

Antidiabetic, hepato-protective and hypolipidemic effects of *Eryngium caucasicum* extract in streptozotocin-nicotinamide induced type 2 diabetes in male rats

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Objective The purpose of this study was to evaluate anti-diabetic, hepato-protective and hypolipidemic effects of *Eryngium caucasicum* extract in nicotinamide-streptozotocin induced type 2 diabetes mellitus model in Wistar rats.

Methods In this study, sixty adult male Wistar rats (150–250 g) were randomly allocated into six groups ($n = 10$) including: (1) healthy control rats, (2) diabetic control, (3) diabetic rats which received Sitagliptin, (4–6) diabetic rats which received respectively 100, 200 and 300 mg/kg oral gavage of *E. caucasicum* extract for 30 days. Diabetes was induced by intraperitoneal injection of nicotinamide and streptozotocin. At the end of experiment, blood samples were collected and fasting blood sugar, insulin, hepatic enzymes, lipid profile and insulin-like growth factor were measured.

Results Administration of *E. caucasicum* in type 2 diabetes mellitus animal models can affect insulin secretion, insulin related indices and lipid profile. Liver enzymes not only did not increase but also decreased significantly. Additionally, *E. caucasicum* increased insulin-like growth factor serum level in a dose-dependent manner. On the whole, it seems that *E. caucasicum* affects diabetes in rats in a dose-dependent manner, as higher doses showed better effects.

Conclusion Here, we showed that administration of *E. caucasicum* in type 2 diabetes mellitus animal model has antidiabetic, hypolipidemic and hepato-protective effects which may be in a dose-dependent manner.

Keywords *E. caucasicum* extract, insulin, lipid profile, liver enzymes, type 2 diabetes mellitus, antidiabetic, hepato-protective, hypolipidemic

Introduction

Diabetes mellitus (DM) is a multifactorial chronic disorder characterized by persistent hyperglycemia in which insulin becomes disabled to perform main function due to weakened insulin secretion, insulin resistance or both.¹ DM is recognized as one of the most prevalent endocrine disorders which have reached epidemic proportions around the world. Based on WHO reports in 2030 diabetes patients will be 333 million or 6.3% of the total population in the world.^{2,3} Type 2 DM (T2DM) is more prevalent.⁴ DM devoted a major challenge to healthcare systems around the world with about 7–13% of the healthcare budget of the worldwide.^{5,6} Prolonged hyperglycemia in DM leads to many chronic complications such as vascular diseases, retinopathy, neuropathy and nephropathy which increase mortality and morbidity among patients with DM.⁷ DM related abnormal lipid metabolism is considered as a major reason for development of atherosclerosis and cardiovascular complications.⁸

Growing evidence suggests that inflammation involved in T2DM pathogenesis, insulin resistance and diabetes-related vascular complications.⁹ Hyperglycemia and increased free fatty acids (FFA) may promote inflammation through inducing glucose utilization which accompanied by changes in oxidative phosphorylation.^{10,11} This setting induces proinflammatory trait in macrophages invading the adipose tissue and other tissues including the pancreatic islets and vascular cells.¹² Glucotoxicity and lipotoxicity also exert oxidative stress and increase the release of active interleukin (IL-1 β).^{10,11} IL-1 β *in situ* intensifies inflammation through expression of

different cytokines in diabetic β -cells, adipose tissues and blood vessels.¹³ So, it has been postulated that targeting inflammation not only attenuates DM but also could prevent its progression and vascular complications.¹⁴

Despite several drugs against diabetes, due to unpleasant side effects like peripheral edema, gastrointestinal discomfort and hypoglycemia, the need for newer drugs with fewer side effects raised.¹⁵ Presently, there is mounting interest in herbal medicines for the treatment of T2DM because of their perceived effectiveness, higher safety and relatively low costs.¹⁶ It has been estimated that more than 1000 herbal remedies are being used against DM.¹⁷ The chemical composition of plants have been implicated as their biological effects to treat DM. Compounds like flavonoids, terpenoids, phenolic compounds and other constituents which show fasting blood glucose (FBS) lowering effects.^{18,19}

