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Original Article

Effects of ethanolic extract of *Ferula gummosa* oleo-resin in a rat model of streptozotocin-induced diabetes

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Abstract

Previous studies have shown that some plants in the genus of *Ferula* (Apiaceae) have antidiabetic effects. The present work was aimed to evaluate effects of *Ferula gummosa* oleo-resin in a rat model of streptozotocin-induced diabetes. Male Wistar rats were randomized into five groups (n = 6): normal control, diabetic control, diabetic rats treated with insulin (3 IU/day), and diabetic rats treated with 100 or 400 mg/kg/day of an ethanolic extract of the oleo-resin. After 4 weeks, blood samples were collected for measuring fasting blood glucose (FBG), lipid profile, aspartate aminotransferase, alanine aminotransferase (ALT), alkaline phosphatase, blood urea nitrogen, and creatinine. In addition, levels of lipid peroxidation, thiol groups, and superoxide dismutase (SOD) activity were evaluated in the liver and kidney. At the end of the fourth week, the level of FBG in rats treated with 100 mg/kg of the extract was lower than that in diabetic control rats (273 ± 39 mg/dL *vs* 471 ± 32 mg/dL). Administration of insulin and the extract had no significant effects on the serum lipids. Insulin and both doses of the extract significantly reduced the activity of ALT. In addition, the extract inhibited lipid peroxidation in the kidney and restored the elevated level of SOD in the liver and kidneys. *Ferula gummosa* oleo-resin has the potential to prevent or delay the complications of diabetes by inhibiting the progression of hyperglycemia and attenuating oxidative stress-induced damage in the liver and kidneys.

Keywords: Diabetes; *Ferula gummosa*; Glucose; Lipid; Sesquiterpene coumarins.

INTRODUCTION

Despite considerable progresses in the understanding of the pathogenesis of diabetes and in the control of blood glucose with currently available hypoglycemic drugs, diabetic complications appear in a large number of the patients (1,2). Studies on the pathophysiological mechanisms of diabetic complications suggest hyperglycemia, dyslipidemia, oxidative stress, and inflammation as the main contributing factors (3,4). In recent decades, investigations on finding new antidiabetic agents from medicinal plants with potential anti-hyperglycemic, hypolipidemic, antioxidant, and anti-inflammatory effects are continued (5,6).

Experimental studies reported that some plants in the genus of *Ferula* (Apiaceae) such as *F. asafetida* and *F. hermonis* show anti-hyperglycemic and hypolipidemic effects (7,8). *F. gummosa* Boiss. is one of the plants of this genus that is commonly known as “Barijeh” and “Ghasni” in Iran (9). In Iranian traditional medicine it is used for the treatment of wounds, neurological disorders, nephropathy, and liver damage (10-12).

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Nevertheless, no academic study has so far evaluated the beneficial effects of *F. gummosa* on diabetic changes in the serum, liver, and kidneys. Many biological activities of the genus *Ferula* such as neuroprotective, nephroprotective, and anti-inflammatory effects are attributed to sesquiterpene coumarin compounds (13-16). These compounds have also shown to attenuate the formation of advanced glycation end products (17). The present work was aimed to evaluate possible beneficial effects of ethanolic extract of *F. gummosa* oleo-resin in rat model of streptozotocin (STZ)-induced diabetes.

MATERIALS AND METHODS

Chemicals and reagents

Pyrogallol, tetraethoxypropane and ethylene diamene tetraacetate (EDTA) were purchased from Merck (Damstadt, Germany). STZ, trichloroacetic acid (TCA), thiobarbituric acid (TBA), 2,20-dinitro-5,50-dithiodibenzoic acid (DTNB), and 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium (MTT) were obtained from Sigma (St. Louis, USA).

Plant material and extraction

The oleo-resin of *F. gummosa* (Boiss.) was collected from 4-6 years old plants in Esfarayen mountains (North-Khorasan Province, I.R. Iran) during June-September 2017. The plant was identified at the herbarium of Ferdowsi University of Mashhad (Voucher specimen No. 34577). The alcoholic extract of the oleo-resin was prepared by maceration method. The plant material (200 g) was suspended in 2 L of ethanol (96% v/v) for 24 h at 40 °C under gentle shaking (18). The extracted solution was centrifuged at 1500 rpm for 5 min to remove insoluble particles. The soluble fraction was dried in an oven at 40 °C to give an yield of 100 g (50%, w/w). The dried extract was kept at 4 °C until use.

