Antidiabetic effect of *Sophora pachycarpa* seeds extract in streptozotocin-induced diabetic mice: a statistical evaluation

Behnam Mahdavi ,[1] Toktam Hajar,[2] Alireza Ghodsi,[3] Majid Mohammadhosseini,[4] Mohammad Mehmandost,[1] Elahe Talebi[1]

Undoubtedly, identification of the chemical composition of organic extracts or secondary metabolites of plant materials and evaluation of their potential bioactivity are among the main objectives of natural products-based investigations. In the present study, we report the chemical composition and antidiabetic activity of *Sophora pachycarpa* (Family Fabaceae) seeds extract (SPE) for the first time. First, the plant seeds were macerated in ethanol. The extract was subjected to analysis on a gas chromatography-mass spectrometry (GC-MS) system to identify the chemical composition. In vivo assay was run to evaluate the antidiabetic activity of the extract. Forty mice were divided into four groups, namely healthy mice, untreated diabetic mice, diabetic mice treated with metformin and diabetic mice treated with SPE. The antidiabetic activity of SPE was analyzed using three statistical methods, namely analysis of variance, K-means, and principal component analysis. According to GC-MS analysis, alkaloids of sophoridine, oleic acid, linoleic acid, and *n*-hexadecanoic acid were among the most abundant constituent components of SPE. The extract also exhibited a notable antidiabetic activity and remarkably decreased the levels of alkaline phosphatase (ALP), serum glutamic pyruvic transaminase (SGPT), and serum glutamic oxaloacetic transaminase (SGOT) enzymes. The statistical analyses revealed there are no significant differences between the ability of SPE and metformin in the regulation of fasting blood sugar level and liver enzymes (ALP, SGPT, and SGOT). A quinolizidine alkaloid, namely sophoridine, along with fatty acids, viz oleic, linoleic, and *n*-hexadecanoic acid, were characterized as the major compounds in *S. tachycardia* seeds extract. The plant extract was also found as a potent agent to reduce blood glucose and liver enzymes.

Significance of this study

What is already known about this subject?

- Diabetes is one of the fastest growing health challenges of the 21st century.
- The use of plants and plant extracts to treat a specific disease and/or disease symptoms appears to have been part of medical care as observed for thousands of years.

What are the new findings?

- Botanicals could be proposed to affect the whole-body metabolism by modulating adipocyte function and thus regulating endocrine secretions that play a role in enhancing the skeletal muscle insulin action.
- Botanicals may regulate hepatic processes, that is, hepatic gluconeogenesis, and may affect whole-body glucose levels.
- The statistical analyses revealed *Sophora pachycarpa* extract regulated fasting blood sugar level and liver enzymes (alkaline phosphatase, serum glutamic pyruvic transaminase and serum glutamic oxaloacetic transaminase) comparable with metformin.

How might these results change the focus of research or clinical practice?

- Herbal products such as *Sophora pachycarpa* extract are a good alternative to metformin for clinical trials.

INTRODUCTION

Diabetes is a disease that occurs when the pancreas does not produce enough insulin or the body cannot completely use the produced insulin.[1–3] Nowadays, type 2 diabetes mellitus has become a global metabolic disease epidemic.[4] In patients with diabetes, the level of blood glucose is highly elevated. It has been well documented that oxidative stress plays an important role in the progression of diabetic complications.[5] Free radicals and reactive oxygen species (ROS) are generated through an increase in blood glucose level, and cells can generate and can damage cellular macromolecules including protein, lipid, and nucleic acids.[6] Aging, obesity, eating habits, and sedentary lifestyle are the main factors that lead to production of ROS, thereby the development of diabetes.[7] A variety of chemical drugs are currently available for treatment of different types of diabetes, many of which can have serious side effects and dire consequences in patients with diabetes. Plants have shown an increasing trend as an alternative to treatment of diabetes, with suitable potency and lower

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/jim-2021-001818).

For numbered affiliations see end of article.

Correspondence to
Dr Behnam Mahdavi, Chemistry, Hakim Sabzevari University, 9617976487 Sabzevar, Iran; b.mahdavi@hsu.ac.ir

Accepted 23 March 2021
Published Online First 12 April 2021

To cite: Mahdavi B, Hajar T, Ghodsi A, *et al*. *J Investig Med* 2021;**69**:1201–1207.

side effects.[1] Medicinal plants can inhibit many enzymes involved in diabetes pathways.[8–10] Therefore, herbal products can be consumed as a functional food for the efficient treatment of diabetes.[11]