The *Eryngium* genus described as the most taxonomically complex and the largest genus of family of Apiaceae (Umbelliferae). *Eryngium* L. consists of more than 250 species in Eurasia, North Africa, America and Australia.^{20,21} *Eryngium caucasicum* which is known as Eryngo is cultivated in middle-east countries like Iran and Turkey.²² In northern Iran this extract has been widely used as different foodstuffs like pickles.²³ Several therapeutic uses were reported for Apiaceae such as stimulant, diaphoretic, diuretic, stone inhibitor, expectorant and anthelmintic.²⁴ In Turkish folk medicine, it has been used as a remedy against various inflammatory disorders, edema, sinusitis, urinary infections or inflammations etc.²¹ *Eryngium*

caucasicum has been used as a reinforcing generative power, diuretic, lenitive and appetizer.^{25,26} Antioxidant, antihypoxic and free radical scavenging and reno-protective effects of *Eryngium caucasicum* Trautv. leaves have been reported.^{23,27,28} Anti-inflammatory activities of other *Eryngium* species cultivated in Turkey have been assessed *in vivo*. Aerial parts and roots reported to possess most activities.²⁹ Several bioactive compounds, mainly phenolic compounds and terpenoids have been purified from *Eryngium* species which are comprising triterpenoid saponins, flavonoids, coumarins and acetylenes.³⁰

In this study, we aimed to investigate antidiabetic, hypolipidemic and hepato-protective potentials of *Eryngo* on nicotinamide-streptozotocin (NA-STZ)-induced T2DM model in rats.

Materials and Methods

Preparation of *E. caucasicum* leaves hydro-alcoholic extract

In this experimental study, fresh leaves of *E. caucasicum* were collected from Mazandaran province, Iran. Department of the Botany of Ahvaz Jundishapur University of Medical Science (AJUMS) scientifically validated the plant. Voucher specimens are deposited in the Herbarium Department of Biology, University of Mazandaran, Iran (No. 1442). The leaves were dried in shade and afterward were crushed and milled by electrical grinders. To prepare *E. caucasicum* leaves of hydro-alcoholic extract, 300 g of *E. caucasicum* leaves powder was dissolved in 1200 mL of a distilled water:ethanol mixture (70:30) and were stored for 72 h at room temperature. After filtering the mixture with Whatman No. 1 filter paper, the mixture was centrifuged at 3500 rpm for 20 min. Condensation was performed by rotary evaporator. Eventually, the supernatant was removed and dried at 37°C, and the obtained semi-solid mass was stocked in refrigerator until injections.

Animals

Sixty adult male Wistar rats between 150 and 250 g were obtained from animal house of AJUMS. All animals were kept in temperature about 22 ± 2°C and 12 h light/12 h dark cycle. All animals were permitted *ad libitum* access to normal laboratory diet and tap water. Maintenance and care of experimental animals complied with the National Research Council of the National Academic.

Induction of type 2 diabetes model

Induction of type 2 diabetes was first performed by an intraperitoneal (IP) injection of a single-dose of NA (120 mg/kg) (dissolved in normal saline) (Sigma-Aldrich Co., St Louis, MO, USA) dissolved in distilled water. After 15 min, a single IP dose of STZ (55 mg/kg) (dissolved in citrate buffer, pH 4.5, 0.1M) (Sigma-Aldrich Co., St Louis, MO, USA) were also injected. The rats were fasted overnight before the induction. The development of T2DM was evaluated by assaying FBS 72 h after NA-STZ injection. FBS higher than 250 mg/dL was considered as diabetes. The other animals with lower serum glucose levels were removed from the experiments.

