Indian Journal of Natural Products and Resources
Vol. 14(3), September 2023, pp. 384-390
DOI: 10.56042/ijnpr.v14i3.4627

Investigation of antidiabetic effect of *Ferula assa-foetida* oleo gum resin and its essential oil on ovariectomised diabetic rats

Jalil Alizadeh Ghalenoei[1], Mohammad Amin Ghafari Sirizi[1], Maryam Yadegari[2] Davoud Javidmehr[3], Mahdieh Jafari Nodoushan[4] and Seyyed Majid Bagheri[1,5]*

[1]Department of Physiology; [2]Department of Anatomy, Shahid Sadoughi University of Medical Sciences, Yazd, 8916188635, Iran

[3]Department of Reproductive Biology, Faculty of Basic Sciences and Advanced Thecnologies in Medicine, Royan Institute, ACECR, Tehran, 16635-148, Iran

[4]Shahid Sadoughi Hospital, Shahid Sadoughi University of Medical Sciences, Yazd, *8916978477*, Iran

[5]Neuroendocrine Research Center, Faculty of Medicine, Shahid Sadoughi University of Medical Sciences, Yazd, 8915173149, Iran

Received 01 August 2022; revised received 01 July 2023; accepted 18 July 2023

The aim of the present study was to evaluate the hypoglycemic activity of asafoetida and essential oil of asafoetida (EOA) in ovariectomised (OVX) diabetic rats. Twenty-four female rats were divided into four groups consisting of 6 rats in each group. OVX Control, OVX diabetic, OVX diabetic and asafoetida (25 mg/kg), OVX diabetic and EOA 25 µL/kg. Fasting Blood glucose, lipid profiles and liver indices were measured, and liver and kidney histopathology was investigated. Urine volume, urea, creatinine, and microalbumin were measured. The neuropathic damage was assessed by the hot plate method. The results showed that only in the asafoetida group the blood sugar, ALT and AST levels decreased significantly. Consumption of food, water, and body weight also decreased in the asafoetida grouponly. Also, regarding histology, relative improvement was observed in kidney and liver tissue in the asafoetida group. A significant decrease in urine volume and improvement in creatinine, urea and microalbumin concentrations, as well as improvement in hot plate test response time, were observed in both treatment groups. It can be concluded that asafoetida is effective in treating diabetes, but its essential oil has no effective activity on diabetes mellitus.

Keywords: Diabetes mellitus, Essential oil, *Ferula assa-foetida*, Ovariectomised rats

IPC code; Int. cl. (2021.01)- A61K 36/00, A61K 36/23, A61P 3/00, A61P 3/10

Introduction:

Diabetes mellitus (DM) is one of the most common chronic diseases worldwide. It is a metabolic disorder characterised physiologically by insulin deficiency or insulin inactivity and clinically by hyperglycemia or impaired glucose tolerance and other disorders[1]. High blood sugar is either caused by a lack of insulin secretion or the body's resistance to insulin and is often associated with impaired metabolism of carbohydrates, proteins and lipids[2]. Complementary therapies and Traditional Medicine is a general knowledge of health-related practices and skills based on indigenous beliefs and experiences, among which medicinal plants play an important role in traditional medicine of different countries[3]. Medicinal plants are considered invaluable and a constant source of biologically active phytochemicals. Apiaceae is a large family of flowering and aromatic plants that grows mostly in dry and temperate regions[4]. The genus of Ferula includes 170 species that grow in areas from Central Asia, the Mediterranean to North Africa[5]. *Ferula assa-foetida* belongs to the Apiaceae family and grows wildly in the central and southern mountains of Iran. It is an herbaceous perennial with an unpleasant odour that grows to about 2 m in height[6]. The oleo gum resin derived from itis called “asafoetida” and is often obtained by incision of the roots or removal of the stems. Asafoetida has a characteristic sulfurous odour and a bitter taste. It consists of three main fractions, including resin (40–64%), gum (25%) and essential oil (10–17%). Abu-Zaiton showed that the ethanolic extract of asafoetida has protective effects in diabetes by preserving pancreatic cell integrity, justifying its traditional uses in preventing diabetic complications[7]. Aqueous extract of *F. assa-foetida* showed that it can decrease blood sugar and insulin levels fifteen and thirty days