The genus *Sophora* belonging to the Fabaceae family is distributed across the globe, particularly in many parts of Asia.[12] From ancient times, the different parts of *Sophora* plants, including roots, stems, seeds, and flowers, have been extensively used in the traditional medicine of many countries.[13] A brief survey of the literature demonstrates that a wide spectrum of medicinal uses has been reported for *Sophora* plants. *Sophora alopecuroides* is an effective agent to treat chronic hepatitis B, cancers, bacterial infections, and inflammations.[14] The plant is known as a potential sedative, central nervous system depressant, and an analgesic remedy.[15] *S. flavescens* is commonly used to treat dermatosis, hepatitis, and arrhythmia in traditional Chinese medicine.[16] The plant is also used to treat fever, bacterial infection, heart disease, rheumatism, and also as pain reliever.[17 18] Furthermore, *S. tonkinensis* is known as a potential remedy in the treatment of diarrhea, gastrointestinal hemorrhage, and eczema.[17] On the other hand, *S. vicifolia* and *S. davidii* are widely used in Chinese traditional medicine, where different organs of these show some remedial effects such as lowering fever, clearing the pharynx, cooling the blood, and reducing swelling. Different herbal species of this genus have also been found to have therapeutic properties to treat dysentery, lung heat cough, and sore throat.[19 20] On the other hand, *S. moorcroftiana* seeds showed cytotoxicity against the human gastric cancer cell line,[21] whereas the extract of *S. pachycarpa*, as an annual plant, shows promising apoptogenic effects on leukemia and breast cancer cell lines.[12 17] The consumption of *S. pachycarpa* seeds of patients with diabetes to reduce their blood glucose level in the plant sampling locality of this research prompted us to assess the in vivo antidiabetic activity of its organic extract. The chemical profile of this extract has also been analyzed using the gas chromatography-mass spectrometry (GC-MS) method.

MATERIALS AND METHODS

Plant extract preparation

The seeds of *S. pachycarpa* were collected in its natural habitat in Neyshabur, Iran (the Global Positioning System information is: 36°17′75″ N, 58°86′30″ E). The plant species was identified by a botanist at Hakim Sabzevari University. The voucher specimen, designated HSUH 504, was deposited at the herbarium of Hakim Sabzevari University. The seeds were dried in the dark at room temperature and then powdered in a mill. Of the prepared sample 50 g was macerated in ethanol:water 80:20 for 72 hours and then gently filtered. In the next step, the extract was concentrated under low pressure at 45°C using a rotary evaporator (Buchi Rotavapor R-114). The crude extract was kept in a cold place before GC-MS analysis and antidiabetic evaluation.

GC-MS analysis

To identify individual components, a hexane solution of *S. pachycarpa* extract was subjected to analysis on an Agilent GC-MS system (Agilent GC 6890A equipped with an Agilent 5973 mass detector) using ZB-5MS capillary column (30.0 m × 0.25 mm internal diameter, 0.25 µm film thickness; Zebron). The employed oven temperature programming was as follows: Accordingly, its initial temperature was adjusted to 50°C for 5 min, then raised to 150°C by a ramp of 5°C per minute. The oven was set at this temperature for 10 min. Finally, the oven temperature was again increased to a final temperature of 260°C using a ramp of 5°C per minute and held at this pressure for 20 min. The injector temperature was 260°C. Helium was used as a carrier gas with a flow rate of 1.0 mL/min. Samples were injected at splitless mode. An ionization voltage of 70eV and an ion source temperature of 200°C over a mass range of 50–500 amu were chosen as the adjusted operational parameters for the mass detector . Peak area was determined using MSD ChemStation from Agilent Technology. A library search was carried out for all peaks using the National Institute of Standards and Technology Mass Spectral Library software. The homologous saturated hydrocarbon standards (C_8–C_{20} and C_{21}–C_{40}) were analyzed using the same column and conditions to calculate the retention indices of compounds.[22 23] The detection of compounds was based on a comparison of the measured retention indices and mass spectral patterns with those available in the literature. All peaks with a match quality of ≥90% were considered and their names were specified.

Animals

In this study, 40 male mice weighing approximately 25–30 g were obtained from Hakim Sabzevari University and kept in standard cages under standard lighting conditions (12:12 hours light/dark) at 22°C±2°C with food and water ad libitum.

Induction of diabetes

All mice were weighed before the experiment. Their blood glucose after 6 hours of fasting was normal (80–130 mg/dL). Diabetes was induced in the mice with a single-dose intraperitoneal injection of 200 mg/kg streptozotocin dissolved in sodium citrate (pH=4–4.5). Symptoms of diabetes, including blood glucose levels above 250 mg/dL, polydipsia, and polyuria, were observed in the mice from 24 hours to 1 week after the injection. The groups were kept in the laboratory for 15–30 days for stabilization of diabetic conditions. Then they were randomly assigned to 4 groups of 10 and treated for 40 days. At the end of the treatment period, the mice were anesthetized with ketamine/xylazine after 6 hours of fasting. Then blood samples taken from the heart were poured into glass tubes and kept at room temperature for an hour. They were then centrifuged at 2000 revolutions per minute) for 10 min and the serum was separated. The sera were kept in a vial at −20°C until glucose, serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT) and alkaline phosphatase (ALP) values were measured. The mice were randomly assigned to 4 groups of 10 as follows:

- First group (NC group): healthy mice that did not receive any treatment.
- Second group (PC group): diabetic mice that only received water by gavage during the treatment period.

- Third group (DD group): diabetic mice treated with metformin at 100 mg/kg by gavage.
- Fourth group (DT group): diabetic mice treated with *Sophora* methanolic extract at 250 mg/kg by gavage.