Study design

All the rats were divided into six groups with 10 rats in each group as follows:

- Group I: 10 healthy control rats (0.5 mL/kg normal saline oral gavage).
- Group II: 10 diabetic rats without treatment (0.5 mL/kg normal saline oral gavage).
- Group III: 10 diabetic rats treated with Sitagliptine (10 mg/kg oral gavage) as a standard drug for diabetes.
- Groups IV–VI: 10 diabetic rats that received hydro-alcoholic extract of *E. caucasicum* at 100, 200 and 300 mg/kg oral gavage respectively. Body weight was recorded weekly.

Sitagliptine and the hydro-alcoholic extract of *E. caucasicum* were administered for 30 days. Sitagliptine was dissolved in distilled water. About 20 h before the end of experiment, animals were deprived of food overnight. All the rats were anesthetized by ether. Blood samples were collected by cardiac puncture. To separate serum, blood samples were centrifuged at 3500 rpm for 20 min. Then, serum samples were stored at -80°C until biochemical measurements.

Biochemical measurements

Fasting blood glucose was measured by Elegance glucometer (CT-X10, Convergent Technologies, Germany) through the lateral tail vein of rats in days 0 and 28. Circulating insulin level was evaluated ELISA kit (Mercodia Corporation, Uppsala, Sweden). The kit has assay sensitivity of 1 mIU/mL. Intra- and inter-assay coefficient of variation (CV) were of 2.1% and 6.5% respectively.

Also, insulin resistance (homeostasis model assessment of insulin resistance; HOMA-IR) and quantitative insulin sensitivity check index (QUICKI) were calculated by the following formula:

$$\text{HOMA-IR: } \frac{\text{Fasting blood glucose (mg/dL)} \times \text{Insulin } (\mu\text{IU/mL})}{405}$$

$$\text{QUICKI: } \frac{1}{(\log \text{FBS (mg/dL)} + \log \text{insulin } (\mu\text{IU/mL}))}$$

The serum level of TC, low-density lipoprotein (LDL), triglyceride (TG), high-density lipoprotein (HDL), enzyme activity of alkaline phosphatase (ALP), aspartate aminotransferase (AST) were assessed by auto-analyzer using commercial kits (Pars Azmoon, Iran). CV for all kits were lower than 7% for intra- and inter-assay.

Insulin-like growth factor (IGF-1) serum level also was assessed by chemiluminescence immunoassay method (Diasorin, Italy). CV for intra- and inter-assay were <0.05.

Statistical analysis

All data were expressed as mean ± standard error of mean (SEM). Differences between all groups were made by one-way analysis of variance (ANOVA) followed by post-hoc test [least significant difference (LSD)]. Statistically significant was considered at $P < 0.05$. All Statistical analysis was performed by SPSS Statistics V. 17.01 (SPSS Inc., Chicago, USA).

Results

Effects of hydro-alcoholic extract *E. caucasicum* on body weight

As depicted in Table 1, STZ-NA diabetes induction, did not change body weight in diabetic control group compared with healthy control group ($P = 0.634$). However, administration of Sitagliptin in diabetic rats lead to significant reduction of body weight in comparison with diabetic control and healthy control group ($P = 0.008$ and 0.028 respectively). After administration of *E. caucasicum* extract in diabetic rats (at dose of 300 mg/kg) body weight increased significantly in comparison with Sitagliptin group ($P = 0.002$).

Effect of hydro-alcoholic extract *E. caucasicum* on fasting blood glucose, insulin level, and insulin-related indexes

Induction of type 2 diabetes using STZ-NA significantly increased FBS in diabetic rats compared with healthy control group ($P = 0.009$). Sitagliptin also decreased FBS in diabetic rats significantly ($P = 0.004$). Furthermore, daily administration of hydro-alcoholic *E. caucasicum* in diabetic rats revealed a dose-dependent significant reduction in FBS in distinct period. *Eryngium caucasicum* administration at 200 and 300 mg/kg doses cause significant reduction in FBS compared with diabetic control group ($P = 0.038$ and 0.004 respectively). In essence although *E. caucasicum* administration at dose of 100 mg/kg revealed no significant change, but reducing trend reported following increasing doses of *E. caucasicum* extract as shown in Table 1.

