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Evaluation Potential Antidiabetic Effects of *Ferula latisecta* in Streptozotocin-Induced Diabetic Rats

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Objectives: The aim of the present work was to evaluate the possible beneficial effects of *F. latisecta* on blood glucose, lipids, and diabetes-related changes in the liver and kidney of streptozotocin-induced diabetic rats.
Methods: Male Wistar rats were randomly allocated into four groups (n = 6): normal control rats, diabetic control rats, diabetic rats treated for 4 weeks with *F. latisecta* root (400 mg/kg/day), and diabetic rats treated with *F. latisecta* aerial parts (400 mg/kg/day).
Results: Induction of diabetes significantly ($p < 0.05$) increased the levels of fasting blood glucose (FBG), triglyceride, total cholesterol, low-density lipoprotein (LDL), blood urea nitrogen (BUN), aspartate aminotransferase (AST), and alanine aminotransferase (ALT). Diabetes also increased ($p < 0.05$) oxidative stress in the kidney and liver (decrease of thiol and increase of superoxide dismutase). The root and aerial parts of *F. latisecta* significantly reduced the level of LDL ($p < 0.05$) and restored the content of thiol ($p < 0.05$) and superoxide dismutase ($p < 0.01$) in the kidney and liver. *F. latisecta* had no significant effect on the levels of FBG, BUN, AST, and ALT. The root of *F. latisecta* also reduced the serum level of total cholesterol ($p < 0.05$) and prevented the progression of hyperglycemia.
Conclusion: These findings suggest that *F. latisecta* may improve diabetic dyslipidemia by reducing serum LDL. Further studies are needed to confirm our findings.

Keywords: diabetes, *Ferula*, glucose, lipids, oxidative stress

INTRODUCTION

An increasing number of diabetic patients use medicinal plants to control their blood glucose [1]. It is estimated that 60-70% of Korean diabetic patients experience complementary and alternative medicine, of which approximately 60% use various types of plants [2, 3]. In recent decades, academic studies have confirmed the beneficial effects of medicinal plants in the management of diabetes [4, 5]. These beneficial effects include improving glycemic control, reducing serum lipids, inhibiting oxidative stress, and ameliorating inflammatory responses [6, 7].

In traditional medicine of Middle East, a number of plants in the genus of *Ferula* (family: Apiaceae) such as *F. hermonis*, *F. assa-foetida*, and *F. narthex* are used for controlling diabetes [8-10]. Results of experimental and clinical investigations are in agreement with the traditional uses of these plants for reducing blood glucose and lipids and for improving diabetic complications [11-15]. For example, it has been shown that *F. assa-foetida* reduced blood glucose and increased serum insulin in alloxan-induced diabetic rats [12]. This plant showed fat lowering, anti-obesity, and liver steatosis protective effects in type 2 diabetic rats [11]. Also, *F. hermonis* was shown to reduce serum lipids and improve erectile dysfunction in the diabetic patient [13].

Ferula latisecta Rech.f. & Aellen is one of the plants of genus *Ferula* which was commonly known as "Koma Hezar-Masjed" and "Sasekoma" in Iran [16-18]. In the folk medicine of northeast Iran, *F. latisecta* is used for treating parasitic diseases, relieve infant stomach ache, and controlling diabetes. In previous studies, it has been shown that the essential oil from the aerial parts of *F. latisecta* has an antimicrobial effect [19, 20]. However, so far no academic study has tested the anti-diabetic activity of this plant. The aim of the present work was to evaluate the possible beneficial effects of *F. latisecta* on blood glucose, lipids, and diabetes-related changes in the liver and kidney of streptozotocin-induced hyperglycemic rats.

