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Original Article

Effect of Saffron and Melissa officinalis L. Supplementation on Glycemic Parameters and Lipid Profile in Patients with Type 2 Diabetes Mellitus: A Double-Blind Clinical Trial

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Abstract

Background: Diabetes is one of the most common diseases in modern societies. The prevalence of type 2 diabetes mellitus (T2DM) is rising and is expected to reach 440 million people by 2030. Although effective steps have been taken in diabetes treatment using common chemical drugs, these drugs are often followed by numerous side effects, necessitating the search for new medications with natural origin, especially those derived from traditional and complementary medicine.

Methods: In this double-blind clinical trial, 90 type 2 diabetic patients were randomly divided into three groups: saffron (30 patients), *Melissa officinalis* (29 patients), and placebo (28 patients). After obtaining informed written consent from each patient, blood samples were collected from all participants, and the corresponding drug was delivered to each patient. After the participants took the medications for three months, blood samples were taken again to analyze the biochemical parameters. Data were analyzed using SPSS version 24, employing both descriptive and inferential statistics.

Results: At the outset of the investigation, no significant differences existed among the three groups regarding the pertinent variables. The results showed that saffron supplement and *M. officinalis* significantly decreased fasting blood sugar (FBS) ($P<0.001$), hemoglobin A1C (HbA1c) ($P<0.05$), triglyceride ($P<0.05$), and total cholesterol ($P<0.001$) compared to pre-intervention stage. No significant effects were observed for other parameters.

Conclusion: This study demonstrated that lemongrass and saffron extracts significantly affected the control of FBS, HbA1c, triglycerides, and blood cholesterol levels in type 2 diabetes patients, suggesting their administration alongside other treatments.

Keywords: Type 2 diabetes, Herbal medicine, Saffron, *Melissa officinalis*, Nutrition

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Introduction

Diabetes is a prevalent metabolic disorder that can develop when the pancreas does not generate enough insulin or when the body cannot properly utilize the generated insulin, leading to an increase in blood sugar and disturbances in carbohydrate, fat, and protein metabolism.[1] Carbohydrates are divided by humans into simpler forms of sugars. Pancreatic beta cells release

insulin.[2] Lack of insulin or insensitivity of its receptors may cause continuous or frequent hyperglycemia, which eventually leads to diabetes. Symptoms of diabetes mellitus include polyuria, polydipsia, weight loss, and sometimes polyphagia and blurred vision. Susceptibility to some infections may also be a symptom of chronic hyperglycemia.[3] Type 2 diabetes includes 90 to 95% of all diabetes cases and occurs in people who are resistant to insulin and usually have a relative insulin deficiency in the beginning. These people usually do not need insulin treatment.[4] Premature mortality, as well as heart, kidney, nervous system diseases, and blindness in diabetic people, is twice as high as in non-diabetic people.[5] The World Health Organization (WHO) reports that about 2% of deaths in our country are caused by diabetes. A 2017 report published by the WHO indicated a substantial rise among 18-year-olds diagnosed with diabetes from 4.7% in 1980 to 8.5% in 2014 globally.[6] Although insulin and oral antidiabetic drugs are crucial for the treatment of diabetes, complications from these medications have remained stable. Studies reveal that chemical drugs, which may have side effects, are inadequate in controlling glucose levels in some patients (1,5). In addition, comprehensive and completely effective treatments for those suffering from multiple metabolic disorders are lacking.[7] Consequently, due to the high prevalence of diabetes and its complications, physicians are looking for alternative or complementary medicines, especially medicinal plants, which have historically played a significant role in treating various health issues.[8] Saffron (*Crocus sativus* L), a member of the Iridaceae family, is predominantly cultivated in Iran, India, Greece, Italy, Spain, and France.[9] Its therapeutic value is attributed to the presence of four main metabolites: crocin, crostin, picrocrocin, and safranal. Flavonoids and carotenoids have also been found in saffron.[10] In addition to antioxidant properties, these components have different properties such as reducing serum lipids and protecting the heart, nerves, and liver, along with anti-cancer, insulin-sensitizing, and anti-inflammatory effects.[11] In vitro and in vivo investigations have revealed that saffron and its compounds can influence hyperglycemia and exhibit antidiabetic properties.[12] *Melissa officinalis L.* belonging to the mint family, is a perennial plant that can grow up to 100 cm. This species originates from southern Europe, Asia, and parts of North and South America. *M. officinalis* is found throughout the Mediterranean region, extending to the Turkish coastline and northern Iran.[13] This plant is rich in flavonoids known for their ability to lower fat and blood sugar levels.[14] Numerous studies have confirmed the effects of flavonoids on blood sugar reduction.[15,16] Research has shown that lemon scent contains substantial amounts of phenolic and flavonoid compounds, including rosmarinic acid and caffeic acid,[14] which have antioxidant, antidiabetic, and blood pressure-lowering effects.[17] Several animal and laboratory studies have demonstrated that *M. officinalis* exhibits hypoglycemic, hypolipidemic,[13] antiglycation activity,[18] and pancreatic amylase inhibitory activity. Research has indicated that lemongrass essential oil can reduce blood sugar due to its antioxidant properties. Since oxidative stress and reactive oxygen species can cause diabetes and related complications, the proper consumption of natural antioxidants such as lemon essential oil may help prevent or improve diabetes symptoms or its complications.[13] Therefore, the main purpose of the study was to investigate the effects of *M. officinalis* and saffron on controlling blood sugar factors and lipid profiles in patients with type 2 diabetes.

