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Hypoglycemic effects of aqueous extract of *Salvia mirzayanii* Rech. F& Esfand in diabetic patients; a randomized controlled trial study

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ABSTRACT

Introduction: Medicinal plants are used in diabetes treatment. *Salvia mirzayanii* Rech. F& Esfand was used for diabetes treatment in Iranian traditional medicine.
Objectives: The main objective of this study is to investigate the antidiabetic effects of aqueous extract of *S. mirzayanii* in diabetic patients.
Patients and Methods: In the present randomized controlled trial study, the patients were divided into trial (n=27) and control (n=25) groups. The trial group received daily one capsule containing 450 mg of aqueous extract of *Salvia mirzayanii*; the control group received daily one capsule containing 450 mg of caramelized flour and 5% aqueous extract of *S. mirzayanii*. Fasting blood samples were collected at the beginning of the study and after 3 months, fasting blood sugar (FBS), HbA_1C, insulin, HOMA-IR index, alanine transaminase (ALT), aspartate transaminase (AST), and lipid profile were evaluated.
Results: Types of used drugs, gender, age, and body mass index (BMI) were not significantly different between trial and control groups before treatment. Additionally, after treatment, BMI did not significantly change between these two mentioned groups. The results showed that FBS and HbA_1C levels did not change significantly in the trial group after treatment; however, in this group, insulin secretion was increased significantly ($P=0.015$). Nevertheless; after treatment, HOMA-IR index did not significantly change between the two mentioned groups. In the trial group, after treatment, liver enzymes (ALT and AST) levels did not change significantly. After the treatment, LDL-C was changed in the trial group.
Conclusion: The herbal drug used in the present study enhanced insulin secretion, and improved LDL-C level in diabetic patients.
Trial Registration: Registration of trial protocol has been approved in the Iranian Registry of Controlled Trials website (identifier: IRCT2015122725712N1; https://en.irct.ir/trial/21454, Ethical code# HUMS.REC.1394.53).

Implication for health policy/practice/research/medical education:
In a randomized controlled trial study on a group of diabetic patients who were divided into, two trial (n=27) and control (n=25) groups, we found that aqueous extract of *Salvia mirzayanii* Rech. F& Esfand enhanced insulin secretion and improved LDL-C level in diabetic patients.
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Original Article

Introduction

Type 2 diabetes mellitus (T2DM) is one of the most common disorders in the world since it affects approximately 120 million people worldwide, which could be doubled in the next 10 years (1). The metabolic aspect of diabetes is characterized by moderate to severe hyperglycemia and impaired metabolism of macromolecules including carbohydrates, proteins, and lipids (2).

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T2DM is the main cause of renal disorder, blindness, and non-traumatic amputations. In this regard, a correlation has been reported between type 2 diabetes with inadequate metabolic regulation and the high prevalence of mortality because of cardiovascular illness and nephropathy. The appropriate regulation of plasma glucose concentrations inhibits microvascular complications. Accordingly, the main effect of medical treatment in patients with T2DM is the regulation of metabolic pathways (3). T2DM is a multifactorial heterogeneous group of metabolic disorder with hyperglycemia and decreased insulin action and/or insulin secretion (4). Nowadays, the use of plants for treating diabetes is favored. However, the medicinal use of herbs is effective in the treatment of diabetes as a multifactorial disorder. The side effects of insulin and oral hyperglycemic factors, increase interests among diabetic patients for using natural products with antidiabetic effects (5). Hence, finding natural compounds for treating diabetes can be considered as a favorable field (6). To treat T2DM, more than 1000 plant species have been consumed worldwide (7). *Salvia* species (sages) are consumed in many parts of the world for treating several disorders. In the present study, the effect of aqueous extract of *Salvia mirzayanii* Rech. F& Esfand in patients with T2DM is evaluated. As the largest genus of Labiatae family, *Salvia* contains approximately 900 species (7,8). Plants of this genus grow all over the world (9-12) and a large number of them have been used for medical purposes (11-14), such as anti-diabetic (15) in various countries (12-14). In a study, it was reported that *Salvia circinata* extract inhibited α-glucosidase (16), an enzyme which increases carbohydrate digestion and induces the occurence of T2DM.

The effects of *Salvia* species extracts have already been investigated in animal models. For instance, methanol extract of *Salvia triloba* leaves decreased hyperglycemia levels in a rat model of streptozotocin/nicotinamide-induced diabetes (17). Additionally, the acute and chronic anti-hyperglycemic effects of methanol extract of *S. mirzayanii* was detected in rats (17), salso methanol extract of *S. mirzyanii* could reduce blood glucose of experimental animals (18).