MATERIALS AND METHODS

1. Materials

The whole parts of *F. latisecta* (root, stem, leaves, and fruits) were freshly collected from Zarrin-Kuh Mountains, Northeast Iran (Fig. 1). The plant was identified at the herbarium of Dargaz Payame Noor University, where a voucher specimen was deposited (No. 477). The roots and aerial parts were separately washed, dried in shadow, and ground into powder using a grinder. Trichloroacetic acid (TCA), streptozotocin, 2,20-dinitro-5,50-dithiodibenzoic acid (DTNB), thiobarbituric acid (TBA), and 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium (MTT) were purchased from Sigma (St. Louis, USA).

Figure 1. Aerial parts of *Ferula latisecta*.

2. Animals

Adult male Wistar rats (220-270 g) were obtained from the Laboratory Animals Research Center at Mashhad University of Medical Sciences. The animals were housed in polypropylene cages under light and temperature-controlled conditions (12 h dark/light cycle; 22 ± 4℃). They had free access to water and rat pellets *ad libitum*. The research was performed in accordance with the internationally accepted principles for laboratory animal use and approved by the animal ethical committee of Mashhad University of Medical Sciences (ethical code: IR.MUMS.fm.REC.1396.623).

3. Experimental design

A total of 24 rats were randomly allocated into four groups (n = 6): normal control rats; diabetic control rats; diabetic rats treated with *F. latisecta* root at dose of 400 mg/kg/day; and diabetic rats treated with 400 mg/kg/day of *F. latisecta* aerial parts (stem, leaves, and fruits). The powder of the root and aerial parts were added to food pellets and the dose of the plant materials was adjusted weekly based on the amount of food intake and body weight. Considering the body surface area for dose translation from animals to humans, a dose of 400 mg/kg in the rat is approximately equal to 64 mg/kg in human (i.e., 4.5 g per day for people weighing 70 kg) [21]. In traditional medicine, the whole parts of *F. latisecta* are added to foods (i.e., soup) or approximately 3-5 g of the leaves is consumed in the form of decoction.

For the induction of diabetes, streptozotocin was injected intraperitoneally at a dose of 65 mg/kg. After 72 h, fasting blood glucose (FBG) was measured by a glucometer (Accu-Check Active, Roche, Mannheim, Germany) and the animals with FBG of 200 mg/dL or higher were considered diabetic [22, 23]. Administration of *F. latisecta* was started 72 h after streptozotocin injection and continued for 4 weeks.

4. Serum biochemical analysis

At the end of the study, blood samples were collected by cardiac puncture after 12 h fasting. The samples were centrifuged for 10 min at 3000 rpm and the obtained serums were analyzed

using an automated biochemistry analyzer (BT 3000 plus, Biotecnica Instruments, Italy). The measured parameters included glucose, triglyceride, cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), blood urea nitrogen (BUN), creatinine, aspartate aminotransferase (AST), and alanine aminotransferase (ALT).

5. Evaluation of lipid peroxidation

The level of lipid peroxidation in the liver and kidney was estimated by measuring malondialdehyde level as the product of lipid peroxidation. A sample of 0.5 mL of the tissue homogenates was mixed with 0.5 mL of deionized water and 0.5 mL of TBA reagent (TCA 15% and TBA 0.37%, HCl 0.25 N). Then, the mixture was incubated at 95℃ for 60 min. After cooling to room temperature, 25 μL of HCl and 1.5 mL of n-butanol were added to the mixture and centrifuged for 10 min at 1000 rpm. The fluorescence intensity of the supernatant was measured at 485 nm excitation and 535 nm emission using a fluorescent plate reader (PerkinElmer VICTOR X5 USA). Tetraethoxypropane was used to prepare a standard curve at concentration ranges between 10-200 μmol/L.