Hypothesis

1. Fasting blood sugar (FBS) levels differ between study groups before and after the intervention.
2. HbA1c levels differ between study groups before and after the intervention.
3. Lipid profile levels differ between study groups before and after the intervention.

Methods and Materials

Study Design and Participants

A 3-month double-blind, randomized clinical trial was conducted at Imam Reza Hospital in Tabriz, Iran, from July 2020 to July 2021. The research protocol was approved by Tabriz University of Medical Sciences (Grant No. 64796). Patients were fully informed about the trial's content and procedures and provided written consent. The study adhered to the revised Helsinki Declaration and was registered in the Iranian Clinical Trials Registry (identifier: IRCT20140617018126N4). The Ethics Committee of Tabriz University of Medical Sciences endorsed the study protocol after a thorough evaluation (IR.TBZMED.REC.1399.160).

Inclusion Criteria

1. Individuals with type 2 diabetes (FBS levels > 126 mg/dL).
2. Taking oral hypoglycemic drugs.
3. Aged 40-70 years.
4. Body mass index (BMI) of 18/5-30 kg/m^2.
5. Willingness to participate in the research.

Exclusion Criteria

1. Diagnosed with type 1 diabetes or other unique forms of diabetes.
2. HbA1c higher than 9%
3. Insulin treatment within the last three months
4. Diagnosed with significant gastrointestinal disorders (e.g., stomach ulcers and gastrointestinal hemorrhage).
5. History of diabetic ketoacidosis, non-ketotic hyperosmolar coma, significant infections, or surgeries in the past month.
6. History of mental illness.
7. Misuse or abuse of alcohol, drugs, or psychedelics.

8. Pregnancy, lactation, or planning to become pregnant.
9. Disorders affecting the cardiovascular system, kidney function, liver health, thyroid and parathyroid glands, or cancer.
10. Chronic complications of diabetes (neuropathy, retinopathy, as per patient records), diabetic nephropathy, hypothyroidism, and hyperthyroidism.
11. Allergy to saffron or *M. officinalis*.

Sample Size

The sample size was determined using G-POWER software, based on previous research.[19-21] Considering the FBS parameters (power = 95%, α = 0.05, SD = 5.28), the sample size was calculated to be 27 patients for each group. Given a potential dropout rate of 15%, 90 participants were randomly allocated into three groups (n = 30 each), with 87 participants remaining until the end of the study.

Randomization and Random Allocation

Participants were randomly assigned to one of the three treatment groups using a randomized block procedure (Random Allocation Software). Concealment procedures, including blocking and allocation were executed by a researcher not involved in a study. The allocation ratio was 1:1:1, assigning participants to three groups: receiving saffron, *M. officinalis*, and placebo. Neither researchers nor patients were aware of the medication each person received.

Measurements

Demographic details such as age, gender, education level, past medication history, and consumption of dietary supplements, along with the details of their dosages and duration were gathered via a self-report questionnaire. Additional data on past adherence to particular diets, current health conditions (e.g., diabetes and other disorders), and previous diabetes history were also gathered. Then, fasting blood samples were taken, and the weight, height, BMI, waist measurement, wrist size, urine samples, and blood pressure were recorded. The medication intake questionnaire was employed to gather information about the medications used by participants. A checklist of potential drug side effects was distributed to all patients involved in the study. Physicians were responsible for completing this checklist, and patients could contact their physician by phone for consultations.