Induction of diabetes in Wistar rats lead to remarkable decrease in insulin serum level compared with control group ($P < 0.001$). Administration of Sitagliptin reversed reduction in insulin significantly ($P = 0.008$). In addition three different doses of *E. caucasicum* extract also improved insulin serum level in diabetic rats (P -value for all doses < 0.001). HOMA-IR the index of insulin resistance were lower in three different doses of *E. caucasicum* extract compared with healthy control group at the end of intervention (P -value < 0.01 for all doses). Sitagliptin administration increased HOMA-IR index significantly compared with diabetic control group ($P = 0.006$). Also there were significant difference in dose of 300 mg/kg and Sitagliptin at the end of trial ($P = 0.011$). QUICKI, other index which shows the health of insulin-producing cells, revealed significant increase in diabetic rats compared with control

group ($P < 0.001$). This increase in QUICKI also was significant for 300 mg/kg dose of *E. caucasicum* compared with control and Sitagliptin group. Only Sitagliptin group 100 and 200 mg/kg dose of *E. caucasicum* showed significant reduction compared with diabetic control group ($P = 0.002$, 0.047 and 0.014 significantly).

Effect of hydro-alcoholic extract *E. caucasicum* on lipid profile and liver enzymes

As demonstrated in Table 2, regarding HDL marginal significant difference were seen only in the 200 mg/kg dose of *E. caucasicum* extract and Sitagliptin group ($P = 0.051$). There were no significant differences between other experimental groups. LDL cholesterol decreased significantly in the Sitagliptin and 300 mg/kg dose of *E. caucasicum* compared with diabetic control group (P -value < 0.05 in both groups). It must be noted that induction of diabetes in Wistar rats increased TC in diabetic control group compared with healthy control group ($P = 0.020$). Treatment of diabetic rats with Sitagliptin and *E. caucasicum* extract in doses of 100 and 300 mg/kg body weight decreased TC significantly compared with diabetic control group ($P < 0.01$). Administration of Sitagliptin and *E. caucasicum* extract in doses of 200 and 300 mg/kg improved serum TG compared with diabetic control group ($P < 0.05$). Also as depicted in Table 2, dose of 300 mg/kg decreased TG serum level more than Sitagliptin group at the end of trial ($P = 0.003$).

Results showed that after induction of diabetes by STZ-NA, serum alanine aminotransferase (ALT) and AST levels were increased compared with control group ($P = 0.020$). Although Sitagliptin and all three experimental doses of plant improved ALT in diabetic rats, but regarding AST dose of 300 mg/kg decreases serum level of AST ($P = 0.005$).

Effect of hydro-alcoholic extract *E. caucasicum* on IGF-1 serum level

As depicted in Fig. 1, induction of diabetes resulted in significant decrease in IGF-1 in all experimental diabetic rats compared with control group ($P < 0.01$). Treatment with Sitagliptin improved serum level of IGF-1 compared with diabetic control group. Administration of plant extract at 100 and 200 mg/kg doses were not efficient as Sitagliptin treatment for improving IGF-1 serum level. However, again in a dose-dependent manner 300 mg/kg of herb extract increased serum level of IGF-1 significantly ($P < 0.001$) which was also higher than first dose ($P = 0.026$).