6. Measurement of total thiol groups

The content of thiol groups in the liver and kidney was measured using the DTNB reagent. A sample of 50 μL of the tissue homogenate was added to 1 mL of Tris-EDTA buffer (pH 8.6). The absorbance was measured at 412 nm against Tris-EDTA buffer alone (A1). Then, 20 μL of DTNB (10 mmol/L in methanol) was added to this mixture and the absorbance was measured again (A2). The optical density of DTNB reagent (B) was also determined. The level of total thiol in the tissues was calculated from the following equation:

$$\text{Thiol concentration (mmol/L)} = [(A2 - A1 - B) \times 1.07 / (0.05 \times 13.6)].$$

7. Superoxide dismutase (SOD) activity assay

The SOD activity in the liver and kidney was assessed by a calorimetric technique as reported previously [24]. The basis of this assay is the inhibition of the formation of superoxide anion as a result of the auto-oxidation of pyrogallol and MTT. The activity of SOD was expressed as unit per mg tissue protein.

8. Statistical analysis

Statistical differences between the study groups were assessed using one-way analysis of variance followed by LSD post hoc test for multiple comparisons. Paired-sample *t*-test was used to compare data obtained before and after treatment. Data are presented as mean ± SEM and a p-value less than 0.05 was statistically significant.

RESULTS

1. The body weight, food consumption, and water intake

The effects of *F. latisecta* intervention on diabetes-induced weight loss, polyphagia, and polydipsia are shown in Table 1.

Table 1. Effects of *F. latisecta* on the body weight, water intake, and food intake

Parameters	Normal control	Diabetic control	Diabetic *F. latisecta* (Root)	Diabetic *F. latisecta* (Aerial parts)
Body weight (g)				
Day 1	250 ± 7	240 ± 7	230 ± 6	240 ± 5
Week 4	300 ± 7$^{\#\#}$	200 ± 11***$^{\#\#}$	195 ± 12***$^{\#\#}$	206 ± 5***$^{\#\#}$
Water intake (mL/24 h)				
Week 1	50 ± 5	91 ± 7*	73 ± 5*	90 ± 4*
Week 4	52 ± 4	117 ± 8***	119 ± 6***	120 ± 8***
Food intake (g/24 h)				
Week 1	24 ± 1	36 ± 4***	30 ± 2*	32 ± 2*
Week 4	22 ± 1	32 ± 4**	27 ± 2*	27 ± 3*

Data are expressed as mean ± SEM (n = 6). *p < 0.05, **p < 0.01, ***p < 0.001 versus normal control; $^{\#\#}$p < 0.01 versus day 1 in the corresponding group.

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At the start of treatment, there was a homogeneity between the animal groups in terms of body weight. At the end of the study, the normal control group showed an increased body weight compared to day 1 ($p < 0.01$). However, a significant decrease in the body weight was observed in the diabetic control group ($p < 0.01$) in spite of a significant increase in consumption of food and water ($p < 0.05$-$p < 0.001$). Treatment with the roots or aerial parts of *F. latisecta* had no significant effect on the body weight, water intake, and food consumption.

2. Blood glucose and lipids

Injection of streptozotocin significantly increased ($p < 0.001$) the level of FBG as compared to normal control rats (Table 2). After 4 weeks, the diabetic control group showed further increase in FBG level (10%). Administration of *F. latisecta* root prevented the progression of hyperglycemia. Treatment with the aerial parts of *F. latisecta* had no significant effect on FBG.

The levels of triglycerides, total cholesterol, and LDL in the serum of diabetic control rats were higher than those in normal control rats ($p < 0.05$). A significant decrease in the levels of total cholesterol ($p < 0.05$) and LDL ($p < 0.05$) was observed in the group treated with *F. latisecta* root when compared to the untreated group. The LDL level was also lower in the group received aerial parts of *F. latisecta* than the group of untreated diabetic rats ($p < 0.05$).

3. Effects of *F. latisecta* on the kidney and liver

The non-treated diabetic rats showed a significant increase in BUN level when compared to the normal control rats ($p < 0.001$, Table 3). Treatment with the roots or aerial parts of *F. latisecta* had no significant effect on the BUN level with respect to the diabetic control group. Induction of diabetes also increased the levels of serum liver enzymes ALT and ALP ($p < 0.01$). Again, the roots and aerial parts of *F. latisecta* had no significant effect on the level of ALT and AST.