Treatment Medications

The physical characteristics of saffron, *M. officinalis*, and placebo capsules were indistinguishable. The capsules, enclosed in white boxes, were to be taken by subjects alongside their food intake. Patients in the saffron group received 250 mg of saffron hydroalcoholic extract capsules every 12 hours for three months. The *M. officinalis* group received *M. officinalis* hydroalcoholic extract capsules every 12 hours for three months, while the placebo group also received two capsules of 250 mg placebo every 12 hours for three months. Patients were instructed to maintain their regular diets and physical activity routines throughout the intervention and were monitored via weekly phone calls to report any side effects.

The saffron extract capsules were obtained from Sina No Andish Company, and the raw materials of *M. officinalis* were obtained from rural areas in East Azerbaijan, where they were crushed, subsequently soaked in 70% alcohol for 48 hours, and filtered. The solvent was extracted using a rotary, and the extract was dried. Further, cornstarch flour was used to prepare the placebo.

Statistical Analysis

The Kolmogorov-Smirnov test was utilized to investigate the normality of the data. One-way ANOVA and, if necessary, the Kruskal-Wallis test were employed to compare the groups at baseline and the research outcomes at the end of the trial. The chi-square test was utilized to analyze qualitative data differences between groups. The results were expressed as mean ± standard deviation, with a significance level of $P < 0.05$. Data were analyzed using the SPSS software version 23.

Results

A total of 97 individuals enrolled in this study. However, three participants from the intervention group discontinued their participation due to personal reasons. The final number of participants in the intervention groups was 30 in the saffron group, 29 in the *M. officinalis* group, and 28 in the placebo group (Figure 1).

The results demonstrated that baseline characteristics do not differ significantly between the study groups, except for the presence of other diseases ($P = 0.016$), alanine aminotransferase (ALT) ($P = 0.008$), alkaline phosphatase ($P = 0.01$), and Urea (0.015), as illustrated in Table 1.

Following a three-month treatment period, a significant difference was observed in mean FBS levels among the three research groups ($P < 0.001$), demonstrating that saffron and *M. officinalis* were notably effective in alleviating FBS compared to the placebo ($P < 0.05$). Additionally, saffron and *M. officinalis* exhibited statistically significant reductions in HbA1c compared to the placebo ($P < 0.05$). Notably, the *M. officinalis* group showed statistically significant changes in insulin resistance levels compared to baseline ($P = 0.025$). Further, the reduction in the triglyceride levels for the saffron and *M. officinalis* groups was 13.1 ± 31.9 and 12.3 ± 73.9 units, respectively, representing a significant difference from the pre-intervention stage. Moreover, saffron and *M. officinalis* could decrease average cholesterol levels by 16.0 ± 38.3 and 19.4 ± 33.3 units, respectively, after the intervention. The results revealed that changes in high-density lipoprotein (HDL) and urea levels among the three groups were statistically significant ($P = 0.004$; $P < 0.001$), with the *M. officinalis* group exhibiting significantly greater changes than the placebo group ($P < 0.01$).

