-oxidant enzymes, glucose, and lipid profiles in alloxan-induced diabetic rats. IJMS 2020;45:199-206.

[9] Afshari M, Mohammadshahi M, Malayeri A, Zaheri L. Antidiabetic, Hepato-Protective and Hypolipidemic Effects of *Eryngium caucasicum* extract in streptozotocin-nicotinamide induced type 2 diabetes in male rats. Iraq Med J 2019;3:2521-8492.

[10] Sadiq A, Rashid U, Ahmad S, Zahoor M, Al Ajmi MF et al. Treating Hyperglycemia From *Eryngium caeruleum* M. Bieb: *in-vitro* α-glucosidase, antioxidant, in-vivo antidiabetic and molecular docking-based approaches. Front Chem 2020;8:558641.

[11] Jaghabir M. Hypoglycemic effects of *Eryngium creticum.* Arch Pharm Res 1991;14:295-297.

[12] Noriega-Cisneros R, Ortiz-Avila O, Esquivel-Gutiérrez E, Clemente-Guerrero M, Manzo-Avalos S et al. Hypolipidemic activity of *Eryngium carlinae* on streptozotocin-induced diabetic rats. Biochem Res Int 2012;2012.

[13] Norouzi M, Valipour Chahardah Charic S. The effect of Eryngium campestre hydroalcoholic extract on glucose and lipid indices of the blood in streptozotocin-induced diabetic male rats. JAR 2021. In Press.

[14] Rehman AU, Hashmi MA, Tehseen Y, Khan A, Khan SS et al. Antidiabetic flavonol glycosides from Eryngium caeruleum. Rec Nat Prod 2017;11:229-234.

[15] Dehghan H, Sarrafi Y, Salehi P. Antioxidant and antidiabetic activities of 11 herbal plants from Hyrcania region, Iran. JFDA 2016;24:179-188.

[16] Kasabri V, Afifi FU, Hamdan I. Evaluation of the acute antihyperglycemic effects of four selected indigenous plants from Jordan used in traditional medicine. Pharm Biol 2011;49:687-695.

[17] Bustanji Y, Issa A, Moulay A, Hudaib M, Tawaha K et al. Hormone sensitive lipase inhibition by selected medicinal plants. JMPR 2011;5:4405-4410.

[18] Paul JH, Seaforth CE, Tikasingh T. *Eryngium foetidum* L.: A review. Fitoterapia 2011; 82:302-308.