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Original Article

Effects of *Satureja khuzestanica jamzad* Supplementation on Inflammatory and Antioxidant Indicators in Type 2 Diabetes Patients: A Randomized Controlled Clinical Trial (RCT)

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Abstract

Background and Aim: As the most common metabolic disorder, type 2 diabetes mellitus is growing exponentially worldwide. *Satureja khuzestanica* (SK) is a native plant of Iran that grows widely in southern Iran. Various animal studies have reported its antimicrobial, antioxidant, anti-inflammatory, and pain-relieving effects to date. The present research aimed to investigate the impact of the daily consumption of SK on inflammatory (IL-6, CRP) and antioxidant indicators (catalase, glutathione peroxidase, glutathione reductase, superoxide dismutase and total antioxidant capacity) in type 2 diabetic patients.

Materials and Methods: In a double-blind, placebo-controlled clinical trial, 78 patients (44 females and 34 male) with type 2 diabetes were included and randomly divided into two groups. One group received SK (capsule containing 500 mg) and the other group received placebo (500 mg talcum powder) once a day for 12 weeks. After the intervention, inflammatory and antioxidant indicators of the two groups were compared.

Results: The levels of total antioxidant capacity, superoxide dismutase, catalase, glutathione reductase, and glutathione peroxidase were remarkably distinct between the intervention and placebo groups, and these antioxidant indices were higher in the intervention group (P<0.05). Moreover, a considerable decrease in weight, CRP and IL-6 levels were observed in patients in the *S. khuzestanica* group.

Conclusion: As the findings of the study revealed, SK supplementation might improve the antioxidant and inflammatory indices of patients with T2DM. The results of this study could potentially offer new additional therapies for diabetes complications with no adverse side effects. These results should be further confirmed in clinical trials.

Keywords: *Satureja khuzestanica*, Diabetes mellitus, Antioxidant indicators, Il-6, C-reactive protein

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Introduction

Diabetes is known as one of the four important non-communicable diseases (1). It is a multifactorial disease characterized by disturbances in the metabolism of carbohydrates, lipids and proteins, and is caused by disturbances in insulin secretion, insulin resistance or both of them (2).

The prevalence of diabetes in the world in 2019 was estimated to be 9.3% (463 million subjects), which would reach 10.2% in 2030, based on the report of the International Diabetes Federation (3). The highest rates of the prevalence of diabetes in the world are related to the Middle East, where Iran is located, and North Africa (MENA). This rate, which was reported to be 12.2% in 2019, is expected to reach 13.3% in 2030 (4). Diabetes leads to various complications in different organs of the body, which are divided into two categories: macrovascular complications such as cardiovascular diseases and microvascular complications (5). These vascular complications are caused by non-enzymatic glycosylation of proteins, changes in cell oxidation and regeneration, increased oxidative stress and inflammatory state, progression of endothelial disorders, and increased risk of thrombosis (6). Various studies have indicated that inflammatory biomarkers increase in diabetes. Among these biomarkers, C-reactive protein (CRP), interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF-α) can be mentioned (7). The mild degree of inflammation plays a key role in the occurrence of impaired glucose homeostasis, impaired insulin function, and the pathogenesis of type 2 diabetes (8). This hypothesis originates from studies that have reported the correlation between increased circulating levels of acute phase inflammatory markers, especially C-reactive protein, with insulin resistance and type 2 diabetes. Moreover, the relationship between circulating IL-6 levels and body mass index, insulin sensitivity and glucose tolerance has been reported (9).

In diabetic patients, there is a risk of developing vascular lesions, which is assumed to be one of the most effective factors in its etiology, oxidative damage caused by free radicals, and reactive oxygen species. The role of free radicals in the pathogenesis of diabetes has been adequately indicated (10). Free radicals are natural products of cell metabolism. Incomplete cleaning of free radicals causes oxidation of lipids, proteins, nucleic acids, and sugars. This may ultimately cause extensive pathological consequences in diabetes (11).

Oxidative stress is caused by the lack of balance between the generation of free radicals and active oxygen species as well as the antioxidant defense system (12). Evidence shows that oxidative stress has a role in the pathogenesis of more than one hundred diseases, including diabetes mellitus. In this context, various mechanisms have been proposed, the most important of which is the increase in the production of free radicals as a result of glucose autoxidation, the activation of the polyol pathway, the formation of glycosylated proteins, the formation of fat peroxide, and reduction of the ascorbic acid level (10,12,13).