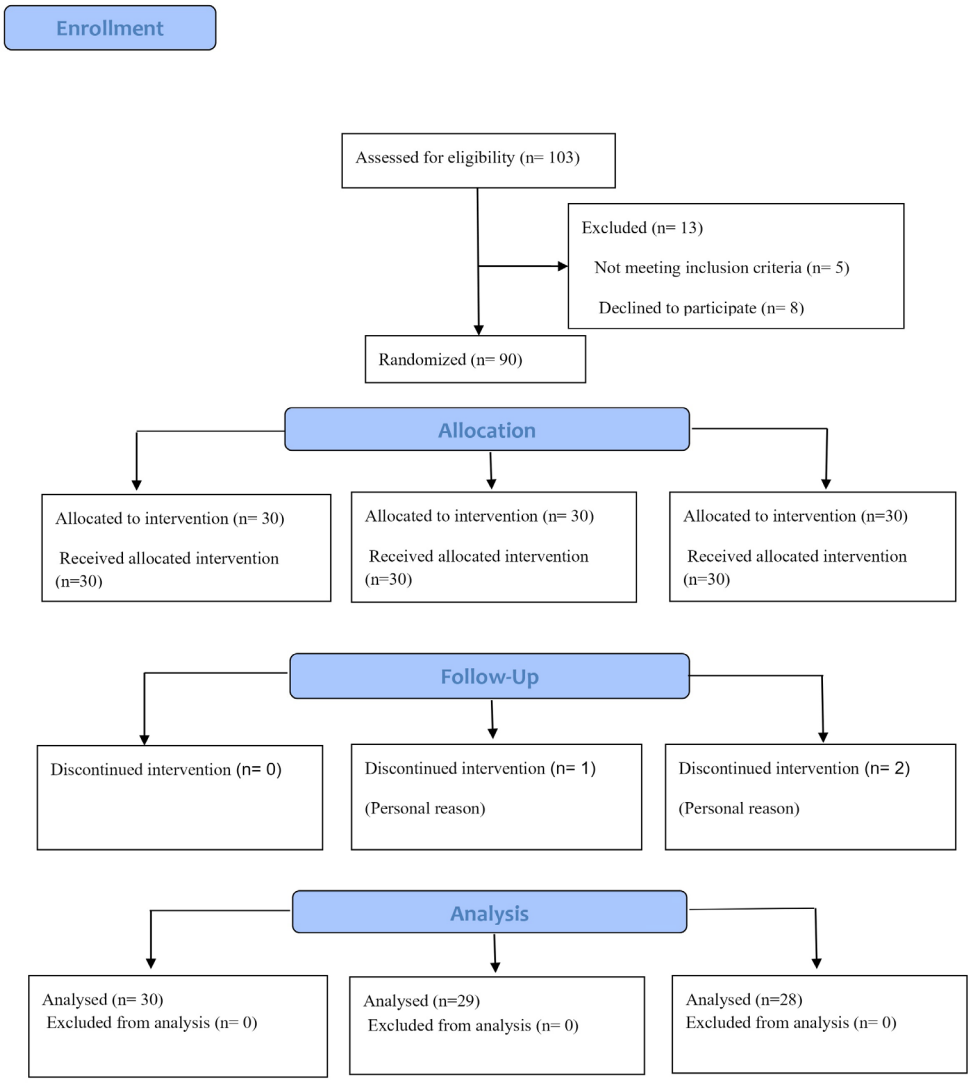

Figure 1. Consort Flow Diagram of the Study

Following the intervention, a considerable difference was detected in the blood creatinine levels of the three study groups ($P = 0.025$), and the intervention led to a significant reduction in the average creatinine levels for both the saffron and *M. officinalis* groups ($P < 0.05$). After the intervention, considerable distinctions were observed in ALT levels among the three groups ($P < 0.05$). Hence, the blood ALT levels in the saffron and *M. officinalis* groups following the intervention were significantly lower than their respective levels before the intervention. The alkaline phosphatase levels were similar among the three groups before the intervention ($P < 0.05$), but following the intervention, a significant difference was observed ($P < 0.001$). No significant differences were observed in insulin, low-density lipoprotein (LDL), and alkaline phosphatase levels among the three study groups ($P > 0.05$), as depicted in Table 2.

Discussion

Considering the expanding trend towards traditional and complementary medicine, this study was designed to explore the effects of saffron and *M. officinalis* on glycemic parameters and lipid profiles in patients with type 2 diabetes. The statistical analysis demonstrated no significant difference in the mean FBS levels before intervention across the three groups, indicating that the groups were homogeneous. Following the intervention, the saffron and *M. officinalis* groups showed significantly lower average FBS levels compared to the placebo group. Additionally, the results indicated that the average FBS in the saffron group was significantly lower than that in the *M. officinalis* group, indicating a stronger effect of saffron on regulating FBS. These results suggest that saffron and *M. officinalis* use could decrease FBS in diabetic patients, which is consistent with the results of other studies. It can be inferred that saffron, through its anti-inflammatory mechanisms, may decrease the prevalence of inflammatory factors and consequently manage related factors such as blood sugar.[22] Furthermore, the results demonstrated that oral intake of *M. officinalis* extract results in a decrease in fasting glucose levels for individuals with type 2 diabetes mellitus (T2DM), consistent with past research.[23] Studies indicated that *M. officinalis* may contribute to