*Correspondent author
Email: boss_bagheri@yahoo.com

after the start of treatment[8]. A study to determine the effect of asafoetida on weight gain, fat accumulation, and liver steatosis found that asafoetida could improve these factors via a change in leptin level[9]. Ethyl acetate extract of *F. assa-foetida* once daily for 28 days significantly decreased serum glucose, triglyceride, cholesterol and LDL levels in diabetic rats[10]. Although several studies have been conducted on asafoetida for its antidiabetic effect, it is unclear which part of this oleo gum resin is effective on diabetes mellitus. Asafoetida essential oil is a volatile part with a pungent smell, mainly composed of sulfide compounds. So far, no complete study has been done on its antidiabetic effects[11]. This essential oil has been shown to have antiproliferative effects on breast cancer cell line[12] and has analgesic properties[13]. Previous studies have shown that organosulfur constituents, such as those found in garlic, can improve diabetes mellitus[14,15]. Based on this evidence, we decided to compare the antidiabetic effect of asafoetida with its essential oil in this study.

Materials and Methods

Animals

Twenty-four female rats born in the animal house of the Faculty of Medicine (Shahid Sadoughi University of Medical Sciences, Yazd, Iran) were prepared and subjected to a standard cycle of 12 h of light: 12 h of darkness. The experiments were carried out according to the recommendations of the Laboratory Animal Care Committee of Shahid Sadoughi University of Medical Sciences, Yazd, with the IAEC approval number of IR.SSU.AEC.1401.021.

Preparation of asafoetida and essential oil

Asafoetida was collected from a mountainous area in Tabas (South Khorasan Province, Iran) in July of 2021, and the plant species was identified and approved by Dr Abbas Zarezadeh at the Yazd Agricultural Research Center with voucher number SSU- 345-71. After drying in ambient air, the gum was soaked overnight in distilled water at room temperature, and the suspension was used orally. The concentration and dose of the suspension were expressed as the crude amount of dried oleo gum used to prepare the stock solution. To isolate the oil from asafoetida, the oleo-gum resin (100 g) was dissolved in 1 litre of distilled water, and the oil was separated using a Clevenger apparatus. Distilled oils were dried using sodium sulfate and stored at 4°C until use[16].

Experimental procedure

Animals were anesthetised with ketamine-xylazine mixture (100 mg/kg, 10 mg/kg, respectively). In the mid-dorsal lumbar region, a 1-2 cm midline incision was made on both the right and left sides, and the ovaries and fallopian tubes were removed[17]. Type 2 diabetes was induced by a high-fat diet (60%) and low-dose STZ injection. Briefly, rats were fed a high-fat diet for four weeks, and then diabetes was induced with a low dose of STZ (35 mg/kg, intraperitoneally). Seven days after STZ injection, fasting blood glucose levels were measured in all rats, and those with blood glucose levels above 200 mg/dL were considered diabetic animals[18]. After induction of diabetes, ovariectomised rats were randomly divided into four groups (6 rats in each group): OVX control, OVX diabetic, asafoetida (25 mg/kg) treated group, EOA group (25 µL/kg). The control groups received the same method and the same volume of saline by gavage for 21 days. Food and water intake were measured daily.

Biochemical and haematological analysis

Serum was prepared by collecting blood from the orbital sinus of rats by centrifugation (3000 rpm, 20 min). The serum was kept frozen until the biochemical assay. Glucose, cholesterol, triglyceride, HDL, Lactate dehydrogenase (LDH), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP) and HbA1c were determined using appropriate kits according to the manufacturer's instructions. After taking blood and mixing it with EDTA, we separated the blood plasma and measured the amount of haemoglobin A1C with the appropriate kit. Also, a sufficient amount of blood was prepared and mixed with EDTA and counted by a cell counter device to count blood cells.

Histopathological analysis

The liver and kidney of rats were removed and fixed in 10% neutral formalin. Then, all samples were cleaned, dehydrated, and embedded in paraffin. 7-micrometre-thick sections were prepared using a microtome (Leica), and the slides were stained with hematoxylin–eosin (H&E) dye and histopathological changes were observed microscopically.

Hot-plate test

One day before the end of the examination, the hot-plate apparatus (Borj Sanat, Iran) was set to 54±0.1°C. Animals were placed on the hot surface inside the Plexiglas cylinder (20 cm in diameter), and

the time (in seconds) spent licking their hind paws or jumping (whichever occurred first) was recorded as the pain response latency (reaction time). Response latency was measured by recording the time between placements in the cylinder and shaking or licking the paws. The cut-off time was set at 35 seconds to minimise skin injury[19].