Statistical analysis

Data were statistically analyzed and expressed as mean±SE. First, Shapiro-Wilk test was done to test the normality of data. If the difference of variance between the groups was significant, analysis of variance (ANOVA) and Tukey test were used; otherwise, an investigation of the variance of the means Welch and Dunnett test was conducted.

To confirm the results obtained by ANOVA, data were also analyzed by means of K-means and principal component analysis (PCA) approaches. K-means clustering aims to partition n observations into K clusters, in which each observation belongs to the cluster with the nearest mean, while PCA is a classic tool to reduce the dimension of data, to visualize the similarities between the biological samples.

RESULTS

GC-MS analysis

According to the obtained results for the characterized chemical profile of *S. pachycarpa* extract using GC-MS analysis (see online supplemental file), 10 compounds were detected in the ethanolic extract of *S. pachycarpa*, which was dominated by alkaloid-like sophoridine (54.6%), followed by the acidic compounds oleic acid (16.8%), linoleic acid (15.88%), and *n*-hexadecanoic acid (7.5%). Sparteine (3.2%) was also identified as another alkaloid in the plant extract.

Antidiabetic activity analysis

Before evaluation of the antidiabetic activity of *S. pachycarpa*, we examined the different concentrations of *S. pachycarpa* seeds extract (SPE) to obtain the extract LD50 (median lethal dose). After treatment of four groups of mice with 50, 40, 30, and 20 mg/kg of SPE, the value of 30 mg/kg was measured for LD50. The results obtained in the present study showed that the treatment of mice with SPE 20 mg/kg body weight/day for 40 days (DT group) caused a significant decrease in fasting blood sugar (FBS), compared with the diabetic untreated group (PC group) ($p<0.05$) (figure 1). This is comparable with the FBS in diabetic mice treated with metformin (DD group). Furthermore, the results indicated that the level of SGOT, ALP, and SGPT enzymes in animals administered with both SPE and metformin decreased significantly compared with the diabetic untreated mice (PC group) ($p<0.05$) (figures 2–4).

The K-means method divided the groups into three clusters. Figure 5 indicates that untreated diabetic mice and healthy animals (PC and NC groups) are in separate clusters and mice treated with metformin and SPE (DD and DT groups) are in one cluster, while the PCA method in which the first two principal components explained 93.8% of the total variance also separated the healthy mice (NC) and untreated diabetic (PC) group (see the left and right sides of figure 5), and animals treated with SPE and metformin (DD and DT groups) were placed together between NC and PC groups (figure 6). The results obtained from K-means and PCA showed that SPE can control blood sugar effectively as well as metformin as a generic drug to control blood sugar.

DISCUSSION

The consumption of medicinal plants and herbal products is well known by people around the world as a sufficient method to control blood glucose levels. So far, many research groups have studied the antidiabetic activity of different plants or herbal products. Apigenin and the extracted polysaccharides from tea, as herbal products, possess antidiabetic property. These products normalize blood glucose and lipid levels.[24 25] Several previous studies have also reported the antidiabetic activity of various plants. For instance, Latifi *et al*[26] have reported the antidiabetic activity of *Ferula assa-foetida*. The plant extract regulates hyperglycemia in diabetic mice with elevated insulin secretion. *Punica granatum* extract showed a positive effect on blood glucose levels in alloxan diabetic rats.[27] The serum glucose

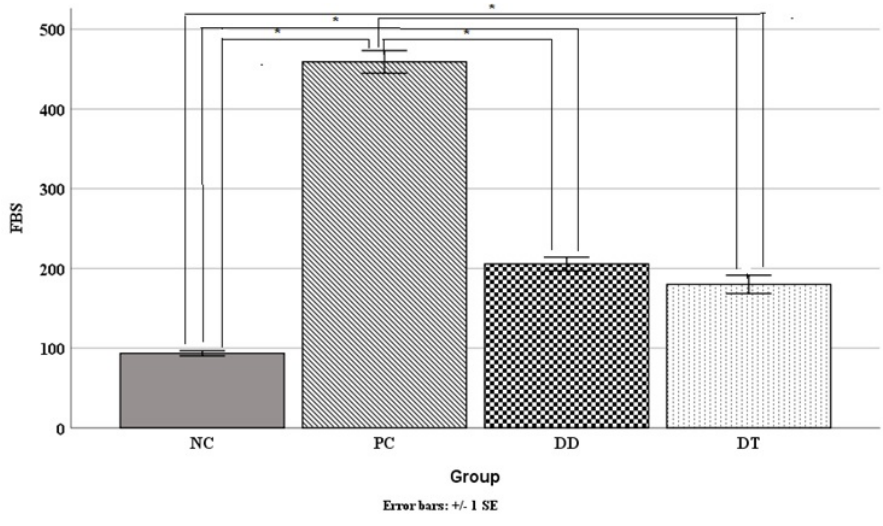

Figure 1 *Sophora pachycarpa* extract and metformin decreased fasting blood sugar (FBS) in diabetic mice. NC, PC, DD, and DT indicate healthy mice, diabetic mice, diabetic mice treated with metformin, and diabetic mice treated with *S. pachycarpa* extract, respectively. Data are presented as mean±SE. *Indicates the difference is statistically significant ($p<0.05$).