High-performance liquid chromatography

Quantitative reverse-phase high-performance liquid chromatography (HPLC) analysis was carried out using a Knauer HPLC system (Berlin, Germany) equipped with K-1001 pumps, K 2600 UV detector, and EZChrom Elite software. The oleo-resin extract was prepared at concentrations of 5 and 6 mg/mL and filtered through a 0.45 µm nylon filter prior to the analysis. The chromatographic separation was done on a C18 (4.6 × 250 mm, 5 µm) column using a mobile phase consisting of 20-100% methanol in deionized water (including 0.05% trifluoroacetic acid). The volume of the sample injection and flow rate was 20 µL and 1 mL/min, respectively. The UV absorbance was set at 320 nm. The amount of sesquiterpene coumarins in the extract was quantified using a standard calibration curve ($y = 37.87x-0.086$, $R^2 = 0.999$) prepared for mogoltacin (0, 0.125, 0.25, and 0.5 mg/mL).

Animals and experimental design

Adult male Wistar rats weighing 210-270 g were used in this study. The investigation was approved by the Animal Ethical Committee of Mashhad University of Medical Sciences (ethics committee agreement code: IR.MUMS.REC.1395.50). A total of 30 rats were randomly divided into five experimental groups (n = 6) as follows: group I, normal control rats; group II, diabetic control rats; group III, diabetic rats treated with 3 IU/day of neutral protamine Hagedorn (NPH) insulin for 4 weeks (19); group IV, diabetic rats treated with the oleo-resin extract of *F. gummosa* at dose of 100 mg/kg per day for 4 weeks; and group V, diabetic rats treated with 400 mg/kg of the extract for 4 weeks.

Considering body surface area for dose translation, 100 and 400 mg/kg in the rat are approximately equivalent to the doses of 16 and 64 mg/kg in human, respectively (20,21).

These doses were chosen for the present work because in traditional medicine the oleo-resin is typically consumed at about 1-3 g/day (i.e., 12-50 mg/kg/day for people weighing 60-80 kg), which is equivalent to 6-25 mg/kg/day of the oleo-resin extract (yield of the extract was 50%). For administration of *F. gummosa*, the food of animals was supplemented with the oleo-resin extract (doses of the extract were adjusted weekly based on the body weight and amount of food intake).

Diabetes was induced by intraperitoneal injection of STZ (65 mg/kg). After three days, fasting blood glucose (FBG) was checked by glucometer using glucostrips (ACCU-CHEK, Roch, Germany) after taking blood sample from tail vein. The animals with FBG level of 200 mg/dL or higher were considered diabetic.

Serum biochemical analysis

At the end of the 4th week of treatment, fasting blood samples were collected by cardiac puncture after euthanasia with carbon dioxide. The levels of blood urea nitrogen (BUN), glucose, triglyceride, total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP) were measured using Parsazmun company kits (Karaj, I.R. Iran).

Measurement of total thiol groups

A sample of the homogenized tissues or serum (50 µL) was added to the tris-EDTA buffer (1 mL, pH 8.6) and optical density was determined at 412 nm against tris-EDTA buffer alone (A1). Then, 20 µL of DTNB reagent (10 mmol/L in methanol) was added to the mixture and after 10 min the absorbance was determined again (A2). The absorbance of DTNB reagent was also recorded (B). The concentration of total thiol was calculated from the following equation:

$$\text{Thiol concentration (mmol/L)} = (A2 - A1 - B) \times 1.07/(0.05\times13.6) \quad (1)$$

Superoxide dismutase activity assay

The activity of superoxide dismutase (SOD) in the serum and samples of the liver and left kidney was evaluated by a calorimetric method based on the inhibition of production of superoxide anion due to auto-oxidation of pyrogallol and MTT oxidation, as described previously (22). SOD activity was expressed as unit/mg protein.

Determination of lipid peroxidation level

A sample of 0.5 mL of the homogenized tissues (liver and kidney) was mixed with 0.5 mL of deionized water, and 0.5 mL of TCA reagent (TCA 15% and TBA 0.37%, HCl 0.25 N). The reaction mixture was incubated for 60 min at 95 °C and after cooling, 25 µL of HCl and 1.5 mL of n-butanol were added to the mixture. After centrifuging at 1000 rpm for 10 min, the fluorescence of the supernatant was measured using fluorescent plate reader (PerkinElmer VICTOR X5, USA) at an excitation of 485 nm and an emission of 535 nm. Tetraethoxypropane was used to prepare a standard curve at concentration ranges between 0.01- 0.2 mmol/L.