Objectives

The main purpose of the present study is to determine the hypoglycemic effect of aqueous extract of *S. mirzayanii* leaves in diabetic patients. Note that this work is the first clinical trial study carried out on human subjects. In the present study, fasting blood glucose, HbA1C, and insulin levels, ALT (alanine transaminase) and AST (aspartate transaminase) levels, lipid profile, and blood pressure were determined.

Patients and Methods

Protocol

This double-blind study was conducted from September 2017 to July 2017 by Department of Biochemistry, Hormozgan University of Medical sciences. The diabetic patients were randomly divided into interventional (n=27) and control (n=25) groups. The interventional group received the capsule containing 450 mg/daily of concentrated aqueous extract of *S. mirzayanii* and the control group received the placebo capsule containing 450 mg/daily of caramelized flour and 5% of aqueous extract of *S. mirzayanii*. The demographic information of all subjects including age, gender, height, weight, body mass index (BMI), systolic and diastolic pressure, and drugs consumption was recorded. Aqueous extract of *S. mirzayanii* in placebo capsule used as coloring and flavoring and this amount of (5%) the extract had no significant effects on the obtained results.

Extraction preparation

Aerial parts of *S. mirzayanii* plants were collected from Genu Mountains in northeast of Bandar-Abbas city Hormozgan province, Iran. They were identified by MM (The third author). Voucher specimen has been preserved at the herbarium of Medicinal Plants Processing Research Center (Voucher # MPRCM 94-84), Shiraz University of Medical Sciences. Herbal drugs were prepared by Department of Phytopharmaceutical (traditional pharmacy), School of Pharmacy, Shiraz University of Medical Sciences, Shiraz, Iran.

Biochemical experiments

The biochemical experiments included determination of fasting blood sugar (FBS), glycosylated hemoglobin (HbA1C), liver enzymes (including AST and ALT), lipid profile (including cholesterol, triglyceride, and LDL-C and HDL-C levels) and serum insulin conducted at the beginning of the study and after three months. Serum was separated from 5 cc blood of fasting patients, the afore-mentioned measurements were performed and the results were compared in the interventional and control groups. Insulin was measured by enzyme-linked immunosorbent assay (ELISA) using Monobind kit (Monobind Inc, lake Forest, CA, USA), and for this measurement, Awareness instrument (USA) was used. HbA1C was measured by Axis-Shield HbA1C calibrator kit, and other factors were measured by an auto-analyzer (BT 3500, Italy).

HOMA-IR (Homeostasis Model Assessment of Insulin Resistance) on the development of type 2 diabetes was measured using the following formula: HOMA-IR = Insulin (μU/dL) × Glucose (mmol/L)/22.5 (11).

Inclusion and exclusion criteria

Inclusion criteria were as follows: patients within the age range of 18 to 65 years, patients having type II diabetes mellitus based on the guidelines of the (WHO 2018), patients with BMI >19 kg/m^2 and <30 kg/m^2, patients without insulin therapy and any other complications. All the selected patients signed the informed consent form.

Exclusion criteria were as follows: pregnant women or women intended to become pregnant, patients with active infections or hepatitis C, B and HIV or TB (or in TB therapy), cancer patients (except patients with skin cancer), using prednisone for the treatment of a chronic disease, smoking cigarettes and drinking alcohol, blood pressure higher than 160/90 mm Hg, taking contraceptive pill by women; moreover, patients with malabsorption, chronic diarrhea, liver and kidney diseases, ischemic heart disease, anemia, heart attack, peripheral vascular disease and diabetic nephropathy were excluded from the study.

Sample size calculation

Two-sample parallel design

H_0: $\mu_1 = \mu_2$ vs H1: $\mu_1 \neq \mu_2$, ($\mu_1 - \mu_2 = \varepsilon$)

$$n_{\text{in each group}} = \frac{2\,\sigma^2(z_{1-\frac{\alpha}{2}} + z_{1-\beta})^2}{(\mu_1 - \mu_2)^2}$$

$$\sigma^2 = \frac{(n_1 - 1)S_1^2 + (n_2 - 1)S_2^2}{n_1 + n_2 - 2}$$

$Z_{1-\beta}$=0.84, $z_{1-\frac{\alpha}{2}} = 1.96$, $z_{1-\beta} = 0.84$

According to the previous studies (19) at least 22 patients in each group are needed (Figure 1).