Urine collection and analysis

All animals were kept in metabolic cages, and urine samples were collected for 8 h and analysed for creatinine, urea and microalbumin using standard methods. Urinary output volumes of all groups were also noted[20].

Statistical analysis

The results are reported as the mean±SEM. Differences between means were obtained by one-way ANOVA (Tukey-Kramer method) using Graph Pad Prism version 8 software (GraphPad Inc., San Diego, CA, United States).

Results

Effect of asafoetida and EOA on biochemical and hematological factors

Serum biochemical parameters are summarised in Table 1. The results showed that in the group treated with asafoetida, the levels of glucose, AST, ALT, and HbA1C decreased significantly compared to the OVX diabetic group(P <0.05). EOA did not cause a significant reduction in any of the mentioned cases. Also, the number of red blood cells and HCT% increased, and platelets decreased significantly in all groups compared to the OVX control group, and the treatments could not improve these indicators. (Table 2, P <0.05).

Table 1 — Effect of asafoetida and EOA on biochemical parameters in different groups

	Control	Diabetes	Asafoetida 25	EOA 25
Glu (mg/dL)	135±14	366±45[a]	229±35[a,b]	425±58[a]
Chol (mg/dL)	88±9.2	99±8.8[a]	90±9.5	92±7.6
TG (mg/dL)	55±4.5	66±7.2[a]	70±6.5[a]	59±41
HDL (mg/dL)	58±4.3	21±2.5[a]	23±2.5[a]	16±1.9[a]
AST (U/L)	142±12	403±38[a]	256±32[a,b]	509±44[a,b]
ALT (U/L)	34±4.8	268±21[a]	138±14.1[a,b]	255±23[a]
LDH (U/L)	1957±182	3014±250[a]	3252±230[a]	3417±311[a]
ALP (U/L)	500±57	1377±29[a]	1231±110[a]	1432±66[b]
HBA1C (mg/dL)	4.6±1.2	16±1.3[a]	11±1.2[a,b]	14±1.9[a]

Data was analysed by ANOVA followed by Tukey's test and expressed as the means±SEM (n =6). a = P <0.05 compared to OVX control group and b = P <0.05 compared to OVX diabetic group.

GLu: Glucose; Chol: cholesterol, TG: triglyceride; HDL: high-density lipoprotein;AST: aspartate aminotransferase; ALT: alanine aminotransferase; LDH: lactate dehydrogenase; ALP; alkaline phosphatase.

Effect of asafoetida and EOA on body weight, water and food intake

The average food, water consumption and body weight in diabetic group animals increased significantly compared to the OVX control group. The values of these factors only in the treatment group with asafoetida 25 significantly decreased compared to the OVX diabetes group (P <0.05, Fig. 1). No significant change was observed in the group treated with EOA.

Effect of asafoetida and EOA on histopathology of liver and kidney

The liver tissue showed no pathological alterations in ovariectomised rats (Fig. 2a). Liver tissues of rats showed normal structure and hepatocytes with normal nuclei and normal sinusoids between the liver cords. Central vein and portal areas with no signs of inflammation or necrosis. Liver tissues of ovariectomised diabetic animals (Fig. 2b) showed vacuolisation of hepatocytes and congested sinusoids with inflammatory cellular infiltration around the central vein and portal areas. Liver cells appeared irregular, and areas of haemorrhage were noticed between the cells. Hypotrophiedkupffer's cells were prominent, and dilated hepatic central vein and blood vessel expansion in the portal area were noticed. In ovariectomised diabetics and asafoetida (25 mg/kg), some of these histopathological changes were reduced. However, hypotrophiedkupffer's cells were also prominent (Fig. 2c). Ovariectomised diabetic and EOA leucocyte infiltration in the portal area was noticed. Hypotrophiedkupffer's cells were also prominent. In some parts, the general structures of the liver were destroyed (Fig. 2d). As shown in Fig. 3a, the renal tissue membrane of ovariectomised rats in the normal group was complete with no connective