4. Effects of *F. latisecta* on tissue oxidative stress

The content of thiol groups in the kidney and liver of diabetic control rats was significantly lower than those in normal control rats ($p < 0.05$) (Table 4). Administration of both the root and aerial parts of *F. latisecta* to diabetic animals significantly increased the thiol content in these tissues ($p < 0.05$). A significant increase in the activity of SOD was observed in the renal

Table 2. Effects of *F. latisecta* on the levels of blood glucose and lipids

Parameters	Normal control	Diabetic control	Diabetic *F. latisecta* (Root)	Diabetic *F. latisecta* (Aerial parts)
FBG Day 1 (mg/dL)	98 ± 5	335 ± 45***	352 ± 14	326 ± 23
FBG Week 4 (mg/dL)	100 ± 12	370 ± 35**	354 ± 68	353 ± 71
Triglyceride Week 4 (mg/dL)	55 ± 10	64 ± 13*	65 ± 12	63 ± 11
TC Week 4 (mg/dL)	66 ± 4	95 ± 8**	78 ± 7$^{\#}$	83 ± 5
LDL Week 4 (mg/dL)	15 ± 2	26 ± 9*	11.5 ± 2.1$^{\#}$	13 ± 1.3$^{\#}$
HDL Week 4 (mg/dL)	40 ± 2	38 ± 2	42 ± 3	46 ± 2

Data are expressed as mean ± SEM (n = 6). FBG, fasting blood glucose; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TC, total cholesterol. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ versus normal control; $^{\#}p < 0.05$ versus diabetic control.

Table 3. Effects of *F. latisecta* on the serum parameters of the kidney and liver functions

Parameters	Normal control	Diabetic control	Diabetic *F. latisecta* (Root)	Diabetic *F. latisecta* (Aerial parts)
Creatinine (mg/dL)	0.67 ± 0.02	0.65 ± 0.02	0.68 ± 0.05	0.64 ± 0.05
BUN (mg/dL)	52 ± 5	130 ± 7***	146 ± 10	138 ± 8
AST (U/L)	132 ± 8	760 ± 196**	760 ± 187	526 ± 139
ALT (U/L)	57 ± 3	513 ± 159**	530 ± 177	302 ± 91

Fasting blood samples were obtained at the end of study (week 4). Data are expressed as mean ± SEM (n = 6). **$p < 0.01$, ***$p < 0.001$ versus normal control.

Table 4. Effects of *F. latisecta* on the levels of thiol groups, malondialdehyde (MDA), and superoxide dismutase (SOD) in the kidney and liver

Parameters	Normal control	Diabetic control	Diabetic *F. latisecta* (Root)	Diabetic *F. latisecta* (Aerial parts)
Thiol (μmol/mg protein)				
Kidney	25 ± 8	5 ± 1.5*	41 ± 12$^{\#\#}$	26 ± 6$^{\#}$
Liver	26 ± 6	5 ± 0.5*	27 ± 7$^{\#\#}$	33 ± 6$^{\#\#}$
MDA (nmol/mg protein)				
Kidney	350 ± 40	1,690 ± 110**	1,180 ± 405	1,770 ± 327
Liver	905 ± 250	970 ± 90	641 ± 142	1,010 ± 173
SOD (Unit/mg protein)				
Kidney	105 ± 5	225 ± 30***	119 ± 12$^{\#\#\#}$	125 ± 17$^{\#\#}$
Liver	100 ± 8	235 ± 25***	73 ± 5$^{\#\#\#}$	147 ± 24$^{\#\#}$

Fasting blood samples were obtained at the end of study (week 4). Data are expressed as mean ± SEM (n = 6). *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ versus normal control; $^{\#}p < 0.05$, $^{\#\#}p < 0.01$, $^{\#\#\#}p < 0.001$ versus diabetic control.

and hepatic tissues of rats in the diabetic control group when compared with the normal control group ($p < 0.001$). Both the root and aerial parts of *F. latisecta* could inhibit the diabetes-induced increase of SOD activity. Measurement of MDA level showed a significant increase of lipid peroxidation in the renal tissue of diabetic rats ($p < 0.01$), which was not affected by *F. latisecta*.