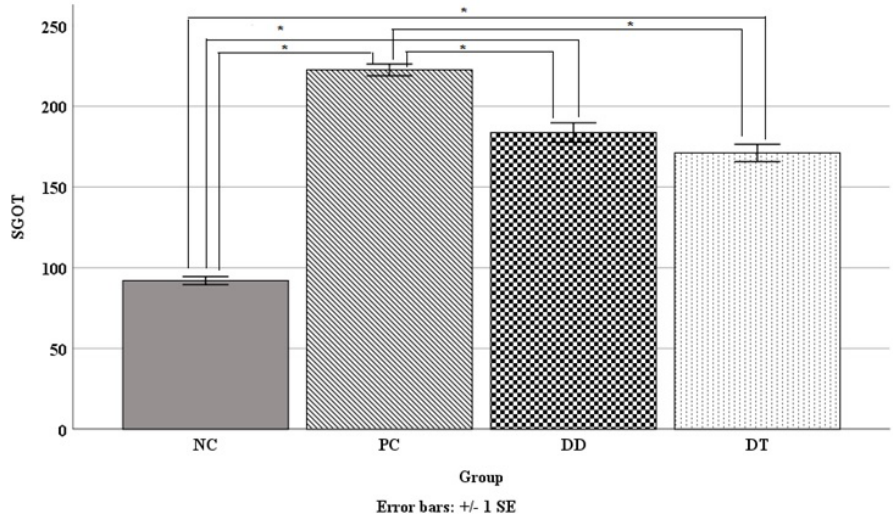

Figure 2 *Sophora pachycarpa* extract and metformin decreased serum glutamic oxaloacetic transaminase in diabetic mice. NC, PC, DD, and DT indicate healthy mice, diabetic mice, diabetic mice treated with metformin, and diabetic mice treated with *S. pachycarpa* extract, respectively. Data are presented as mean±SE. *Indicates the difference is statistically significant (p<0.05).

level in diabetic rats reduced after treatment of *Eugenia florida* extract.[28] The blood glucose level of diabetic mice significantly decreased after treatment of *Datura stramonium* extract.[29] Different plants of the Fabaceae family have been subjected for evaluation of their antidiabetic activity. For example, *Erythrina senegalensis* extract improves hypoglycemic metabolic disorder. The plant extract significantly decreases blood glucose and body weight in induced diabetic mice.[30] *Abrus precatorius* is rich in alkaloid compounds. The plant has been introduced as a good alternative to treat diabetes, after the plant extract increasingly reduced hyperglycemia in diabetic rats.[31] *Mimosa pudica* extract exhibited antidiabetic activity in induced diabetic rats.[32] *Pentaclethra macrophylla* extract was able to decrease the blood sugar level in induced rats.[33] *S. alopecuroides* extract improved hyperglycemia and insulin resistance in diabetic mice.[34] It is difficult to make a detailed comparison of our findings in this research with previous studies; however, the results of this research revealed that the decreased blood sugar level in diabetic mice after treatment of SPE is higher than the plants mentioned above. The plants' secondary metabolites, such as phenolic compounds, flavonoids, saponins, and alkaloids, are known as the major agents responsible for the bioactivity of the plant extracts, such as antioxidant, antimicrobial, antiviral, and antidiabetic activity.

Chemical evaluation of different *Sophora* species exhibited that alkaloids, flavonoids, prenylated flavonoids, and isoflavonoids are the major and most important classes of compounds in the genus.[35] Boozari *et al*[17] have reported the presence of alopecurones A and B, sophoraflavanone G, sophoraisoflavanone A, and 3-isoprenylgenistein in *S. pachycarpa* roots as main flavonoids. Quinolizidines are

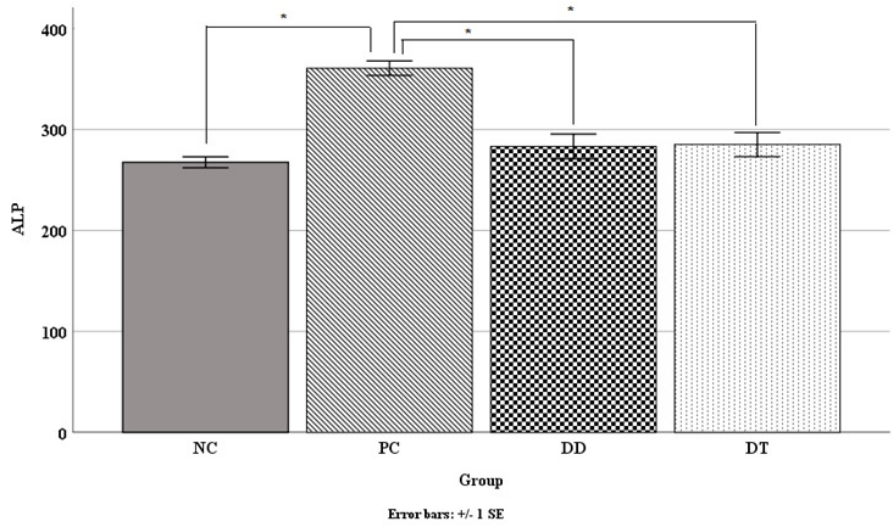

Figure 3 *Sophora pachycarpa* extract and metformin decreased alkaline phosphatase in diabetic mice. NC, PC, DD, and DT indicate healthy mice, diabetic mice, diabetic mice treated with metformin, and diabetic mice treated with *S. pachycarpa* extract, respectively. Data are presented as mean±SE. *Indicates the difference is statistically significant (p<0.05).