Table 1. Effect of hydro-alcoholic extract of *E. caucasicum* (E.C.) on body weight, fasting blood glucose, insulin, HOMA-IR and QUICKI in nicotinamide-streptozotocin-induced diabetic Wistar rats

	Healthy control	Diabetic control	Diabetes ± Sitagliptin	Diabetes ± 100 mg/kg E.C.	Diabetes ± 200 mg/kg E.C.	Diabetes ± 300 mg/kg E.C.
Weight (g)	221.08 ± 6.96	216.52 ± 7.04	193.67 ± 6.45 ^{ab}	240.28 ± 6.87 ^c	209.30 ± 6.55	211.12 ± 6.35
FBS (mg/dL)	107.50 ± 34.5	157.28 ± 59.00 ^a	104.57 ± 22.32 ^b	130.16 ± 18.49	120.42 ± 16.25 ^b	103.85 ± 17.72 ^b
Insulin (μU/mL)	7.04 ± 0.99	2.16 ± 0.66 ^a	5.75 ± 0.82 ^{ab}	3.46 ± 0.61 ^{a,b,c}	4.17 ± 0.92 ^{abc}	3.54 ± 0.86 ^{abc}
HOMA-IR	0.190 ± 0.080	0.084 ± 0.038 ^a	0.150 ± 0.041 ^b	0.11 ± 0.024 ^a	0.122 ± 0.023 ^a	0.089 ± 0.019 ^{ac}
QUICKI	0.352 ± 0.021	0.406 ± 0.041 ^a	0.362 ± 0.021 ^b	0.378 ± 0.012 ^b	0.372 ± 0.013 ^b	0.393 ± 0.019 ^{ac}

^a $P < 0.05$ compared with the control group. ^b $P < 0.05$ compared with the diabetic control group. ^c $P < 0.05$ compared with the diabetic animals received Sitagliptin. E.C., *Eryngium caucasicum*; FBS, fasting blood glucose; HOMA-IR, the homeostatic model assessment-insulin resistance; QUICKI, quantitative insulin-sensitivity check index. Results are expressed as mean ± standard error of mean (SEM), one-way ANOVA and post-hoc LSD test.

Table 2. Effect of hydro-alcoholic extract of *E. caucasicum* (E.C.) on lipid profile and liver enzymes in nicotinamide-streptozotocin-induced diabetic Wistar rats

	Healthy control	Diabetic control	Diabetes ± Sitagliptin	Diabetes ± 100 mg/kg E.C.	Diabetes ± 200 mg/kg E.C.	Diabetes ± 300 mg/kg E.C.
LDL (mg/dL)	20.83 ± 7.16	29.91 ± 19.22	17.97 ± 4.70 ^b	21.73 ± 4.12	23.80 ± 6.82	18.11 ± 4.95 ^b
HDL (mg/dL)	50.30 ± 4.23	33.71 ± 5.12	30.14 ± 4.81	30.66 ± 3.82	35.14 ± 6.36 ^c	31.28 ± 2.05
TC (mg/dL)	58.83 ± 10.88	72.85 ± 16.49 ^a	54.28 ± 9.08 ^b	58.83 ± 5.77 ^b	65.00 ± 10.63	54.28 ± 3.35 ^b
TG (mg/dL)	37.50 ± 9.43	46.14 ± 24.16	30.85 ± 9.63 ^b	32.16 ± 8.20	30.28 ± 8.61 ^b	24.42 ± 8.24 ^b
ALT (mg/dL)	45.83 ± 7.46	77.28 ± 12.86 ^a	57.28 ± 17.13 ^b	52.16 ± 26.79 ^b	44.57 ± 11.64 ^b	47.14 ± 17.41 ^b
AST (mg/dL)	115.50 ± 14.54	156.14 ± 24.65 ^a	138.71 ± 20.28	141.50 ± 48.09	137.42 ± 35.42	109.00 ± 24.93 ^b

^a*P* < 0.05 compared with the control group. ^b*P* < 0.05 compared with the diabetic control group. ^c*P* < 0.05 compared with the diabetic animals received Sitagliptin. Results are expressed as mean ± standard error of mean (SEM), one-way ANOVA and post-hoc LSD test. E.C., *E. caucasicum*; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TC, total cholesterol; TG, triglyceride.