Table 2 — Haematological parameters in different groups

	WBC (10^3 cells/µL)	RBC (10^6 cells/µL)	Hb (g/dL)	HCT (%)	PLT (10^3 cells/µL)
Control	5.2±1.1	6.6±1.3	14.1±3	41±4.5	1305±121
Diabetes	6.2±1	9±5[a]	18±4[a]	58±5.4[a]	616±52[a]
Asafoetida 25	4.8±1.1	9±2[a]	17±3	56±5.3[a]	659±67[a]
EOA 25	5±0.9	8.2±2.1[a]	16±2	52±5.2[a]	597±63[a]

Data was analysed by ANOVA followed by Tukey's test and expressed as the means±SEM (n = 6). a = P <0.05 compared to OVX control group. WBC: white blood cell; RBC: red blood cell; HB: haemoglobin; HCT; hematocrit; PLT: platelet.

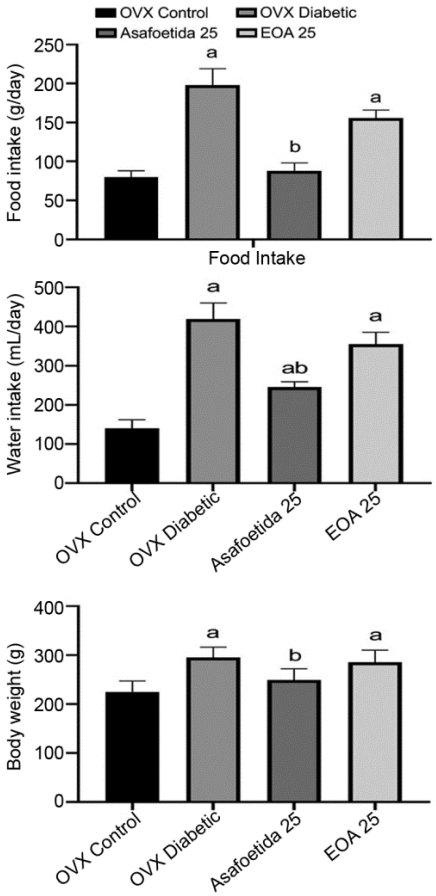

Fig. 1 — Effect of asafoetida and EOA on body weight, food and water intake. Data was analysed by ANOVA followed by Tukey's test and expressed as the means±SEM (n =6). a = P <0.05 compared to OVX control group and b = P <0.05 compared to OVX diabetic group.

hyperplasia. It had a complete glomerular structure, no capillary substrate membrane hyperplasia, and intact renal tubules. In some parts, inflammatory cell infiltration in the renal tubule structure was seen. The renal tissue of ovariectomised diabetic animals (Fig. 3b) showed glomerular membrane hyperplasia renal tubular dilation. Glomerular sclerosis and lesion was also seen. Tubular hypertrophy, thickening of the tubular basement membrane and glomerular basement membrane (GBM) thickness and interstitial inflammatory cell infiltration were seen. As can be seen, milder glomerular damage was seen in the group treated with asafoetida (25 mg/kg) extract (Fig. 3c) compared with diabetic groups. The histopathological changes were reduced, but it was not significant. Ovariectomised diabetic and EOA (Fig. 3d) showed glomerular sclerosis and lesions. Inflammatory cell infiltration in the renal tubule and vessel was prominent.

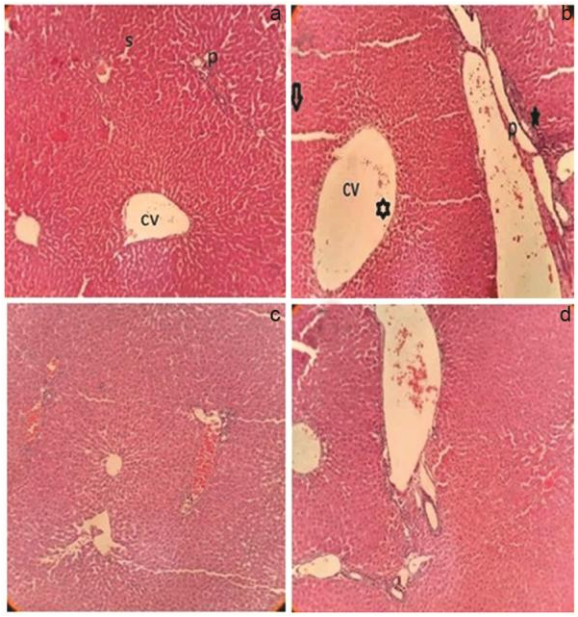

Fig. 2 — Histologic evaluation of liver tissue of the rats in different groups. H&E × 100. a) Ovariectomised rat; b) ovariectomised diabetic; c) ovariectomised diabetic and asafoetida (25 mg/kg); and d) Ovariectomised diabetic and EOA. The congested sinusoids and infiltration of inflammatory cells around central vein (cv) were showed with hallmarks.