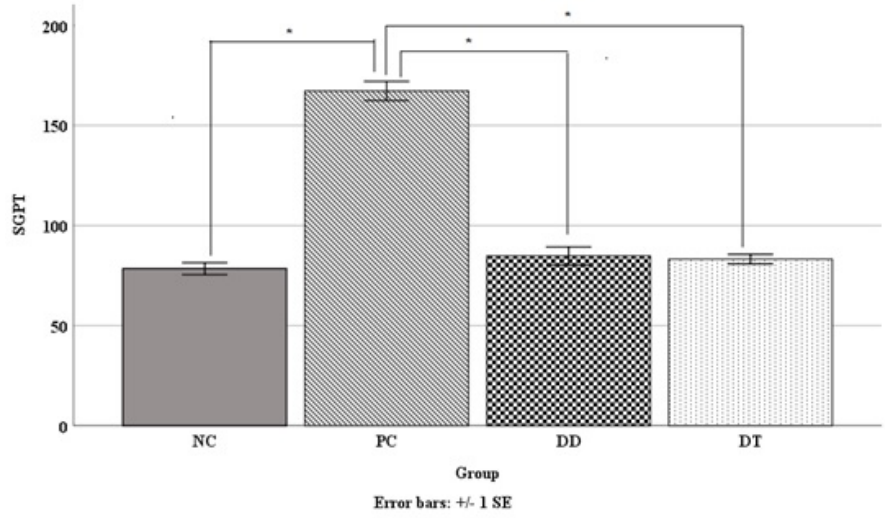

Figure 4 *Sophora pachycarpa* extract and metformin decreased serum glutamic pyruvic transaminase in diabetic mice. NC, PC, DD, and DT indicate healthy mice, diabetic mice, diabetic mice treated with metformin, and diabetic mice treated with *S. pachycarpa* extract, respectively. Data are presented as mean±SE. *Indicates the difference is statistically significant (p<0.05).

the major alkaloids in the *Sophora* genus.[35] According to a previously published report, alkaloids such as 7R-hydroxysophoramine, 12β-hydroxysophocarpine, sophoramine, 14β-hydroxymatrine, matrine, sophoridine, sophocarpine, adenocarpine, and baptifoline were isolated from the aerial parts of *S. alopecuroides*.[15] Fruits, flowers, and leaves of *S. viciifolia* were rich in alkaloids of oxysophocarpine, oxysophoridine, sophocarpine, oxymatrine, and sophoridine.[19]

It has been reported that *Sophora* seeds comprise remarkable alkaloids.[13] Sophoridine, which is identified as the main compound in the seed extract of *S. pachycarpa*, is a matrine-type alkaloid. Previous studies have reported the bioactivity of matrine-type quinolizidine alkaloids, which are well known to possess promising antitumor, anti-inflammatory, antibacterial, and antiviral activities.[18]

Matrine exhibits different types of pharmacological activities, such as anticancer, anti-inflammation, antidiabetic, and antiviral properties.[36] Mahzari *et al*[37] reported reduced hepatosteatosis and improved attenuated hyperglycemia in matrine-induced type 2 diabetic model. The plants of the genus *Retama* are rich in quinolizidine alkaloids and are well known as potent antidiabetic agents in the traditional medicine of the Mediterranean.[38] The isolated quinolizidine alkaloids from *Lupinus* species exhibited

Figure 5 Healthy and untreated diabetic mice were placed in separate clusters (clusters 2 and 3) and mice treated with metformin and *Sophora pachycarpa* extract in another cluster (cluster 1) using the K-means method. NC, PC, DD, and DT indicate healthy mice, diabetic mice, diabetic mice treated with metformin, and diabetic mice treated with *S. pachycarpa* extract, respectively.