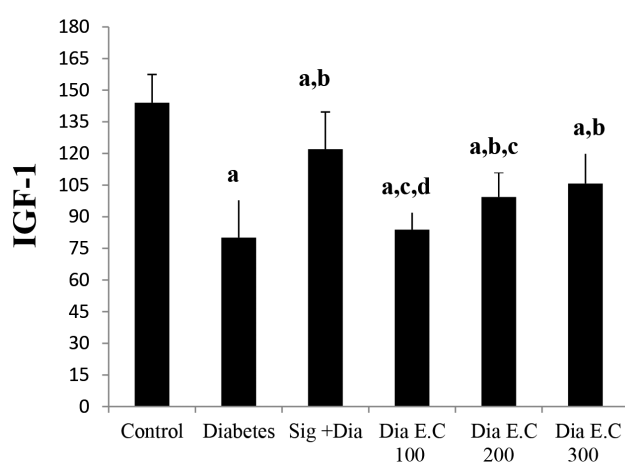


Fig. 1 Effect of hydro-alcoholic extract of *E. caucasicum* (E.C.) on serum insulin-like growth factor (IGF-1) level in nicotinamide-streptozotocin-induced diabetic Wistar rats. Values outlined as mean ± standard error of mean (SEM), One-way ANOVA and post-hoc LSD test. Dia, diabetic; E.C., *E. caucasicum*; Sig, Sitagliptin; 100, 100 mg/kg hydro-alcoholic extract E.C.; 200, 200 mg/kg hydro-alcoholic extract E.C.; 300, 300 mg/kg hydro-alcoholic extract E.C. ^a*P* < 0.05 compared with the control group. ^b*P* < 0.05 compared with the diabetic control group. ^c*P* < 0.05 compared with the diabetic animals received Sitagliptin. ^d*P* < 0.05 compared with the diabetic animals received 300 mg/kg hydro-alcoholic extract E.C.

Discussion

In this study, we investigated the effect of *E. caucasicum* in STZ-NA rats, T2DM animal model. In this study, consistent with reports of earlier investigators insulin serum level reduced significantly in diabetic group. STZ increase reactive oxygen species generation through intracellular nitric oxide (NO) and lead to β -cell dysfunction.³¹ Our result showed that *E. caucasicum* extract significantly decrease FBS in high doses (200 and 300 mg/kg of Eryngo extract). Administration of *E. caucasicum* in diabetic rats also improved insulin secretion significantly. The insulin secretory effects of *E. caucasicum* were higher than Sitagliptin as well. The possible mechanism related to phenolic content of *E. caucasicum* extract to restore the function of pancreatic tissue. Anti-diabetic potential of phenolic compounds has been widely investigated.³² Several phenolic compounds reported to be useful for glycemic

control through multiple mechanisms.^{33,34} Enhanced insulin-mediated glucose uptake through glucose transporter 4-mediated process,³⁵⁻³⁷ improvement of pancreatic β -cell function through antioxidant activity and liver glucose homeostasis.^{38,39} In addition inflammation is among several pathways which have been suggested for anti-diabetic effects of phenolic compounds.³³ One of interesting mechanisms is through the potential prebiotic effects of dietary polyphenols to increase the population of *Bifidobacteria* which has been associated with improved glucose tolerance and lowered inflammatory biomarkers such as the IL-6, and IL-1 β and tumor necrosis factor α (TNF- α).^{40,41} Previous studies reported that *Eryngium* species are rich medicinal plant of phenolic and flavonoids compounds with antioxidant and anti-inflammatory activities.⁴²⁻⁴⁷ Also, saponins have blood glucose lowering effect which also found especially in *E. caucasicum*.⁴⁸ The insulin-related indexes including QUICKI and HOMA-IR also were calculated. HOMA-IR reported as a strong clinical and epidemiological tool for assessment of insulin resistance.⁴⁸ Hence, these results indicate that *E. caucasicum* extract have favorable effects on QUICKI compared with diabetic group; however despite the insulin secretory effect of *E. caucasicum*, HOMA-IR not showed favorable changes after administration of *E. caucasicum* extract. On the other hand several studies have evaluated the effect of IGF-I on insulin sensitivity and T2DM.⁴⁹ Large longitudinal studies reported a higher risk of insulin resistance, metabolic syndrome and worse glycemic control in subjects with low IGF-I serum concentrations.⁵⁰⁻⁵³ Here, we showed that administration of *E. caucasicum* dose-dependently increase circulating IGF-1 in diabetic rats. The biological mechanism and possible effect has to be elucidated in more detail in future studies.