Table 1. Baseline Characteristics of Participants in the Survey

Variable		Group			*P* Value
		Saffron (n = 30)	Melissa officinalis (n = 29)	Placebo (n = 28)	
Age		60.6 ± 6.9	59.1 ± 9.22	60.4 ± 6.3	0.52
Gender	Male	19	17	18	0.225
	Female	11	12	10	
Family History of Diabetes	Yes	23	19	17	0.408
	No	7	10	11	
Other Diseases	Hyperlipidemia	0	0	1	0.016
	Hypertension and hyperlipidemia	4	0	4	
	Acute coronary syndrome	0	1	0	
	Other	8	13	8	
	None	8	6	13	
BMI		29.92 ± 4.3	29.56 ± 3.91	28.17 ± 2.5	0.173
FBS		163.06 ± 44.3	160.2 ± 36.8	160.8 ± 61.9	0.973
HbA1c		7.04 ± 1.2	7.1 ± 0.77	7.4 ± 1.15	0.615
Insulin		9.78 ± 3.9	10. 97 ± 4.1	11.79 ± 5.16	0.078
Insulin resistance		4.28 ± 1.17	4.32 ± 2.41	4.5 ± 2.13	0.054
Triglycerides		169.7 ± 93.8	181.7 ± 49.9	171.2 ± 30.8	0.147
Cholesterol		165.3 ± 48.9	159.5 ± 34.6	161.2 ± 86.9	0.744
HDL		38.42 ± 5.5	38.37 ± 6.25	39.5 ± 3.3	0.854
LDL		94.6 ± 38.5	85.13 ± 33.44	100.5 ± 18.2	0.051
Urea		32.1 ± 6.6	27.4 ± 3.1	33.0 ± 9.5	0.015
BUN		14.96 ± 3.25	15.8 ± 2.5	16.8 ± 5.4	0.082
Creatinine		0.76 ± 0.73	0.81 ± 0.21	0.8 ± 0.12	0.265
AST		32.2 ± 8.3	20.3 ± 6.04	18.4 ± 8.0	0.01
ALT		27.7 ± 11.5	30.3 ± 12.8	20.5 ± 7.7	0.008
ALP		167.2 ± 41.6	178.1 ± 25.9	177.8 ± 2	0.32

Note. BMI: Body mass index; FBS: Fasting blood sugar; HbA1c: Hemoglobin A1C; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; BUN: Blood urea nitrogen; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase.

lowering blood sugar through increased production of hepatic glucokinase and GLUT4 transporter, diminished expression of glucose-6-phosphatase (G6Pase), and a decrease in the expression of phosphoenolpyruvate carboxykinase.[24] Regarding the impact of saffron and *M. officinalis* on HbA1c levels in individuals with type 2 diabetes, the research results indicated a notable reduction in HbA1c levels for both *M. officinalis* and saffron, both within and between the study groups. Findings from a study conducted by Asadi et al in 2018 revealed that saffron intake leads to a substantial decrease in HbA1c levels.[25] Similarly, the results of another study demonstrated that saffron has a significant effect on both FBS and HbA1c levels.[26] However, a study conducted by Barari et al in 2018 revealed no significant reduction in HbA1c levels due to saffron intake and aerobic exercise, which is inconsistent with our study results [27]. The discrepancies in results may be due to the variations in study duration and saffron dosage. Regarding the effect of *M. officinalis* on HbA1c, findings indicated that consuming *M. officinalis* oral capsules decreases the HbA1c levels in patients with type 2 diabetes, aligning with results from other studies. The inhibitory effect of *M. officinalis* on pancreatic alpha-amylase and alpha-glucosidase may explain the reduction in HbA1c and post-meal blood sugar levels in our study. According to our findings, saffron consumption led to a significant reduction in average triglyceride and total cholesterol levels, while exerting no significant effect on LDL and HDL levels. Research conducted by Tajaddini et al indicated that saffron intake effectively reduces blood triglyceride levels in diabetic patients, as observed in our study.[28] However, another study revealed that saffron consumption for 12 weeks does not yield significant changes in lipid profiles. Moreover, Asbaghi et al reported no significant change in lipid levels after administering saffron hydroalcoholic extract.[29] Due to these inconclusive findings, further research is required to provide a clearer understanding of the effect of saffron on lipid profile. In addition, the results revealed that the triglyceride and cholesterol concentrations in the *M. officinalis* group decreased significantly after the intervention. Although a significant increase in HDL concentration was observed, it had no impact on LDL levels. The anti-hyperlipidemic effects of *M. officinalis*, as demonstrated in the study,