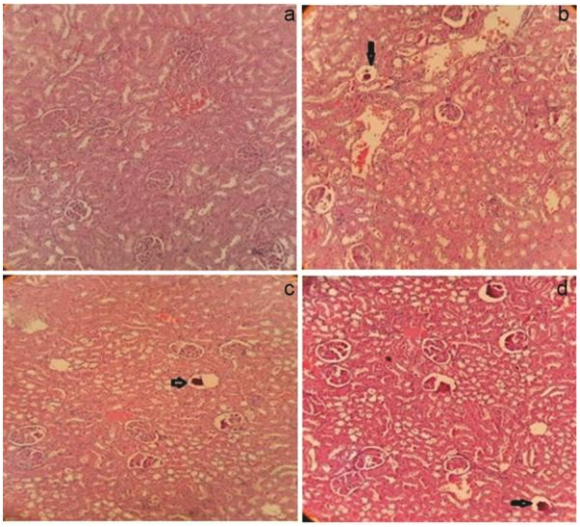

Fig. 3 — Histologic evaluation of renal tissue of the rats in different groups. H&E × 100. a) Ovariectomised rat; b) ovariectomised diabetic; c) ovariectomised diabetic and asafoetida (25 mg/kg); and d) Ovariectomised diabetic and EOA. The Diminished and distorted glomeruli were showed with (arrow).

Effect of asafoetida and EOA on urine volume, urea and creatinine

The results showed that the volume of urine in the OVX diabetic group increased significantly compared to normal (3.5±0.6 vs 13.2±1.6, P <0.05 respectively), and these amounts decreased significantly in the treatment groups (5.2±1 and 7 ±1.3, P <0.05). Also,

Table 3 — Urine creatinine, urea, microalbumin concentration and urine volume in different groups

	Control	Diabetic	Asafoetida 25	EOA 25
Urine volume (cc)	3.5±0.6[b]	13.2± 1.6[a]	5.2±1[b]	7±1.3[ab]
Urea (g/dL)	2900±220[b]	2200±190[a]	3180±320[b]	2860±295[b]
Creatinine (g/dL)	35±6.2[b]	13.2±2.6[a]	26.8±3.2[b]	32.4±5.7[b]
Micro Albumin (g/dL)	9±2.1[b]	18.2±4.3[a]	12.4±1.4[b]	12.4±2.2[b]

Data was analysed by ANOVA followed by Tukey's test and expressed as the means±SEM (n =6). a = P <0.05 compared to OVX control group and b = P <0.05 compared to OVX diabetic group.

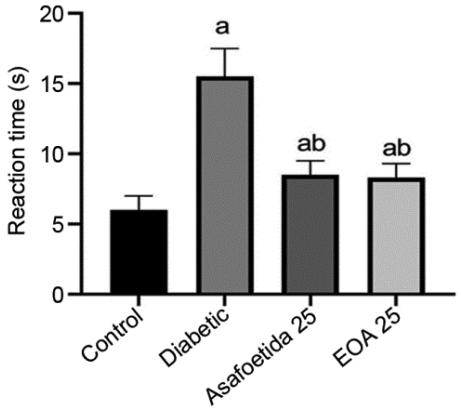

Fig. 4 — Effect of asafoetida and EOA on hot plate test in different groups. Data was analysed by ANOVA followed by Tukey's test and expressed as the means±SEM (n =6). a = P 0.05 compared to OVX control group and b = P <0.05 compared to OVX diabetic group.

the concentration of urea and creatinine in the OVX diabetic group decreased compared to the OVX control, and microalbumin was significantly increased. In the groups treated with asafoetida and EOA, these concentrations improved significantly (P <0.05, Table 3).

Effect of asafoetida and EOA on hot plate test

The results showed that the OVX diabetic group had a significantly longer response time than the OVX control group (15.5±2 vs 6±1, P <0.01). This time was significantly reduced in asafoetida and EOA-treated groups (8.5±1.1 and 8.3±1.2, respectively, P <0.05, Fig. 4).