The liver is a vital insulin-dependent organ and is severely affected during diabetes mellitus.^{54,55} Hepatocellular damage in T2DM model described by raise in serum level of ALT and AST.⁵⁶ In our investigation the serum level of liver enzymes also increased significantly in diabetic group compared with control group. The reversal of ALT and AST activity toward near normalcy interpreted as the prevention of cellular and tissue damage under diabetic conditions.^{55,57,58} The *E. caucasicum* extract caused a significant reduction in level of AST and ALT in treated diabetic groups which shows its hepato-protective effects. ALT improved in all doses and AST only in highest dose. Previously reno-protective effects

of *E. caucasicum* extract has been contributed to its ability to scavenge free radical.⁵⁹ Other species of Eryngium family also showed hepato-protective effects. Especially one study demonstrated that *E. caucasicum* Trautv. extract due to the presence of high phenolic compounds has protective effects on tricyclazole induced hepatotoxicity.⁶⁰ The antioxidant effect of *E. caucasicum* extract is suggested.

Reduced lipoprotein lipase activity lead to unbalanced lipoprotein metabolism during diabetes.^{61,62} On the other hand free fatty acid influx stimulates hepatic triglyceride synthesis and over production of LDL.⁶³ Also a noticeable increase in sterol regulatory element-binding protein-1 and fatty acid synthase expression in STZ-diabetic rats has been reported.⁶⁴ LDL and TG serum level improved only in highest dose of *E. caucasicum*. HDL did not show any significant effect however in comparison with Sitagliptin, 200 mg/kg of *E. caucasicum* lead to higher HDL serum level. TC also improved in lowest and highest doses. The probable mechanisms regarding dyslipidemia comprising stimulation of cholesterol-7-alpha-hydroxylase, which converts cholesterol into bile acids; inhibition of HMG-CoA reductase; inhibition of cholesterol absorption from the intestines due to the formation of complexes with compounds such as glycosides and saponins.^{65,66} In addition increase in insulin secretion and changes lipolysis which are under the control of insulin.⁶⁷ Saponins reported to stimulate the decline and excretion of plasma cholesterol, and improved lipid metabolism.^{68,69}

Previous study also reported that other Eryngium species improve lipid profile in diabetic rats.⁷⁰

In recent years oxidative stress may represent the key role in the pathogenesis of secondary diabetic complication. Hyperglycemia is a main cause for elevated free radical levels and oxidative damage.^{71,72} On the whole antioxidant and anti-inflammatory effects of *E. caucasicum* could be contributed to possible protective effects against diabetes complication.

Conclusion

In conclusion we showed that administration of *E. caucasicum* in T2DM animal model improved insulin secretion, insulin related indexes and lipid profile. Liver enzymes not only have not increased but also decreased significantly; IGF-1 serum level increased in dose dependent manner after administration of *E. caucasicum*. On the whole it seems that *E. caucasicum* impact on diabetes rats in a dose-dependent manner, as higher doses showed better effects. However in future studies other dose-escalating intervention must be performed; in which higher doses evaluated in order to clarify the exact dose-response effect of *E. caucasicum*. Also toxicity in diabetes must be elucidated in future studies.

Conflicts of Interest

None. ■

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