Statistical analysis

Comparisons between groups were performed using one-way analysis of variance followed by the LSD post hoc test for multiple comparisons. Data obtained before and after treatment were compared by paired-sample *t*-test. The results were presented as mean ± SEM and probability level of less than 0.05 was considered significant.

RESULTS

HPLC analysis of the oleo-resin extract of Ferula gummosa

The HPLC chromatograms of ethanol extract of *F. gummosa* oleo-resin and standard are shown in Fig. 1. The retention time of mogoltacin, as the standard for sesquiterpene coumarin compounds, was 15.7 min. Using the standard curve, the content of sesquiterpene coumarins in the extract was estimated to be 370 mg/g.

Effects of the oleo-resin extract on the body weight, food, and water intakes

Table 1 indicates that the initial body weight was not statistically different between the experimental groups. At the end of the study, normal animals showed an increased body weight compared to their initial weight ($P < 0.01$). On the other hand, the diabetic control group showed a significant decrease in the body weight ($P < 0.01$) despite increased food and water intakes ($P < 0.01$). While, treatment with insulin suppressed diabetes-induced weight loss and polydipsia, the effect of the oleo-resin extract on the body weight, food consumption, and water intake remained statistically insignificant.

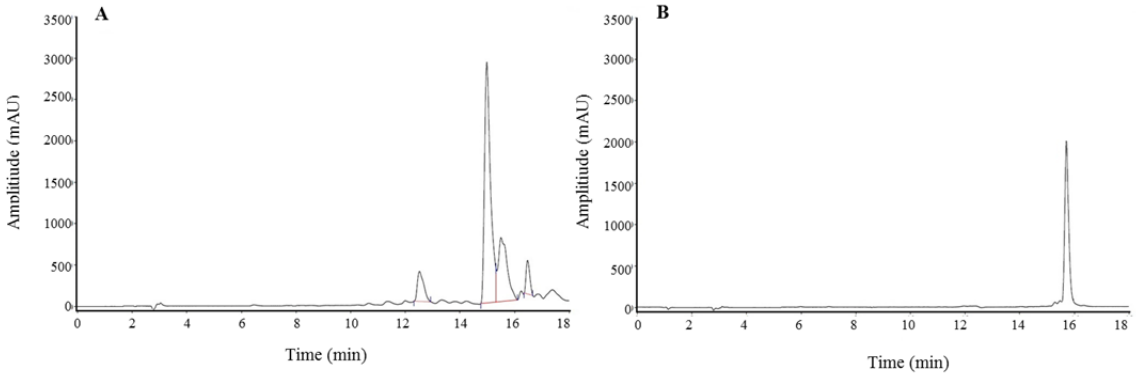

Fig. 1. HPLC chromatograms of ethanolic extract of the (A) oleo-resin of *F. gummosa* and (B) mogoltacin as internal standard.

Table 1. Effects of *Ferula Gummosa* oleo-resin on the body weight, food intake, water intake, and the weight of liver and kidneys of diabetic rats. Values are expressed as mean ± SEM (n = 6). Significant differences were observed (*P < 0.01 and ***P < 0.001, respectively) in comparison with normal control; $^{\#}$ and $^{\#\#}$ show significant differences (P < 0.05 and P < 0.01, respectively) versus diabetic control; and $^{\times}$ shows significant differences (P < 0.01) versus day 1 in the corresponding group.

Parameters	Time	Normal control	Diabetic control	Insulin-treated diabetes	*F. gummosa*-treated diabetes (100 mg/kg)	*F. gummosa*-treated diabetes (400 mg/kg)
Body weight (g)	Day 1	253 ± 7	230 ± 11	237 ± 5	248 ± 4	242 ± 8
	Week 4 (weight gain)	303 ± 8$^{\times}$ (+20%)	187 ± 13*$^{\times}$ (-19%)	278 ± 6$^{\#\#\times}$ (+17%)	213 ± 4*$^{\#\times}$ (-14%)	210 ± 10*$^{\times}$ (-13%)
Food intake (g/24 h)	Week 4	21 ± 1	37 ± 2.5*	33 ± 2.5*	39 ± 2*	38 ± 1.5*
Water intake (mL/24 h)	Week 4	56 ± 4	122 ± 10*	98 ± 10*$^{\#}$	105 ± 5*	100 ± 13*
Liver weight (g)	Week 4	11.2 ± 0.6	8.1 ± 0.4***	11.8 ± 0.84$^{\#\#}$	10.1 ± 0.2	10.4 ± 0.5$^{\#}$
Kidney weight (g)	Week 4	1 ± 0.04	1.02 ± 0.06	1.06 ± .06	1.15 ± .03	1.08 ± 0.06