Satureja khuzestanica is a plant native to Iran that grows widely in the south of Iran (14). Carvacrol is the major component of *Satureja khuzestanica* essential oil. Other compounds identified in this plant are flavones, triterpenoids, steroids and tannins. Both carvacrol and flavonoids can have antioxidant activities (15). Glucose lowering, antimicrobial, antiviral, antioxidant, antifungal, anti-inflammatory, analgesic and vasodilatory effects of its various species have been reported in previous studies (14-18). It seems that the antioxidant properties of *Satureja Khuzestanica* are efficient against diseases related to oxidative stress such as diabetes (14). Since the effects of *Satureja Khuzestanica* on inflammatory and antioxidant indicators in animal models have been investigated in several studies and limited human studies have been reported, this research was carried out to examine the effect of the daily consumption of *Satureja khuzestanica* on inflammatory indices (IL-6, CRP) and antioxidant indicators (catalase, glutathione peroxidase, glutathione reductase, superoxide dismutase and total antioxidant capacity) in type 2 diabetic patients.

Materials and Methods

Study Design and Subjects

In this double-blinded, randomized controlled clinical trial study seventy-eight patients with type 2 diabetes mellitus (T2DM) aged between 18 and 60 years were included from an endocrinology clinic in Khorramabad, Iran. These patients had been suffering from type 2 diabetes mellitus for at least one year. Other inclusion criteria included a body mass index (BMI) between 18.5 and 40 kg/m^2, lack of comorbid uncontrolled diseases, receiving only oral hypoglycemic medications for diabetes, not being on weight loss or weight gain diets, and lack of pregnancy and lactation for women. Exclusion criteria were exhibition of a severe reaction to *SK*, alteration of treatment during the study, and the need for insulin injections. The flow of allocation, follow-up, and analysis of the study have been indicated in Figure 1.

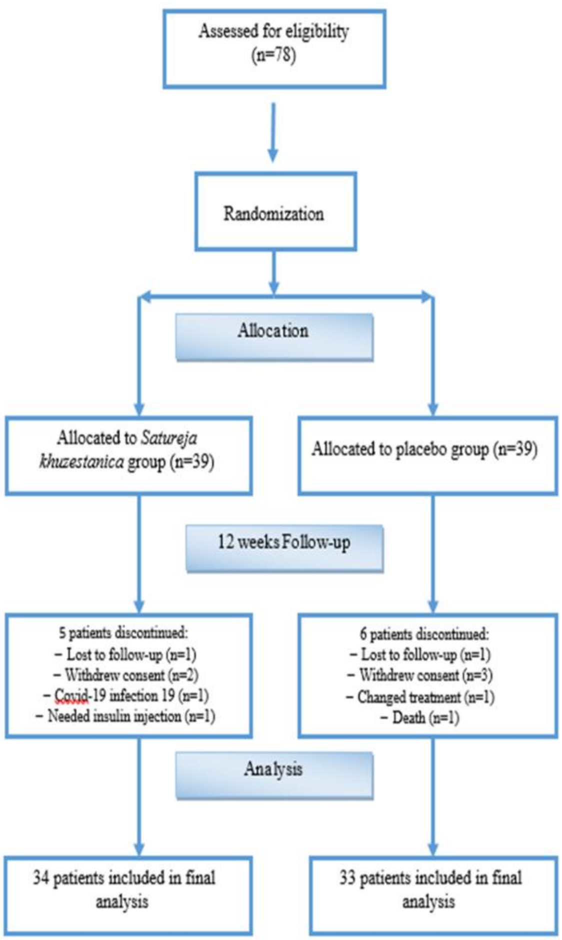

Figure 1. Study flowchart.

Sample Size

The sample size in each study arm was evaluated to be 32 persons using the following formula (19), considering the alpha error of 0.05, beta error of 0.20 and based on the mean alterations of CRP in the intervention and placebo groups of the previous study (14). Since the study was longitudinal and there was a possibility of dropout of the subjects under study, three persons (taking into account the dropout rate of 20%) were added to each study arm.

$$N = 2 \times \left(\frac{z_{1-\alpha} + z_{1-\beta}}{\delta - \delta_0} \right)^2 \times s^2$$

Randomization and Blinding

In this study, the participants were randomly assigned to either the intervention or placebo groups using the block randomization method. The participants enrolled in the study were given three bottles of capsules, depending on their assigned group. There were 28 capsules in every bottle. Both SK and placebo capsules were placed in similar bottles. A person not involved in patients' visits, allocation, or follow-up filled the bottles with capsules. A biweekly follow-up phone call was conducted to highlight the importance of taking the drugs and monitoring for potential side effects. Twelve weeks later, the participants were visited and requested to give back the unused capsules. If more than 20% of them were left, the person was excluded from the study. No detail about the contents of the bottles was given to the doctor, the patient, or the person responsible for assigning the groups.