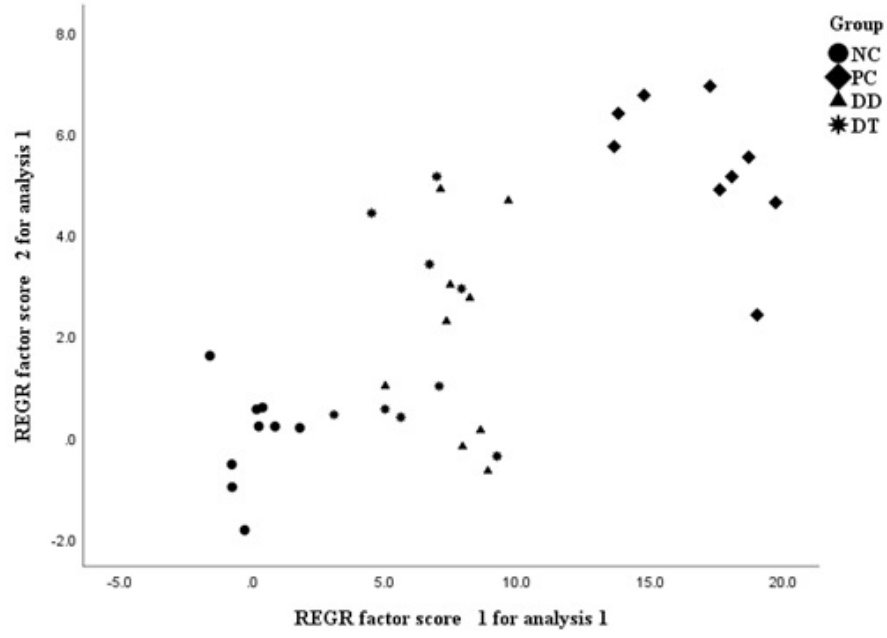

Figure 6 Healthy and untreated diabetic mice were placed in separate clusters and mice treated with metformin and *Sophora pachycarpa* extract in another cluster using principal component analysis with REGR (regression) factor score . NC, PC, DD, and DT indicate healthy mice, diabetic mice, diabetic mice treated with metformin, and diabetic mice treated with *S. pachycarpa* extract, respectively.

antidiabetic properties in Wistar rats through improvement of insulin secretion.[39]

The significant antidiabetic effect of *S. pachycarpa* could be attributed to the presence of various phytoconstituents. Some alkaloids and flavonoids have hypoglycemic activity. On the other hand, the present study showed elevated liver enzymes that are not uncommon in diabetes and are known as a risk factor that can be decreased after treatment of *S. pachycarpa* extract.[40]

Antidiabetic activity is one of the pharmacological properties of alkaloids. These compounds have a direct effect on glucose metabolism.[41 42] On the other hand, it has been reported that the plants are rich in fatty acids such as linoleic acid and exhibited antidiabetic activity.[43 44] It could be inferred that the presence of alkaloids and acidic compounds in *S. pachycarpa* most probably corresponds to the antidiabetic activity of the plant extract.

CONCLUSION

The results of this study indicate that *Sophora pachycarpa* is rich in sophoridine as a quinolizidine alkaloid and some fatty acids such as oleic, linoleic, and *n*-hexadecanoic acid. An additional in vivo study proved that the plant extract has potential to exert antidiabetic effects in streptozotocin-induced diabetic mice. The extract decreased FBS in plasma and improved liver enzymes including ALP, SGPT, and SGOT in diabetic mice. Different statistical analyses including ANOVA, K-means (cluster analysis), and PCA revealed there are no significant differences in the obtained results from the animal group treated by *S. pachycarpa* extract or metformin. The findings of the present study provide many pharmacological reasons in favor of *S. pachycarpa* and thus support its pragmatic use to treat metabolic disorders associated with diabetes. However, more evaluations are needed to study its safety and efficiency in human clinical trials.

Author affiliations
[1]Department of Chemistry, Faculty of Science, Hakim Sabzevari University, Sabzevar, Iran
[2]Department of Biology, Faculty of Science, Hakim Sabzevari University, Sabzevar, Iran
[3]Department of Statistics, Faculty of Mathematics and Computer Science, Hakim Sabzevari Univrersity, Sabzevar, Iran
[4]Department of Chemistry, College of Basic Sciences, Shahrood Branch, Islamic Azad University, Shahrood, Iran

Acknowledgements The authors would like to thank Hakim Sabzevari University for technical support.

Contributors BM: conceptualization, supervision, original draft preparation. TH: methodology, original draft preparation. AG: statistical software, analyses, interpretation of data. MMo: writing-reviewing and editing. MMe and ET ran the laboratory experimentals.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval All animal procedures were approved and conducted following the guidelines of Hakim Sabzevari University Ethical Committee (no. IR.HSU.REC.1398.015).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data sharing is not applicable to this article as no new data were created or analyzed in this study.

regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

ORCID iD
Behnam Mahdavi http://orcid.org/0000-0002-0427-8339

REFERENCES

1 Xiong M, Huang Y, Liu Y, *et al*. Antidiabetic activity^{y} of ergosterol from *Pleurotus ostreatus* in KK-A ^{y} with spontaneous type 2 diabetes mellitus. *Mol Nutr Food Res* 2018;62:1700444.
2 Nampoothiri S, Esakkidurai T, Pitchumani K. Evaluation of antidiabetic, anti-inflammatory and LDL oxidation inhibitory potential of Alpinia galanga and *Alpinia calcarata*-An in vitro study. *Trends Phytochem Res* 2017;1:227–34.
3 Ojah E, Moronkola DO. In-vitro alpha amylase and alpha glucosidase inhibitory potential of leaf hexane, ethyl acetate and methanol fractions of *Pterocarpus soyauxii* Taub. *Trends Phytochem Res* 2020;4:37–44.
4 Li C-J, Chen P-N, Li H-J, *et al*. Potential antidiabetic fumiquinazoline alkaloids from the marine-derived fungus *Scedosporium apiospermum* F41-1. *J Nat Prod* 2020;83:1082–91.
5 Gowd V, Bao T, Wang L, *et al*. Antioxidant and antidiabetic activity of blackberry after gastrointestinal digestion and human gut microbiota fermentation. *Food Chem* 2018;269:618–27.
6 Doan HV, Riyajan S, Iyara R, *et al*. Antidiabetic activity, glucose uptake stimulation and α-glucosidase inhibitory effect of *Chrysophyllum cainito* L. stem bark extract. *BMC Complement Altern Med* 2018;18:1–10.
7 Melo da Cunha JdaS, Alfredo TM, Dos Santos JM, *et al*. Antioxidant, antihyperglycemic, and antidiabetic activity of *Apis mellifera* bee tea. *PLoS One* 2018;13:e0197071.
8 Mohammadhosseini M. The ethnobotanical, phytochemical and pharmacological properties and medicinal applications of essential oils and extracts of different *Ziziphora* species. *Ind Crops Prod* 2017;105:164–92.
9 Mohammadhosseini M, Sarker SD, Akbarzadeh A. Chemical composition of the essential oils and extracts of Achillea species and their biological activities: a review. *J Ethnopharmacol* 2017;199:257–315.
10 Mohammadhosseini M, Venditti A, Akbarzadeh A. The genus Perovskia Kar.: ethnobotany, chemotaxonomy and phytochemistry: a review. *Toxin Rev* 2019;31:1–22.
11 Alam F, Shafique Z, Amjad ST, *et al*. Enzymes inhibitors from natural sources with antidiabetic activity: a review. *Phytother Res* 2019;33:41–54.
12 Shour S, Iranshahy M, Pham N, *et al*. Dereplication of cytotoxic compounds from different parts of *Sophora pachycarpa* using an integrated method of HPLC, LC-MS and ^{1}H-NMR techniques. *Nat Prod Res* 2017;31:1270–6.
13 Pourahmad Jaktaji R, Mohammadi P. Effect of total alkaloid extract of local *Sophora alopecuroides* on minimum inhibitory concentration and intracellular accumulation of ciprofloxacin, and acrA expression in highly resistant *Escherichia coli* clones. *J Glob Antimicrob Resist* 2018;12:55–60.
14 Jia F, Zhou Q, Li X, *et al*. Total alkaloids of *Sophora alopecuroides* and matrine inhibit auto-inducer 2 in the biofilms of *Staphylococcus epidermidis*. *Microb Pathog* 2019;136:103698.
15 Choudhary MI, Parvez K, Ahmed A. Quinolizidine alkaloids from Sophora alopecuroides. *J Nat Prod* 2000;63:190–2.
16 Yang Z, Wang Y, Cheng J, *et al*. Solid self-microemulsifying drug delivery system of Sophoraflavanone G: prescription optimization and pharmacokinetic evaluation. *Eur J Pharm Sci* 2019;136:104953.
17 Boozari M, Nejad Ebrahimi S, Soltani S, *et al*. Absolute configuration and anti-cancer effect of prenylated flavonoids and flavonostilbenes from *Sophora pachycarpa*: Possible involvement of Wnt signaling pathway. *Bioorg Chem* 2019;85:498–504.
18 Wan C-X, Luo J-G, Ren X-P, *et al*. Interconverting flavonostilbenes with antibacterial activity from *Sophora alopecuroides*. *Phytochemistry* 2015;116:290–7.
19 Lin B-B, Liu X, Wu S-Q, *et al*. Phytochemicals content, antioxidant and antibacterial activities of *sophora viciifolia*. *Chem Biodivers* 2019;16:e1900080.
20 Huang Y, Hao J, Tian D, *et al*. Antidiabetic activity of a flavonoid-rich extract from Sophora davidii (Franch.) Skeels in KK-Ay mice via activation of AMP-activated protein kinase. *Front Pharmacol* 2018;9:760.
21 Su G, Yang W, Meng W, *et al*. Anti-proliferation effects of ethanolic extracts from *Sophora moorcroftiana* seeds on human hepatocarcinoma HepG2 cell line. *Nat Prod Res* 2018;32:1472–5.
22 Mahdavi B, Yaacob WA, Din LB. Phytochemical study of medicinal smokes from *Etlingera brevilabrum* leaves. *J Herb Med* 2018;13:52–62.