Table 2. Effects of *Ferula Gummosa* oleo-resin on the levels of FBG and serum lipids of diabetic rats. Values are expressed as mean ± SEM (n = 6). *P < 0.05, **P < 0.01, ***P < 0.001 versus normal control; $^{\#}P$ < 0.05 versus diabetic control.

Parameters	Normal control	Diabetic control	Insulin-treated diabetes	*F. gummosa*-treated diabetes (100 mg/kg)	*F. gummosa*-treated diabetes (400 mg/kg)
FBG Day 1 (mg/dL)	99 ± 5	346 ± 39***	393 ± 20***	300 ± 21***	326 ± 23***
FBG Week 4 (mg/dL)	97 ± 11	421 ± 56***	299 ± 65*	275 ± 60*$^{\#}$	349 ± 57**
Changes related to day 1	-2%	+22%	-24%	-8%	+7%
Triglyceride (mg/dL)	56 ± 11	72 ± 15	55 ± 16	55 ± 15	60 ± 12
Total cholesterol (mg/dL)	65 ± 4	96 ± 8**	88 ± 5**	76 ± 6	82 ± 7*
LDL (mg/dL)	14 ± 1	26 ± 9*	21.5 ± 3.5	16.5 ± 1.3	18 ± 1.5
HDL (mg/dL)	45 ± 4	38 ± 2	44 ± 2	42 ± 2	45 ± 3

F. gummosa, Ferula Gummosa; FBG, fasting blood glucose; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

The weight of the liver was significantly lower in the diabetic control rats than the normal control animals at the end of the study. Treatment with insulin and *F. gummosa* (400 mg/kg) significantly increased the liver weight when compared to the diabetic control group (P < 0.05).

Effects of the oleo-resin extract on serum glucose and lipids

As shown in Table 2, the FBG level significantly increased in STZ-diabetic rats as compared to normal control rats (P < 0.001). The diabetic control rats displayed a further increase in FBG after 4 weeks (35%).

Administration of insulin inhibited the progression of hyperglycemia though nonsignificant. At the end of the fourth week, the level of FBG in rats treated with 100 mg/Kg of the oleo-resin extract (but not 400 mg/kg) was significantly lower than that in diabetic control rats. However, the change in FBG level related to day 1 was not statistically significant in groups treated with insulin or the oleo-resin extract.

A significant increase in the levels of serum total cholesterol ($P < 0.01$) and LDL ($P < 0.05$) was observed in the diabetic control group when compared to normal control group. Neither insulin nor the oleo-resin extracts significantly reduced the levels of total cholesterol or LDL. The level of triglyceride was not significantly increased in diabetic animals after 4 weeks of STZ injection.

Effects of the oleo-resin extract on parameters of kidney and liver functions

Serum level of the BUN was significantly increased in the diabetic control group compared to normal control animals ($P < 0.001$, Table 3). Treatment with insulin significantly reduced the BUN levels with respect to the diabetic control group ($P < 0.01$). Such reduction was not observed in the groups treated with the oleo-resin extract. Induction of diabetes also resulted in a significant increase in the activities of serum ALT and ALP ($P < 0.001$). Insulin treatment could reduce the activities of these enzymes ($P < 0.01$). Similarly, the activity of ALT was recovered significantly in the group treated with 100 mg/kg of the oleo-resin extract ($P < 0.05$).

Effects of the oleo-resin extract on parameters of oxidative stress

As shown in Table 4, a significant decrease in the content of thiol groups was observed in the serum and renal and hepatic tissues of rats in the diabetic control group when compared with normal control group ($P < 0.05$). Insulin treatment increased the thiol content in serum and in the tissues but this effect was statistically significant only in the liver ($P < 0.01$). The oleo-resin extract of *F. gummosa* had no significant effect on the content of thiol groups in the serum and tissues.