Preparation of the Supplement and Placebo

The aerial parts of the SK were gathered during the flowering phase. Khorraman Co. (Khorramabad, Iran) was responsible for preparing and drying the plants. The dried SK leaves were ground completely in a mechanical grinder. The resulting powder was filled into 500 mg capsules. Placebo capsules were also made with an equal quantity of talcum powder, which consists of hydrated magnesium silicate and has the chemical formula $Mg_3Si_4O_{10}(OH)_2$. The SK and placebo capsules were both placed in identical bottles.

Measurements

The patients were informed about the subject, purpose and methods of the study. Trained interviewers gathered information on age, gender, dietary intake (based on 24-hour food recall), medical history, medication use, and smoking habits. When the patients were finally selected according to the eligibility criteria and signed the informed consent, anthropometric indices, and clinical as well as biochemical outcomes were assessed at baseline and 12 weeks after the intervention using the following methods. Dietary intakes were assessed using 24-hour food recall for three days (including a weekend day). The patients were asked to avoid any alteration in their diet during the study.

The modified Nutritionist IV program was used to calculate nutrients intakes from the 24-hour food recall. Physical activity was evaluated using the international physical activity questionnaire (IPAQ). The concise version of IPAQ (seven items) with information on weekly time spent walking, vigorous, moderate, intense and sedentary activities was employed. Finally, metabolic equivalent minutes per week (MET -min/wk.) were calculated, and their sum was determined as physical activity. Weight was calculated using digital scale (SECA, Germany) with a precision of up to 0.1 kilograms, while the patients were wearing light clothes without shoes or socks. Measurement of the patients' heights was carried out using a stadiometer (SECA, Germany) with a 0.5 cm precision in a standing position with the neck straight and looking straight ahead and shoulders in normal alignment. BMI calculation was conducted via dividing weight in kilograms by height in meters squared. Waist circumference was calculated using an unstretched shape tape meter to the nearest 0.1 cm precision, at the level of the umbilicus without any pressure.

Blood samples were taken from all the participants after 12–14 h overnight fasting, between 7:00 and 9:00 a.m. All the blood samples were centrifuged within 30 to 45 minutes of collection. The total antioxidant capacity was measured using the spectrophotometric method and the kits of Kiazist Life Science Company (Hamadan, Iran). These kits were used to measure catalase, glutathione reductase, glutathione peroxidase and superoxide dismutase by calorimetric/fluometric assay. CRP and IL-6 were measured using ELISA kits of the Bionic Company.

Intervention

All the patients received three SK capsules (containing 500 mg of dried leaves) or a placebo capsule (containing 500 mg of talcum powder). They were required to take the capsules once a day after lunch for 12 weeks. The participants were able to withdraw from the study if they experienced side effects or were not satisfied with the continuation of the study. After 12 weeks, their anthropometric indices, and clinical as well as biochemical outcomes were measured again.

Ethical Consideration

The study was approved by the Medical Ethical Committee of Lorestan University of Medical Sciences (Ethics code: IR.LUMS.REC.1398.221), and this trial was registered in the Iranian clinical trial system with the patented number of IRCT20191106045348N1. All the patients signed the written informed consent.

Statistical Analysis

Statistical analysis was carried out using the STATA14 software. The quantitative variables were indicated as mean±SD. Kolmogorov–Smirnov, and Shapiro–Wilk tests were used to examine the distribution. An independent t-test was applied to compare the mean of variables before the intervention. The analysis of covariance (ANCOVA) test was used to compare the mean of outcome variables between the groups, with adjustment of baseline values as possible confounding variables. P-value less than 0.05 was considered statistically significant.