Table 2. Changes in the Understudy Groups Before and After Intervention

Variable	Stage	Group			*P* Value for Changes
		Saffron (n = 30)	*Melissa officinalis* (n = 29)	Placebo (n = 28)	
FBS	Before	163.06 ± 44.3	160.2 ± 36.8	160.8 ± 61.9	0.973
	After	110.3 ± 21.7	134.9 ± 20.6	158.8 ± 56.9	<0.001
	Changes	52.9 ± 43.9	25.37 ± 29.2	2.00 ± 8.95	< 0.001
HbA1c	Before	7.04 ± 1.2	7.1 ± 0.77	7.4 ± 1.15	0.615
	After	6.5 ± 0415	6.66 ± 0.41	7.3 ± 0.89	< 0.001
	Changes	0.54 ± 1.12	0.43 ± 0.83	0.1 ± 0.71	0.021
Insulin	Before	9.78 ± 3.9	10.97 ± 4.1	11.79 ± 5.16	0.078
	After	8.52 ± 2.29	9.72 ± 4.86	10.85 ± 2.66	0.003
	Changes	1.26 ± 3.99	1.25 ± 3.97	0.93 ± 4.6	0.92
Insulin resistance	Before	4.28 ± 1.17	4.32 ± 2.41	4.5 ± 2.13	0.054
	After	4.17 ± 26.08	3.98 ± 0.35	4.41 ± 1.52	0.182
	Changes	0.11 ± 0.6	0.34 ± 0.73	0.09 ± 1.75	0.075
Triglyceride	Before	169.7 ± 93.8	181.7 ± 49.9	171.2 ± 30.8	0.147
	After	156.6 ± 86.9	169.4 ± 86.2	169.1 ± 33.1	0.019
	Changes	13.1 ± 31.9	12.3 ± 73.9	2.1 ± 12.5	0.1
Cholesterol	Before	165.3 ± 48.9	159.5 ± 34.6	161.2 ± 86.9	0.744
	After	149.3 ± 31.6	140.1 ± 34.7	153.5 ± 21.2	0.104
	Changes	16.0 ± 38.3	19.4 ± 33.3	7.7 ± 17.1	0.037
HDL	Before	38. 42 ± 5.5	38.37 ± 6.25	39.5 ± 3.3	0.854
	After	39.7 ± 6.6	42.44 ± 4.5	40.3 ± 2.5	< 0.001
	Changes	1.3 ± 8.4	3.9 ± 5.2	0.8 ± 5.6	0.004
LDL	Before	94.6 ± 38.5	85.13 ± 33.44	100.5 ± 18.2	0.051
	After	82.2 ± 27.8	72.04 ± 30.9	89/9 ± 14.8	0.437
	Changes	12.4 ± 38.4	13.09 ± 33.0	10.6 ± 13.2	0.089
Urea	Before	32.1 ± 6.6	27.4 ± 3.1	33.0 ± 9.5	0.015
	After	31.4 ± 5.5	36.27 ± 5.97	32.7 ± 8.3	0.017
	Changes	-0.73 ± 6.96	8.8 ± 4.8	-0.32 ± 6.58	< 0.001
BUN	Before	14.96 ± 3.25	15.8 ± 2.5	16.8 ± 5.4	0.082
	After	15.13 ± 2.6	16.3 ± 2.9	16.92 ± 4.1	0.056
	Changes	0.17 ± 3.42	0.5 ± 4.07	0.12 ± 3.64	0.127
Creatinine	Before	0.76 ± 0.73	0.81 ± 0.21	0.8 ± 0.12	0.265
	After	0.68 ± 0.08	0.74 ± 0.11	0.75 ± 0.1	0.025
	Changes	0.08 ± 0.06	0.07 ± 0.18	0.05 ± 0.07	0.475
AST	Before	32.2 ± 8.3	20.3 ± 6.04	18.4 ± 8.0	0.01
	After	19.6 ± 4.9	19.58 ± 4.2	20.0 ± 6.0	0.971
	Changes	3.6 ± 8.52	0.75 ± 8.33	1.67 ± 4.06	0.056
ALT	Before	27.7 ± 11.5	30.3 ± 12.8	20.5 ± 7.7	0.008
	After	20.1 ± 7.7	25/75 ± 6/8	24.3 ± 9.0	0.005
	Changes	7.6 ± 11.3	4.5 ± 10.46	3/82 ± 11.1	< 0.001
ALP	Before	167.2 ± 41.6	178.1 ± 25.9	177.8 ± 2	0.32
	After	173.7 ± 45.4	176.4 ± 30.5	182.3 ± 33.5	< 0.001
	Changes	6.5 ± 21.3	1.7 ± 34.1	4.5 ± 31.7	< 0. 095