Table 3. Effects of *Ferula gummosa* oleo-resin on the serum parameters of kidneys and liver functions in diabetic rats. Values are expressed as mean ± SEM ($n = 6$). *$P < 0.05$, **$P < 0.01$, and ***$P < 0.001$ versus normal control; $^{\#}P < 0.05$, $^{\#\#}P < 0.01$, and $^{\#\#\#}P < 0.001$ versus diabetic control.

Parameters	Normal control	Diabetic control	Insulin-treated diabetes	*F. gummosa*-treated diabetes (100 mg/kg)	*F. gummosa*-treated diabetes (400 mg/kg)
BUN (mg/dL)	50 ± 5	102 ± 11***	63 ± 6$^{\#\#}$	99 ± 8***	98 ± 6***
Creatinine (mg/dL)	0.67 ± 0.02	0.63 ± 0.03	0.67 ± 0.02	0.58 ± 0.03	0.60 ± 0.02
AST (U/L)	130 ± 7	180 ± 19	200 ± 37	162 ± 12	174 ± 19
ALT (U/L)	55 ± 3	221 ± 37***	119 ± 15*$^{\#\#}$	153 ± 23**$^{\#}$	136 ± 27*$^{\#}$
ALP (U/L)	371 ± 25	1700 ± 181***	546 ± 97$^{\#\#\#}$	1816 ± 152***	1621 ± 283***

Table 4. Effects of *Ferula Gummosa* (*F. gummosa)* oleo-resin on the levels of thiol groups, superoxide dismutase (SOD), and malondialdehyde (MDA) in the serum, kidneys, and liver in diabetic rats. Values are expressed as mean ± SEM (n = 6). *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ versus normal control; $^{\#}P < 0.05$, $^{\#\#}P < 0.01$, and $^{\#\#\#}P < 0.001$ versus diabetic control.

Parameters	Specimens tested	Normal control	Diabetic control	Insulin-treated diabetes	Diabetic *F. gummosa* (100 mg/kg)	Diabetic *F. gummosa* (400 mg/kg)
Thiol groups (µmol/mg protein)	Serum	2.8 ± 0.7	0.7 ± 0.5**	1.8 ± 0.6	0.6 ± 0.2**	1.5 ± 0.4
	Kidney	28.7 ± 9	9.2 ± 4.5*	13.7 ± 3.2	5 ± 1.2**	8 ± 0.8*
	Liver	25 ± 4.5	5 ± 0.3**	26 ± 6$^{\#\#}$	3.5 ± 1.3**	8 ± 0.7
SOD (Unit/mg protein)	Serum	32 ± 5	50 ± 9	36 ± 9	35 ± 4.4	27 ± 3.5$^{\#}$
	Kidney	108 ± 8	223 ± 26***	116 ± 17$^{\#\#\#}$	183 ± 23	79 ± 14$^{\#\#\#}$
	Liver	98 ± 7.4	240 ± 27***	142 ± 46$^{\#}$	143 ± 20$^{\#\#}$	159 ± 13$^{\#}$
MDA (nmol/mg protein)	Kidney	365 ± 56	1687 ± 105***	248 ± 32$^{\#\#\#}$	1090 ± 220$^{\#\#}$	736 ± 136$^{\#\#\#}$
	Liver	925 ± 253	1010 ± 105	528 ± 380	1191 ± 225	1142 ± 132

Induction of diabetes significantly increased the levels of SOD and MDA in the renal tissue ($P < 0.001$). In diabetic groups treated with insulin and the oleo-resin extract, the levels SOD and MDA significantly reduced in the kidney ($P < 0.01$). Similarly, both insulin and the oleo-resin extract could decrease the elevated level of SOD in the hepatic tissue of diabetic rats ($P < 0.05$).

DISCUSSION

The oleo-resin of *F. gummosa* is traditionally used to treat diabetes in north-east Iran. Also, previous studies reported that some plants in the genus of *Ferula* have anti-hyperglycemic and hypolipidemic effects and prevent progression of diabetic complications (7, 8). Therefore, the present study was designed to evaluate if *F. gummosa* has any beneficial effects on diabetic changes in STZ model of hyperglycemic rats. In this study model, the oleo-resin extract of *F. gummosa* could inhibit the progression of hyperglycemia and attenuated tissue oxidative stress. Considering that chronic hyperglycemia and oxidative stress play significant roles in the pathophysiology of diabetic complications, *F. gummosa* may be a complementary agent for preventing or delaying the complications of diabetes.