Discussion

Diabetes mellitus is a metabolic disorder and a global alarm due to insufficient production of insulin in the pancreas. Hyperglycemia also causes disorders such as retinopathy, atherosclerosis, increased coagulation, coronary heart disease and Alzheimer's disease[21]. The World Health Organization has identified more than 400 different plants for the treatment of diabetes, yet only a few have been scientifically and medically evaluated[22]. The presence of phenolic compounds, flavonoids, terpenoids and coumarins is the cause of antidiabetic properties of medicinal plants. Briefly, this research showed that only asafoetida can reduce fasting glucose and HbA1C, but asafoetida and its essential oil had no effect on the lipid profile of diabetic animals. These results are consistent with previous evidence of the hypoglycemic effects of asafoetida. Several articles on the antidiabetic effects of asafoetida have all emphasised its hypoglycemic effect. Investigation of inhibitory activity of ethanol, methanol and aqueous extracts of *F. assa-foetida* seeds on DPP-IV and α-glucosidase *in vitro* showed that *F. assa-foetida* seeds extract is effective on both enzymes[23]. Thirty days of treatment with asafoetida significantly improved hyperglycemia, decreased liver glycogen and increased body weight in alloxan-induced diabetic rats[24]. It was observed that asafoetida treatment also significantly improved histological degenerative changes in Langerhans islet β cells. Studies have also shown that the aqueous extract of asafoetida can positively affect the activity of antioxidant enzymes in brain cells in diabetic rats[25]. This extract at doses of 100 and 200 mg/kg for one month led to a significant decrease in MDA levels and a significant increase in the levels of SOD, GST, and CAT enzymes in the brain cells of diabetic animals. Esmailidehaj *et al.*, showed that an enriched-asafoetida diet of 0.5% for 4 weeks could significantly decrease fasting blood sugar, HbA1C, oxidative stress and hepatic enzymes and plasma level of insulin increased[26]. Also, the results showed that asafoetida causes weight loss and food consumption and can affect the metabolism rate. The potential of asafoetida on fat metabolism has been studied, and it is shown that taking asafoetida significantly reduced body weight and abdominal fat at doses of 25 and 50 mg/kg, and this effect was associated with decreased serum leptin levels[9]. Although several studies have shown that asafoetida has hypoglycemic and antidiabetic effects, limited studies have been performed on its mechanism of action. In a study to evaluate the molecular mechanism of the effect of asafoetida on the cell line of C2C12 mice, 10 micrograms per mL of asafoetida extract increased GLUT4 transfer to the cell membrane in the C2C12 cell line by activating the PI3K/Akt signalling pathway[27]. A significant reduction in liver factors such as AST and ALT was seen, which indicates its conservative effect on the

liver. The hepatoprotective effects of asafoetida have been previously studied and shown to be effective in protecting the liver at low doses[28]. So far, no study has been performed on the effect of asafoetida on diabetic nephropathy. However, in this study, it was found that asafoetida has a protective effect on kidneys and indicators such as urine volume, creatinine, urea, and microalbumin are significantly in the asafoetida treatment group has improved. Also, EOA caused a significant improvement in these markers, which indicates the positive effect of this essential oil on kidney function. Histopathological observations also confirm these findings that at the histological level, asafoetida and its essential oil have almost caused the prevention of diabetic nephropathy. Diabetic neuropathy is another side effect of diabetes that causes damage to the peripheral and central nervous system. The results of the hot plate test showed that asafoetida and its essential oil can reduce the incidence of these injuries, and latency time significantly decreased in treated animal groups. In a previous study, it was found that the ethyl acetate extract of asafoetida for 28 days can reduce neuropathy damage in diabetic rats[29]. Asafoetida has a variety of compounds that cannot be accurately attributed to any of its therapeutic properties. This gum contains sulfide parts, sesquiterpene coumarins, flavonoid and terpenoid compounds, each of which can have several pharmacological effects. Although studies on the antidiabetic effects of asafoetida have been performed to date, little effort has been made to determine which fractions affect diabetes. One of the main objectives of this study is to answer the question of whether the sulfide part present in asafoetida essential oil is an effective factor in lowering blood sugar. Based on our results, no. Our results showed that asafoetida essential oil could not reduce blood sugar or improve lipid profile. However, its effect on diabetic nephropathy is relatively significant and has reduced urine volume, creatinine, urea and urinary microalbumin. It also had a positive effect on reducing diabetes neuropathy. It is not clear how these compounds work, but the presence of antioxidant compounds, as well as neuroprotective compounds in asafoetida, may play a role.