DISCUSSION

Some plants of the genus *Ferula* are used in the traditional medicine of the Middle East for management of diabetes [8-10]. The aim of this study was to examine the beneficial effects of *F. latisecta* on blood glucose, lipids, and diabetes-related changes in the kidney and liver of streptozotocin-induced hyperglycemic rats. Streptozotocin induces diabetes by reducing insulin production and secretion because of the destruction of the pancreatic beta cells [25]. Therefore, the animals show symptoms of type-1 diabetes including hypoinsulinemia, hyperglycemia, polyuria, polydipsia, and weight loss [26, 27]. In this model of diabetic rats, the root, and aerial parts of *F. latisecta* could not improve symptoms of diabetes (polydipsia, polyuria, and weight loss).

Regarding blood glucose, the untreated diabetic group displayed a further increase in FBG level at week 4 compared to day 1. Although the level of FBG in *F. latisecta* root group was not statistically different from the diabetic control group, the root could inhibit the further increase in FBG level. Although this is the first study to evaluate the effect of *F. latisecta* on blood glucose, one previous study reported that *F. assa-foetida*, one other plant in the genus of Ferula, reduces blood glucose and increases serum insulin in diabetic rats [12]. One of the limitations of the present work is that we did not perform a glucose tolerance test after *F. latisecta* administration. It is possible that this plant can reduce postprandial hyperglycemia, which should be examined in future studies.

Dyslipidemia is one of the main risk factors for developing diabetic complications particularly cardiovascular diseases [25, 28]. Diabetic dyslipidemia is characterized by an increase of serum triglyceride and LDL and a decrease of HDL level [29]. A large number of patients with diabetes do not reach a normal level of serum LDL despite treatment with current hypolipidemic drugs (e.g., statins) [30, 31]. Therefore, studies for finding new hypolipidemic agents are still desirable. In our study, diabetic rats presented dyslipidemia, as judged by increased levels of total cholesterol, triglycerides, and LDL. Treatment with *F. latisecta* root significantly reduced the elevated levels of LDL and total cholesterol. LDL is the primary goal of lipid-lowering therapy in diabetic patients, however, despite current drug therapy, a large number of these patients do not reach the goal level for LDL (less than 100 mg/dL) [30].

The hypolipidemic effect of *F. latisecta* may be helpful in preventing cardiovascular events in diabetic patients.

Streptozotocin-induced diabetes is associated with an increase in the activity of serum ALT and AST [23, 32, 33]. Elevation of the activity of these enzymes is an indicator of liver disorders (e.g., fatty liver disease and decreased hepatic insulin sensitivity) and is observed more frequently among diabetic

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individuals than healthy subjects [34-37]. Although *F. latisecta* could reduce streptozotocin-induced oxidative stress (restoring the levels of SOD and thiol) in the liver and kidney, it was not able to decrease serum level of liver enzymes. This may be due to the inability of *F. latisecta* to improve FBG and metabolic symptoms of diabetes (i.e., weight loss, polyphagia, and polydipsia).

CONCLUSION

The findings of the present study suggest that *F. latisecta* may improve diabetic dyslipidemia by reducing serum LDL. Also, although this plant has no hypoglycemic effect, its root can prevent the progression of hyperglycemia in the streptozotocin model of type-1 diabetes. Further studies are needed to confirm our findings.

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CONFLICT OF INTEREST

The authors report no declarations of interest.

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