Results and Discussion

Seventy-eight patients that had met the inclusion criteria were randomly divided into the *S. khuzestanica* and placebo groups. Eleven patients discontinued the study for various reasons, and finally the analysis was performed on sixty-seven patients. Baseline demographic, and anthropometric, biochemical, as well as clinical characteristics, and macronutrients intake in the two groups have been indicated in Table 1. There were no statistically significant differences between the two groups of patients ($P>0.05$).

Table 2 shows alterations in the outcomes of diabetic patients in the *S. khuzestanica* and placebo groups. Significant increases in total antioxidant capacity, catalase, superoxide dismutase, glutathione reductase, and glutathione peroxidase one the one hand, and considerable decreases in weight, CRP and IL-6 levels on the other hand were observed in the patients in the *S. khuzestanica* group. No adverse effects were reported by the participants.

This research was carried out in order to investigate the effect of *Satureja Khuzestanica* supplement on inflammatory and antioxidant indicators in patients with type 2 diabetes.

The levels of total antioxidant capacity, superoxide

Table 1. Baseline Characteristics of Diabetic Patients in the *Satureja khuzestanica* and Placebo Groups.

Variable	*Satureja khuzestanica* group (n=34)	Placebo group(n=33)	P-Value*
Sex (female/male) n (%)	21 (61.7)/13 (28.3)	21 (63.63)/12 (26.27)	0.87
Age (year)	55.5 (7.4)	54.7 (6.4)	0.75
Duration of diabetes (year)	6.1 (3.9)	8 (5.4)	0.11
Height (cm)	163.5 (11.1)	164.5 (10.1)	0.7
Weight (kg)	78.7 (13.2)	80.1 (13.7)	0.69
BMI (kg/m2)	29.4 (4.4)	29.6 (4.2)	0.94
WC (cm)	102.9 (8.5)	101.7 (7.1)	0.91
SBP (mmHg)	127.3 (13.7)	124.3 (11.1)	0.33
DBP (mmHg)	80.7 (5.9)	81.7 (6)	0.84
CAT (µmol)	168.45 (40.7)	165.86 (86)	0.63
SOD (U/ml)	12.81 (0.20)	12.64 (0.22)	0.55
GR (U/ml)	10.06 (0.79)	9.36 (0.74)	0.52
GPx (U/ml)	321.61 (21.16)	291.90 (21.96)	0.3
TAC (nmol/ml)	1338.41 (32.31)	1357.06 (36.52)	0.7
IL-6 (pg/m)	6.19 (2.35)	6.50 (2.61)	0.6
CRP (mg/L)	2.94 (0.27)	2.74 (0.3)	0.65
FBS (mg/dl)	163.9 (28.4)	165 (23.3)	0.86
HbA_1c (%)	7.7 (0.8)	7.9 (0.7)	0.27
Total energy intake (kcal/day)	2128.1 (565.2)	2213 (447.3)	0.49
Dietary carbohydrate intake (g/day)	249.8 (77.6)	271.1 (70.8)	0.24
Dietary protein intake (g/day)	79.2 (28.4)	79.3 (26)	0.91
Dietary fat intake (g/day)	94.3 (38.4)	95.1 (23.1)	0.86
Physical activity (MET min/week)	605.1 (705.7)	581.3 (452.3)	0.87

BMI: Body mass index, WC, Waist circumferences, SBP: systolic blood pressure, DBP: diastolic blood pressure, CAT: catalase, SOD: Superoxide dismutase, GR: Glutathione reductase, GPx: Glutathione peroxidase, TAC: Total antioxidant capacity, IL-6: Interleukin-6, CRP: C - reactive protein, FBS: Fasting blood sugar, HbA1c: Glycosylated hemoglobin. *Independent t-test was used. The data have been presented as mean (Sd)

Table 2. Changes in the outcomes of diabetic patients in the *Satureja khuzestanica* and placebo groups.