23 Mohammadhosseini M, Akbarzadeh A, Flamini G. Profiling of compositions of essential oils and volatiles of *Salvia limbata* using traditional and advanced techniques and evaluation for biological activities of their extracts. *Chem Biodivers* 2017;14:e1600361.
24 Zhou Y, Wang Z, Xu L. 39 Studies on the antidiabetic activity of apigenin in mice with streptozotocin-induced diabetes. *J Investig Med* 2016;64:A14.
25 Liu Y, Li S, Cheng Y. 41 Antidiabetic activity of tea polysaccharides in mice with alloxan-induced diabetes. *J Investig Med* 2016;64:A15.
26 Latifi E, Mohammadpour AA, H BF, Fathi B, *et al*. Antidiabetic and antihyperlipidemic effects of ethanolic *Ferula assa-foetida* oleo-gum-resin extract in streptozotocin-induced diabetic wistar rats. *Biomed Pharmacother* 2019;110:197–202.
27 Gharib E, Montasser Kouhsari S, Kouhsari SM. Study of the antidiabetic activity of *Punica granatum* L. fruits aqueous extract on the alloxan-diabetic wistar rats. *Iran J Pharm Res* 2019;18:358–68.
28 Bastos RG, Salles BCC, Bini IF, *et al*. Phytochemical composition, antioxidant and in vivo antidiabetic activities of the hydroethanolic extract of *Eugenia* Florida DC. (Myrtaceae) leaves. *South African Journal of Botany* 2019;123:317–32.
29 Belayneh YM, Birhanu Z, Birru EM, *et al*. Evaluation of in vivo antidiabetic, antidyslipidemic, and in vitro antioxidant activities of hydromethanolic root extract of *Datura stramonium L.* (Solanaceae). *J Exp Pharmacol* 2019;11:29–38.
30 Bilanda DC, Bidingha Ronald À Goufani, Djomeni Dzeufiet PD, Dzeufiet PDD, Fouda YB, *et al*. Antihypertensive and antidiabetic activities of *Erythrina senegalensis* DC (Fabaceae) stem bark aqueous extract on diabetic hypertensive rats. *J Ethnopharmacol* 2020;246:112200.
31 Lébri M, Lagou SM, Bahi C. Phytochemical screening and antidiabetic effect of aqueous extract of *Abrus precatorius* Linn (Fabaceae). *Science et Technique, Sciences de la Santé* 2019;42:157–68.
32 Parasuraman S, Ching TH, Leong CH, *et al*. Antidiabetic and antihyperlipidemic effects of a methanolic extract of *Mimosa pudica* (Fabaceae) in diabetic rats. *Egyptian J Basic Appl Sciences* 2019;6:137–48.
33 Odoh U, Osadebe P, Asogwa C. Studies on the antidiabetic effects of methanol extract of *Pentaclethra macrophylla* Benth (Fabaceae) stem bark on alloxan-induced diabetic model. *J Pharmacogn Phytochem* 2020;9:617–21.
34 Lv Y, Zhao P, Pang K, *et al*. Antidiabetic effect of a flavonoid-rich extract from *Sophora alopecuroides* L. in HFD- and STZ- induced diabetic mice through PKC/GLUT4 pathway and regulating PPARα and PPARγ expression. *J Ethnopharmacol* 2021;268:113654.
35 Aly SH, Elissawy AM, Eldahshan OA, *et al*. The pharmacology of the genus *Sophora* (Fabaceae): An updated review. *Phytomedicine* 2019;64:153070.
36 Chen X, Yan J, Yu S, *et al*. Formulation and in *vitro* release kinetics of Mucoadhesive blend gels containing matrine for buccal administration. *AAPS PharmSciTech* 2018;19:470–80.
37 Mahzari A, Zeng X-Y, Zhou X, *et al*. Repurposing matrine for the treatment of hepatosteatosis and associated disorders in glucose homeostasis in mice. *Acta Pharmacol Sin* 2018;39:1753–9.
38 León-González AJ, Navarro I, Acero N, *et al*. Genus retama: a review on traditional uses, phytochemistry, and pharmacological activities. *Phytochemistry Reviews* 2018;17:701–31.
39 Rasouli H, Yarani R, Pociot F, *et al*. Anti-diabetic potential of plant alkaloids: revisiting current findings and future perspectives. *Pharmacol Res* 2020;155:104723.
40 Leeds JS, Forman EM, Morley S, *et al*. Abnormal liver function tests in patients with type 1 diabetes mellitus: prevalence, clinical correlations and underlying pathologies. *Diabet Med* 2009;26:1235–41.
41 Patel OPS, Mishra A, Maurya R, *et al*. Naturally occurring carbazole alkaloids from *Murraya koenigii* as potential antidiabetic agents. *J Nat Prod* 2016;79:1276–84.
42 Agrawal R, Sethiya NK, Mishra SH. Antidiabetic activity of alkaloids of *Aerva lanata* roots on streptozotocin-nicotinamide induced type-II diabetes in rats. *Pharm Biol* 2013;51:635–42.
43 Palomer X, Pizarro-Delgado J, Barroso E, *et al*. Palmitic and oleic acid: the yin and yang of fatty acids in type 2 diabetes mellitus. *Trends Endocrinol Metab* 2018;29:178–90.
44 Mejri F, Selmi S, Martins A, *et al*. Broad bean (Vicia faba L.) pods: a rich source of bioactive ingredients with antimicrobial, antioxidant, enzyme inhibitory, anti-diabetic and health-promoting properties. *Food Funct* 2018;9:2051–69.