Ethical issues

This investigation is in accordance with the Helsinki Declaration of 2013 that was approved by Ethical Committee of Hormozgan University of Medical Sciences (# HUMS.REC.1394.53) and by Iranian Randomized Controlled Trial (IRCT registration number; IRCT2015122725712N1; https://en.irct.ir/trial/21454). This controlled trial is double-blinded (neither the administrator nor the subjects know which subjects received drug). The patients were informed about the advantages and possible risks of the consumed drug.

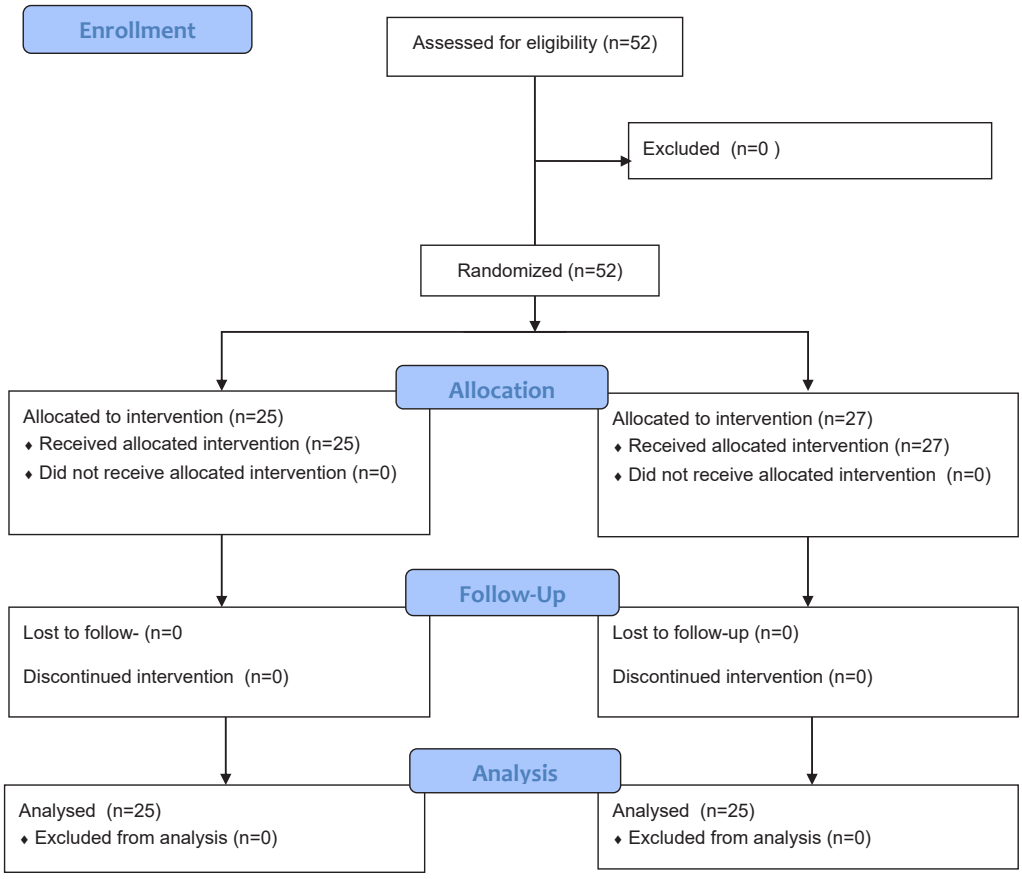

Figure 1. CONSORT (consolidated standard of reporting trial) chart for study.

Statistical analysis

Statistical analysis was performed using (SPSS version 19). To compare gender ratio, systolic and diastolic blood pressures, and drug usage between the groups, Chi-Square, Mann-Whitney U, and Fisher's tests were performed, respectively. Moreover, to compare other variables, independent *t* test and paired *t* test were applied. *P* values less than 0.05 were considered as a significant difference.

Results

At the beginning of this study there was no significant difference between age ($P=0.369$, Table 1), BMI ($P=0.374$), systolic ($P=0.500$) and diastolic pressures ($P=0.295$, Table 2), ratio of gender ($P=0.430$, Table 1), ratio of drug use such as metformin ($P=0.183$), atorvastatin ($P=0.071$), aspirin ($P=0.492$), losartan (P=0.845) and repaglinide ($P=0.488$) between trial and control groups (Table 3). Moreover, after the treatment, no significant change was observed regarding BMI and systolic and diastolic blood pressures between trial and control groups.

We found that fasting serum HbA1C and fasting blood glucose levels were not changed significantly in the trial group after the treatment, while insulin level was increased in the trial group after treatment (Table 4). HOMA-IR Index in control group before (10.1±7.5 µU/dL) and after intervention (13.5±11.4 µU/dL) was not significantly changed $P>0.05$, also this index did not significantly change in trial group before (4.8±2.26 µU/dL) and after (8.84±5.04 µU/dL) intervention ($P<0.05$).