Conclusion

One of the characteristics of medicinal plants is that they have few side effects, increasing the tendency to use them. Studies of the effects of various extracts of the genus of Ferula have shown their effectiveness in improving diabetes. There are also a few studies on the beneficial effects of these plants in reducing appendicitis, such as retinopathy or nephropathy. Most studies have focused on the effects of different extracts in reducing diabetes and less on the purification and separation of effective compounds. Finally, it can be concluded that asafoetida in a low dose can also be effective in improving diabetes, but apparently, its effective compounds on diabetes are not in the essential oil section, and its other fractions should be evaluated.

Conflict of interest

The authors declare no conflict of interest related to this article.

References

1 Clark Jr C M and Lee D A, Prevention and treatment of the complications of diabetes mellitus, *N Engl J Med*, 1995, **332**(18), 1210–1217.

2 Alam U, Asghar O, Azmi S and Malik R A, General aspects of diabetes mellitus, *Handb Clin Neurol*, 2014, **126**, 211–22.

3 Yuan H, Ma Q, Ye L and Piao G, The traditional medicine and modern medicine from natural products, *Molecules*, 2016, **21**(5), 559-578.

4 Amiri M S and Joharchi M R, Ethnobotanical knowledge of Apiaceae family in Iran: A review, *Avicenna J Phytomed*, 2016, **6**(6), 621-635.

5 Moran J, Van Rijswijk B, Traicevski V, Kitajima E W, Mackenzie A M, *et al.*, Potyviruses, novel and known, in cultivated and wild species of the family Apiaceae in Australia, *Arch Virol*, 2002, **147**(10), 1855–1867.

6 Bagheri S M, Maghsoudi M J and Yadegari M, Preventive effect of *Ferula assa-foetida* oleo gum resin on histopathology in cuprizone-induced demyelination mice, *Int J Prev Med*, 2020, **11**, 179-184.

7 Abu-Zaiton A S, Antidiabetic activity of *Ferula assa-foetida* extract in normal and alloxan-induced diabetic rats, *Pak J Biol Sci*, 2010, **13**(2), 97–100.

8 Rahbarian R and Sadooghi S D, Investigating the effects of aqueous extract of asafoetida resin on the serum level of insulin and blood glucose in type 1 diabetic rats, *J Shahrekord Univ Med Sci*, 2014, **16**(3), 16-21.

9 Azizian H, Rezvani M E, Esmaeili D M, Bagheri S M, Anti-obesity, fat lowering and liver steatosis protective effects of *Ferula assa-foetida* gum in type 2 diabetic rats: Possible involvement of leptin, *Iran J Diabetes Obes*, 2012, **4**(3), 120-126.

10 Rafiee S, Mojadadi M-S, Molavi M and Nazemi S, Effect of ethyl acetate extract of *Ferula asafoetida* Oleo-gum resin on the glucose level and lipid profile in streptozotocin-induced diabetic Rats, *Jundishapur J Nat Pharm Prod*, 2020, **15**(2), 1-9.

11 Hassanabadi M, Ebrahimi M, Farajpour M and Dejahang A, Variation in essential oil components among Iranian *Ferula*

assa-foetida L. accessions, *Ind Crops Prod*, 2019, **140**, 111598.

12 Bagheri S, Javidmehr D, Ghaffari M and Ghoderti-Shatori E, Chemical compositions and antiproliferative effect of essential oil of asafoetida on MCF7 human breast cancer cell line and female wistar rats, *Cancer Transl Med*, 2020, **6**(2), 34-39.

13 Bagheri S M, Mohamadsadeghi H and Hejazian E S, Antinociceptive effect of seed's essential oil of *Ferula assa-foetida* in Mice, *Int J Clin Exp Physiol*, 2017, **4**(1), 34–37.

14 Ou C, Tsao S, Lin M and Yin M, Protective action on human LDL against oxidation and glycation by four organosulfur compounds derived from garlic, *Lipids*, 2003, **38**(3), 219–224.