Variable	*Satureja khuzestanica* group (n=34)	Placebo(n=33)	P-Value*
Weight (Kg)	-0.72 (-0.26)	-0.13 (0.21)	0.03
BMI (Kg/m^2)	-0.25 (0.1)	-0.04 (0.07)	0.07
WC (cm)	-1.14 (0.38)	-0.34 (0.28)	0.06
CRP (mg/l)	-0.21 (0.1)	0.06 (0.16)	<0.001
TAC (nmol/ml)	169.88 (31.59)	16.66 (25.34)	<0.001
CAT (U/ml)	17.24(4.45)	3.46 (3.18)	<0.001
SOD (U/ml)	0.30 (0.08)	-0.05 (0.09)	<0.001
GR (U/ml)	0.58 (0.20)	0.1 (0.16)	<0.001
GPx (U/ml)	50.26 (11.48)	10.24 (17.68)	<0.001
IL-6 (U/ml)	-0.15 (0.11)	0.1 (0.1)	<0.001
SBP (mmHg)	-2.17 (1.03)	-0.84 (0.8)	0.57
DBP (mmHg)	-1.21 (0.51)	-0.51(0.54)	0.22

BMI: Body mass index, WC: Waist circumference, CRP: C-Reactive Protein, TAC: Total antioxidant capacity, CAT: Catalase, SOD: Superoxide dismutase, GR: Glutathione reductase, GPx: Glutathione peroxidase, IL-6: Interleukin-6, SBP: systolic blood pressure, DBP: diastolic blood pressure. *ANCOVA test was used. The data have been presented as mean (Sd).

dismutase, catalase, glutathione reductase, and glutathione peroxidase were remarkably distinct in the intervention and placebo groups, and these antioxidant indices were higher in the intervention group. Moreover, a considerable decrease in weight, CRP and IL-6 levels were observed in patients in the group.

The activity of superoxide dismutase, glutathione peroxidase and catalase were considered to evaluate the antioxidant status. Recently, a growing interest has risen in finding natural antioxidants from plant materials to replace synthetic antioxidants. It has been indicated in scientific reports and laboratory studies that plants have many types of substances with antioxidant activities (20). It is likely that plants, especially those with high levels and strong antioxidant compounds, significantly contribute to the treatment of oxidative stress disorders such as diabetes. *S. khuzestanica*, a plant native to Iran, has antioxidant properties and is beneficial against diabetes and its complications (21). In a study conducted by Ahmadvand *et al*., the activities of superoxide dismutase, glutathione peroxidase, and catalase as indicators of antioxidant enzyme status were significantly reduced in untreated diabetic animals compared with the control group. Moreover, treatment with *Satureja Khuzestanica* could maintain the activity of superoxide dismutase, glutathione peroxidase, and catalase in the serum, and the level of glutathione in the treated animals was at the same level or even higher than the control group (22). The findings of the study carried out by Ahmadvand et al. are in line with the results of the present study.

It has been indicated that free radicals such as superoxide can cause cell and tissue damage across lipid peroxidation and promote carcinogenesis, inflammation, premature aging, cardiovascular disease, and tissue damage in patients with diabetes (23, 24). Some plant extracts and antioxidants, such as vitamin E and coenzyme Q10, and antioxidant indicators protect cells from oxidative stress and damage, and moderate cell damage by converting toxic free radicals into non-toxic products. Thus, the use of antioxidants and plant extracts with antioxidant properties as complementary therapy might be beneficial in the treatment of diseases associated with oxidative stress (25).

Many studies have shown that several plant extracts increase antioxidant activities and have protective effects on lipid peroxidation in various diseases. The results of this study are consistent with other studies and showed that *S. khuzestaiica*, similar to other natural antioxidants, could increase the activity of superoxide dismutase, glutathione peroxidase, and catalase. Hence, with beneficial impacts on antioxidant enzymes, they can prevent or reduce the effects of tissue damage (22). Carvacrol is an antioxidant of peroxyl radicals capable of having anti-inflammatory activities. Researchers have indicated the role of oxidative stress as a central factor in the initiation and progression of diabetes complications such as vascular and nephropathy disorders. Currently, the exact molecular protective mechanisms of the *S. Khuzestanica* cannot be fully explained with these results. Acceleration of antioxidant enzymes might reduce the complications of diabetes such as nephropathy in diabetic patients (26).

Lipid peroxidation is an automatic chain reaction that produces free radicals in the cell membrane, and malondialdehyde (MDA) is one of the most important aldehyde metabolites of free radicals which is produced through lipid peroxidation. Diabetes can cause the production of superoxide followed by hydroxyl radicals in place of ubiquinone, which immediately produces free radical-mediated lipid peroxidation and increases the concentration of MDA (15). Carvacrol, the main components of *Satureja khuzestanica* acts as a strong antioxidant and can improve oxidative stress by inhibiting xanthine oxidase, eliminating free radicals, blocking oxidative reactions, and strengthening cellular antioxidant capacity. Furthermore, *Satureja* species contains flavonoids that have inhibitory effects on phosphodiesterases. Thus, *Satureja khuzestanica* might reduce lipid peroxidation due to the inhibition of phosphodiesterases (27).