After the intervention, LDL-C level (Table 5) was reduced in the trial group ($P<0.199$). In the trial group after treatment, there were no significant differences in AST ($P=0.093$) and ALT ($P=0.135$) levels (Table 6).

Table 1. Gender, age, distributions of the case and control groups before and after treatment

Groups	Gender	Age
Control	44% male 56% female	55.4±8.48
Case	33.3% male 66.7% female	53.37±7.68
P value	0.43	0.369

Discussion

In the present study, we investigated the hypoglycemic effect of aqueous extract of *S. mirzayanii* in diabetic patients.

The results of other studies revealed that species of *Salvia* containing three flavonoids, namely, luteolin 7-O-glucoside, luteolin 7-O-glucuronide, and diosmetin 7-O-glucuronide which have inhibitory effects on α-glucosidase with IC_{50} values similar to that of acarbose as a standard (22). In addition, compounds like catechins and rosmarinic acid were isolated from *Salvia* species such as *Salvia choloroleuca*, *Salvia santolinifolia*, and *Salvia mirzayanii* by HPLC analysis (23).

In clinical trial studies of diabetes, probably some symptoms of DM such as polydipsia, polyphagia, body weight loss, (24) and blood pressure should be considered as significant factors for managing DM and related complications (24).

In the current study, diastolic and systolic pressures and BMI were not significantly different between trial and control groups before and after treatment with herbal drug, ($P=0.473$, $P=0.641$ and $P=0.987$, respectively).

HbA1C is a gold standard in the evaluation of diabetes

Table 2. BMI distribution and systolic and diastolic blood pressures of the case and control groups before and after treatment

Groups	BMI (kg/m²)			Diastolic (mm Hg)			Systolic (mm Hg)		
	Before treatment	After treatment	*P* value	Before treatment	After treatment	*P* value	Before treatment	After treatment	*P* value
Control	25.84±3.9	25.1±0.66	0.3	129.6±20	123.80±19.5	0.206	76±7.07	73.00±9.46	0.146
Case	24.92±3.37	25.20±3.51	0.47	123.46±15.48	121.30±14.71	0.234	77.31±6.04	73.00±8.50	0.092
P value	0.376	0.987		0.295	0.743		0.50	0.641	

Table 3. Percentage of drugs use in the case and control groups

Groups	Metformin	Atorvastatin	ASA (aspirin)	Losartan	Repaglinide
Control	Use 84% Not use 16%	Use 72% Not use 38%	Use 76% Not use 24.0%	Use 20% Not use 80%	Use 28% Not use 72%
Case	Use 96.3 Not use 3.7	Use 92.6 Not use 7.4%	Use 85.2 Not use 14.8	Use 22.2% Not use 77.8%	Use 37% Not use 63%
P value	0.183	0.071	0.492	0.845	0.488

Table 4. FBS, HbA_1C, insulin levels before and after treatment in the case and control groups

Groups	FBS (mg/dL)			HbA_1C (percentage)			Insulin (µIµ/dL)		
	Before treatment	After treatment	*P* value	Before treatment	After treatment	*P* value	Before treatment	After treatment	*P* value
Control	167.2±53.6	157.08±51.3	0.479	7.25±1.07	7.15±1.3	0.729	10.1±7.5	13.5±11.4	0.375
Case	190.09±51.6	191.5±74.3	0.464	7.66±1.32	7.9±1.5	0.0697	9.3±5.9	15.6±12.3	0.015
P value	0.124	0.342		0.229	0.003	0.379	0.530	0.32	

µIµ: micro international unit.

Table 5. HDL-C, LDL-C and total cholesterol levels before and after treatment in the case and control groups

Groups	HDL (mg/dL)			LDL (mg/dL)			Cholesterol (mg/dL)		
	Before treatment	After treatment	*P* value	Before treatment	After treatment	*P* value	Before treatment	After treatment	*P* value
Control	40.9±8.03	48.40±13.37	0.02	89.56±31.49	97.4±34.36	0.460	157.1±37.15	164.4±43.05	0.532
Case	39.9±11.43	45.37±10.85	0.004	108.78±30.86	99.8±37.46	0.199	171.2±53.5	167.7±54.3	0.772
P value	0.714	0.372		0.031*	0.81		0.279	0.522	

Table 6. ALT, AST and TG levels before and after treatment in the case and control groups