STZ is a cytotoxic agent that leads to degeneration of pancreatic beta cells and therefore induces symptoms of type-1 diabetes, i.e., hypoinsulinemia, hyperglycemia, polydipsia, polyuria, and weight loss (23,24). In the present study, as expected, insulin could inhibit weight loss and reduced water intake in diabetic rats. While untreated diabetic rats showed a further increase in FBG at week 4 compared to day 1, insulin inhibited the progression of hyperglycemia in insulin-treated animals. Nevertheless, the FBG levels in the insulin-treated group were not statistically different from those of diabetic control group, in part, due to improper blood sampling time. Blood sample was taken 24 h after the last insulin dosing while the average duration of action for NPH insulin is about 10-15 h (25). Likewise, although the oleo-resin extract of *F. gummosa* inhibited further increase in FBG levels, it did not improved hyperglycemia considerably. This sugar lowering effect of *F. gummosa* was seen at lower dose of oleo-resin (100 mg/kg), but not at higher dose (400 mg/kg), indicating that the antihyperglycemic effect of the extract is dose-independent between 100 and 400 mg/kg. One of the limitations of the present study is that we did not evaluate glucose tolerance test after administration of the extract. It is possible that *F. gummosa* can reduce postprandial hyperglycemia, which should be investigated in future studies. Also, both insulin and *F. gummosa* were unable to significantly reduce the serum levels of total cholesterol and LDL after 4 weeks of treatment. Therefore, effects of *F. gummosa* on long-term (> 4 weeks) diabetes-induced dyslipidemia should be studied in future research.

The pathophysiological mechanism that underlines microvascular and macrovascular complications of diabetes suggests oxidative stress as one of the main pathogenic factors. The increased oxidative stress is mostly a result of hyperglycemia and dyslipidemia enhancing susceptibility of damage to lipids, proteins, and DNA (4,26). In the present study, administration of insulin attenuated oxidative stress in the liver and kidneys and reduced the elevated levels of serum ALT and ALP. Elevated levels of aminotransferases are a common indicator of liver injury and are observed more frequently among diabetic patients than healthy individuals (27). Similar to insulin, administration of *F. gummosa* significantly decreased the levels of ALT and restored the liver weight in diabetic rats. In addition, *F. gummosa* significantly reduced the elevated levels of lipid peroxidation and SOD activity in the kidneys of diabetic groups. In agreement with our findings, antioxidant and anti-inflammatory effects of *F. gummosa* have been shown in different tissues such as the kidneys and liver (10,12). For example, it has been shown that *F. gummosa* reduces acetaminophen-induced liver damage through attenuation of oxidative stress (12). Also, hydroalcoholic extract of *F. gummosa* was shown to protect kidneys against nitric oxide deficiency-induced inflammation and oxidative stresses (10).

In the present study, induction of diabetes significantly increased SOD activity in the serum, kidneys, and liver. In the STZ model of diabetes, the level of this enzyme has been reported to decrease, increase, or unchanged by various investigators. For instance, Ogunyinka *et al.* reported that STZ significantly reduced hepatic SOD activity in diabetic rats (28). Aliciguzel *et al.* observed no changes in the activity of SOD in the liver, brain, and kidneys after the induction of diabetes (29). On the other hand, Huang *et al.* showed an increase in both gene expression and activity of SOD in STZ-diabetic rats (30). Also, some clinical studies reported higher activity of extracellular and erythrocyte SOD among diabetic patients compared to non-diabetic subjects (31,32). It has been suggested that the level of serum SOD may be a marker of hyperglycemia-induced vascular injury (33). Since *F. gummosa* has been able to maintain SOD activity in diabetic rats close to that of normal control rats, it is probably able to reduce hyperglycemia-induced oxidative damage to the vascular endothelium, which should be confirmed in future studies.

Many beneficial effects of the genus *Ferula* are attributed to sesquiterpene coumarin compounds such as feselol, conferone, umbelliprenin, ferulsinaic acid, and mogoltacin (13-15,17,34). Although most studies have focused on the anticancer effects of these compounds (13), in some studies their beneficial effects in diabetes have also been taken into consideration.

CONCLUSION

Results of the present study suggest that ethanolic extract of *F. gummosa* oleo-resin has the potential to prevent or delay the complications of diabetes by inhibiting the progression of hyperglycemia and attenuating oxidative stress-induced damage in the liver and kidneys.

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