S. khuzestanica prevents malathion-induced toxicity by improving oxidative stress parameters. Since free radicals play a central role in the pathogenesis and complications of diabetes, any natural or synthetic compound that can decrease oxidative stress is of high significance in the management of diabetes (28). The results of another study by Ahmadvand showed that *Satureja khuzestanica* could have significant antioxidant activity (26), which is in line with the results of the present study. Our findings about the antioxidant properties of *Satureja Khuzestanica* are consistent with the results of the study conducted by Assaei et al., who reported the antioxidant and anti-lipid peroxidation activities of this plant (15).

The study conducted by Assaei et al. showed that the essential oil of *S. khuzestanica* increased the activity of glutathione peroxidase due to its vitamin E, and the combined treatment of both antioxidants could significantly increase the activity of glutathione peroxidase compared with the administration of each one alone (15). In our study, the intervention of *S. khuzestanica* increased glutathione peroxidase activity compared with the placebo group.

According to the results of the present study, the levels of IL-6 and CRP in the intervention group were significantly lower than the control group. In the study by Zhao et al, which was conducted with the aim of evaluating the anti-inflammatory properties of carvacrol in diabetic rats, the results showed that carvacrol could reduce the level of inflammatory cytokines IL-6, IL-1, and TNF-α in the serum of rats (29). The findings of this study are in line with our findings. In the present study, the level of IL-6 was significantly lower in the group receiving *S. khuzestanica* after the intervention.

It was shown in the study conducted by Tabibzadeh et al. that the oral intake of carvacrol, particularly the dose of 15 mg/kg of body weight per day, could reduce the levels of malondialdehyde, IL-1β, IL-6 and TNF-α in diabetic patients, and also increase the activities of catalase, superoxide dismutase, and glutathione peroxidase compared with the control group (30).

The findings of the present study are in line with the results of the study conducted by Tabibzadeh. Since carvacrol is the main ingredient of *S. khuzestanica* (31), it was probably responsible for the reduction of IL-6 and the increase of antioxidant indices in our study.

Contrary to our results, the study conducted by Hafezi et al. indicated that both doses of *Satureja Khuzestanica* extract could significantly increase the body weight of male rats (32). Different sample size, dosage as well as duration of the consumption of *Satureja khuzestanica* are probably the reasons for this discrepancy.

Among the strengths of this study compared with previous similar studies, we can point out items such as the higher dose of *Satureja khuzestanica* supplement, the longer duration of the intervention, and the assessment of food intake at the beginning of the study using a 24-hour food recall questionnaire. Furthermore, the effects of basic variables were adjusted using the analysis of covariance test in this study. As the findings of this study indicated, *Satureja khuzestanica* could increase the antioxidant indices of catalase, superoxide dismutase, glutathione peroxidase, glutathione reductase, and total antioxidant capacity; while it decreased the CRP and inflammatory cytokine IL-6. Moreover, as it has been indicated in previous studies, *Satureja Khuzestanica* has anti-inflammatory, antioxidant, antimicrobial and anti-diabetic properties because it contains carvacrol. Knowledge of various properties of carvacrol can contribute to the development of new therapeutic strategies, and conducting clinical trials on animals and humans can maximize the potential benefits of these extracts in people with diabetes. Furthermore, the introduction of new herbal medicines such as *S. khuzestanica* as a low cost and safe medicine can be useful. Further pharmacological studies are necessary to establish the potential therapeutic uses of this plant and its active compounds. One of the limitations of the present study is its small sample size. It is suggested that more human studies with larger sample size be conducted in order to determine the impact of *S. khuzestanica* supplement on inflammatory and antioxidant indicators in patients with type 2 diabetes.

Conclusion

The results of this study revealed significant differences between the intervention and placebo groups with regard to the levels of total antioxidant capacity, superoxide dismutase, catalase, glutathione reductase or glutathione peroxidase; whereas they are significantly higher in the *S. khuzestanica* group. Moreover, patients in the *Satureja khuzestanica* treatment group exhibited significant reductions in weight, CRP and IL6 levels. Thus, the use of *Satureja khuzestanica* as a supplement to the medicinal regimen of type 2 diabetic patients is recommended due to its antioxidant effect.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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