Note. FBS: Fasting blood sugar; HbA1c: Hemoglobin A1C; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; BUN: Blood urea nitrogen; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase.

could potentially be linked to the inhibition of HMG-CoA reductase enzyme expression and a decrease in the expression of SREBP-1c and related genes that contribute to fatty acid syntheses such as acetyl-CoA carboxylase (ACC1), stearoyl-CoA desaturase 1 (SCD), and fatty acid synthase (FAS).[30] Given the inconsistencies in findings

from research on *M. officinalis* and lipid profiles in diabetic individuals, further clinical trials are needed to provide a comprehensive understanding. Regarding the effect of saffron and *M. officinalis* on renal function in individuals with type 2 diabetes, our findings indicated that mean levels of blood urea nitrogen (BUN) and creatinine decreased in the saffron-treated group, but these changes were not statistically significant. This finding is consistent with other studies. Although the effect of saffron extract on renal function has rarely been investigated in human studies, a recent animal investigation demonstrated a substantial decrease in BUN and creatinine in diabetic rats following the administration of crocin (derived from saffron).[31]

It is believed that the antioxidant properties of crocin contribute to its protective effect on renal function, as suggested by the study authors.[31] Additionally, in the current study, there was a significant increase in blood urea and creatinine in *M. officinalis* group compared to the placebo group. In contrast to our research findings, a study conducted by Zarei et al discovered that *M. officinalis* extract improves renal performance in diabetic rats by reducing urea and creatinine levels.[32] Another study showed that *M. officinalis* extract has renal protective effects against diabetes and improves renal function in diabetic rats.[33] The disparities in these findings can be attributed to differences in research methods and plant dosages. To advance our understanding of type 2 diabetes, more clinical trials are necessary, as previous studies used animal models that may not accurately represent human conditions. Regarding the effect of saffron and *M. officinalis* on inflammatory factors in individuals with T2DM, our study revealed that saffron does not significantly decrease C-reactive protein (CRP) blood levels, which is consistent with the results of other studies. Additionally, based on the results of the current research, *M. officinalis* did not noticeably reduce CRP levels in the blood of type 2 diabetes patients. In contrast, Asadi et al found that the consumption of *M. officinalis* by diabetic patients resulted in a significant decrease in CRP levels.[23] According to the systematic review conducted by Zamzuri et al, *M. officinalis* resulted in considerable changes in hs-CRP.[34] This can be attributed to some factors, including variations in sample size, *M. officinalis* dosage, study duration, and diabetes severity.

Strengths and Limitations

This was the first research examining the effects of *M. officinalis* and saffron on diabetes, and a comprehensive assessment of patients was carried out at the onset and end of the study. The study faced several limitations, including a small sample size, a short patient follow-up period, and the inability to conduct tests after the study's termination.

Conclusion

According to the study's findings, saffron and *M. officinalis* can reduce FBS and triglycerides in individuals with T2DM, and they can be used alongside conventional medical treatments. Future research should consider a larger sample size and extended duration should be considered for future research studies and should explore the effects of larger doses of saffron and *M. officinalis*.

Ethics statement

The Ethics Committee of the Tabriz University of Medical Sciences endorsed the study protocol following a thorough evaluation. (Ethical Code: IR.TBZMED.REC.1399.160).

Disclosure of funding source

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Conflict of interests declaration

The authors declare no conflict of interests.

Data availability statement

The data generated and analyzed in the study are fully presented in this published article.

Author contributions

Conceptualization: Behnam sadighi, Mostafa Araj-Khodaei.
Data curation: Somaiyeh Taheri-Targhi.
Formal analysis: Sarvin Sanaie.
Funding acquisition: Mostafa Araj-Khodaei.
Investigation: Zahra Yousefi,Mostafa Araj-Khodaei.
Methodology: Seyed Kazem Shakouri, Majid Mobasseri.
Supervision: Mostafa Araj-Khodaei.
Validation: Majid Mobasseri.
Writing–original draft: Behnam Sadighi,Zahra Yousefi, Mostafa Araj-Khodaei.
Writing–review & editing: Reza Yarani, Somaiyeh Taheri-Targhi , Sarvin Sanaie.

Consent for publication

Not applicable.

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