Groups	ALT (U/L)			AST (U/L)			Triglyceride (mg/dL)		
	Before treatment	After treatment	*P* value	Before treatment	After treatment	*P* value	Before treatment	After treatment	*P* value
Control	21.2±10.25	27.76±12.4	0.057	21.32±4.2	24.5±6.17	0.035	136.2±70	112.6±62.1	0.354
Case	26.09±16.8	28.5±15.26	0.135	22±7.5	23.6±8.9	0.093	142.9±80	125.8±70.2	0.075
P value	0.214	0.845		0.683	0.68		0.816	0.574	

while numerous studies showed that the level of HbA1C is strongly correlated with the glycemic control over a period of 2 to 3 months (25). However, in some conditions HbA_1C level may not reliably reveal the glycemic control in diabetic patients (26).

High doses of antioxidant agents such as vitamins C and E have been reported to decrease the level of HbA1C by reducing the rate of hemoglobin glycation; however, the pharmacological doses of antioxidant agents in which this event occurs, is not clear (25-27).

The results of this study presented no significant differences between FBS and HbA1C levels in trial and control groups before and after treatment. Similar results were reported in another clinical trial study, in which the trial group was treated with aqueous extract of *Salvia officinalis* (28). In this study, unreduced blood glucose and HbA_1C levels in the trial group may indicate that *S. mirzayanii* extract has no effect on gluconeogenesis and postprandial blood glucose, respectively.

However, in the present study, the herbal drug increased the secretion of insulin in the trial group, but HOMA-IR is not altered before and after intervention in both control and trial groups. It is reported that elevation in HOMA-IR had a strong effect on the development of type 2 diabetes among subjects (29).

Elsewhere, it was reported that extract of *Momordica charantia* L (25) was agonist to, insulin; a finding obtained from animal pancreas revealed a consistent hypoglycemic effect in diabetic patients.

In another study, aldose reductase inhibitory activity (30) of rosmarinic acid derived from the root of *Salvia grandifolia* was reported (31).

Aldolase reductase is a key enzyme in polyol pathway that converts glucose to sorbitol and accumulates reactive oxygen species in various tissues of diabetic patients (32).

In diabetic status, high levels of serum lipids are attributed to the increased function of lipolytic in adipose tissue (31,32). We found that the mean total cholesterol, HDL-C, and TG levels after the intervention had no significant differences in the trial and control groups. However, a significant difference is observed between LDL-C levels of the trial group compared to the placebo group. In other words, LDL-C level of the trial group (89.6±31.5 mg/dL) is more than the control group (108.8±30.9 mg/dL). Since this difference is not observed after treatment, it is suggested that the administration of the *S. mirzayanii* capsule, decreased LDL-C levels.

In another study, it was reported that the mean triglyceride, LDL-C, and HDL-C levels in the trial group had no significant differences before and after treatment

by *S. officinalis*. However, administration of *S. officinalis* extracts reduced total cholesterol of trial group, which can be an indicator of the beneficial effect of this extract on patients with hyperlipidemia (27).

In our study, there were no significant differences in the levels of ALT and AST before and after treatment in the trial group. However, AST level was increased in the control group from 21.3±4.2 mg/dL to the normal value of 24.5±6.2 mg/dL.

Hence, it can be stated that the drug has no adverse effects on liver enzymes, suggesting its safe application.

Conclusion

Considering the results obtained in the present work, lack of a change in FBS and HbA_1C levels may be explained by the fact that patients do not take the drug regularly. To obtain better results, we suggest using a larger study population and administering the patients with two herbal capsules every day. In fact, higher doses might be needed to decrease fasting blood glucose and glycosylated hemoglobin levels. Using capsule containing *S. mirzayanii* extract decreases LDL-C level that can be an indicator of favorable effects of this drug in hyperlipidemic patients. The results showed that this drug had no unwanted and toxic effect on the liver, implying that it is safe for the liver. Further controlled studies may be needed on this subject.

Study limitations

There was a limitation in finding diabetic patients who accepted to participate in the current study and consumed regularly capsule containing *S. mirzayanii* extract. If this study was performed with a larger population with the administered capsules (herbal capsules) containing more *S. mirzayanii* extract, the obtained results could be impressive more.

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Authors' contribution

MM and SM designed the study. PS performed the experiments. RM collected data from patients and helped in performing the experiments. MZ prepared the capsules. SM wrote and revised the article.

Conflicts of interest

There are no conflicts of interest related to various aspects such as financial support by commercial firms.

Ethical considerations

Ethical issues (including plagiarism, double publication) have been completely considered by the authors.

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