15 Walag A M P, Ahmed O, Jeevanandam J, Akram M, Ephraim-Emmanuel B C, *et al*., Health benefits of organosulfur compounds, In *Functional Foods and Nutraceuticals*, (Springer), 2020, 445–472.

16 Bagheri S M, Yadegari M, Porentezari M, Mirjalili A, Hasanpor A, *et al*., Effect of *Ferula assa-foetida* oleo gum resin on spermatic parameters and testicular histopathology in male wistar rats, *J Ayurveda Integr Med*, 2015, **6**(3), 175-180.

17 Ko B S, Kim D S, Kang S, Ryuk J A and Park S, Prunus mume and *Lithospermum erythrorhizon* extracts synergistically prevent visceral adiposity by improving energy metabolism through potentiating hypothalamic leptin and insulin signalling in ovariectomised rats, *Evid-Based Complement Altern Med*, 2013, **2013**, 750986.

18 Zhang M, Lv X Y, Li J, Xu Z G and Chen L, The characterisation of high-fat diet and multiple low-dose streptozotocin induced type 2 diabetes rat model, *Exp Diabetes Res*, 2008, **2008**, 704045.

19 Bagheri S M, Hedesh S T, Mirjalili A and Dashti R M H, Evaluation of anti-inflammatory and some possible mechanisms of antinociceptive effect of *Ferula assa foetida* oleo gum resin, *J Evid Based Complement Altern Med*, 2016, **21**(4), 271–276.

20 Bagheri S M, Yadegari M, Behpur M and Javidmehr D, Antilithiatic and hepatoprotective effects of *Ferula assa-foetida* oleo-gum-resin on ethylene glycol-induced lithiasis in rats, *Urol Sci*, 2018, **29**(4), 180-185.

21 Susan van D, Beulens J W J, Yvonne T van der S, Grobbee D E and Nealb B, The global burden of diabetes and its complications: an emerging pandemic, *Eur J Cardiovasc Prev Rehabil*, 2010, **17**(1_suppl), 3–8.

22 Kooti W, Farokhipour M, Asadzadeh Z, Ashtary-Larky D and Asadi-Samani M, The role of medicinal plants in the treatment of diabetes: A systematic review, *Electron Physician*, 2016, **8**(1), 1832-1842.

23 Yarizade A, Kumleh H H and Niazi A L I, *In vitro* antidiabetic effects of *ferula assa-foetida* extracts through dipeptidyl peptidase iv and α-glucosidase inhibitory activity, *In vitro*, 2017, **10**(5), 357-360.

24 Helal E G E, Mostafa A M, MhMood A F and Kahwash A A, Hypoglycemic and hyperinsulinemic effects of *Ferula assa-foetida* on diabetic male albino rats, *Egypt J Hosp Med*, 2005, **21**(1), 95–108.

25 Rahbarian R, Sepehri M H and Sadoughi S D, Effect of aqueous extract of *Ferula assa-foetida* and avicennia marina on oxidative stress parameters of brian cells in diabetic rats, *J Neyshabur Univ Med Sci*, 2017, **5**(1), 19-29.

26 Esmailidehaj M, Kahtenaroon M, Rezvani M E, Azizian H and Ranjbar A, Enriched-asafoetida diet attenuates hyperglycemia, oxidative stress and endothelial dysfunction in type 2 diabetic rats, *Physiol Pharmacol*, 2022, **26**(1), 7–19.

27 Azari M, Mohiti-ardekani J, Abedini S and Mozayan M R, Effect of ferula asafoetida on cytoplasmic membrane glucose transporter Isotype-4 of C2C12 cell line, *Int J Med Lab*, 2014, **1**(1), 46–53.

28 Bagheri S M, Yadegari M, Zare-Mohazabiye F, Momeni-Asl H, Mirjalili A, *et al.*, Effect of *Ferula assa-foetida* oleo-gum-resin on gastric ulcer in indomethacin-ulcerated rats, *J Curr Res Sci Med*, 2018, **4**(1), 42-46.

29 Nazemi S, Rudsarabi H, Amin B, Farahani H, Zarmehri H A, *et al.*, Anti-neuropathic pain effects of ethyl acetate extract of Ferula asafoetida oleo-gum-resin in streptozotocin-induced diabetic rats, *Nat Prod J*, 2021, **11**(4), 546–552.