

The effect of saffron (*Crocus sativus* L.) hydroalcoholic extract on metabolic control in type 2 diabetes mellitus: A triple-blinded randomized clinical trial

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Background: Metabolic control is a major concern in preventing diabetic complications. Saffron as a natural source of antioxidants could play a role in alleviating diabetes insults. The aim of this study was to investigate effect of saffron hydroalcoholic extract on metabolic control in type 2 diabetes (T2D) mellitus. **Materials and Methods:** This randomized triple blind study was included 54 T2D patients which randomly received either saffron (Group 1) or placebo (Group 2) twice daily other than routine antidiabetic treatments for 8 weeks. Serum concentration of fasting blood sugar (FBS), 2-h plasma glucose, hemoglobin A1c (HbA1c), total cholesterol, triglyceride (TG), low-density lipoprotein, and high-density lipoprotein were measured as the markers of metabolic control. Anthropometric measures and blood pressure were also measured at the baseline, every 2 weeks during the intervention and the end of the study. Data analyzed using repeated measure analysis of variance test. **Results:** The baseline metabolic parameters were the same in two group ($P > 0.01$). FBS serum level significantly decreased within 8 weeks in the saffron group (128.84 ± 31.86) as compared to the placebo (153.76 ± 41.23), ($P < 0.001$). There was no statistical difference in other metabolic parameters such as serum lipids, blood pressure, and HbA1c ($P > 0.01$). **Conclusion:** Saffron hydroalcoholic extract may improve blood glucose control by reducing FBS in T2D patients. However, saffron extract has no significant effect on other aspects of diabetic control in diabetic patients.

Key words: Diabetes mellitus, fasting blood glucose, lipid, metabolic syndrome, saffron extract

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INTRODUCTION

Type 2 Diabetes (T2D) is a chronic disease with considerable morbidity and mortality. T2D is considered as a public health problem globally.^[1,2] Studies have shown a dramatic increase in the prevalence of diabetes in Iran during the last decade.^[3] Hyperglycemia, hyperlipidemia, and hypertension are the most important complications of diabetes.^[4] In addition, poorly controlled diabetes may

cause some macro and microvascular complications, including neuropathy, retinopathy, atherosclerosis, and nephropathy which finally increase the risk of mortality.^[5,6] Therefore, metabolic control is an effective preventive strategy in T2D to decrease the severe complications. Due to the high prevalence of diabetes and the wide range of catastrophic complications, the medical providers are continuously searching for additive and alternative remedies, especially in the field of herbal medicine, to use as an adjuvant for better diabetic control.^[7,8]

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The dried stigma of saffron (*Crocus Sativus* L.) is a native additive commonly used in Iran. Saffron has been used for many years in Iran as the most expensive traditional spice.^[9-11] It contains three main secondary metabolites including soluble crocin, picrocrocin, and safranal as well as crocetin.^[12,13] Antioxidant and anti-inflammatory properties of saffron extract have been attributed to the presence of these secondary metabolites; which in order result in major effects of saffron in different physiologic and psychological condition.^[14,15]

To the best of our knowledge, no clinical trial has investigated the effect of saffron on serum lipid and glucose concentrations and on blood pressure in T2D patients, so far. In a recent study, daily consumption of 3 g saffron tea reduced blood lipids in T2D patients, however, it is not clear that these effects were due to saffron or tea. Furthermore, changes in blood glucose were not significant after consumption of saffron tea in that study.^[16] In an animal model study, saffron injection reduced hyperglycemia, hyperlipidemia, and oxidative stress in diabetic rats;^[17] however, it may be completely different in a humans.

Given these reasons and lack of study in this area, this randomized, placebo-controlled, and triple-blind clinical trial was done to investigate the effect of the saffron hydro-alcoholic extract on serum concentrations of glucose and lipids and blood pressure in patients with T2D mellitus.

MATERIALS AND METHODS

Participants

This study was an 8-week randomized triple-blind clinical trial which was done in accordance with the Declaration of Helsinki of 1975, as revised in 2008 and good clinical practice guidelines. The study was conducted on outpatients of Natanz Diabetes Society (NDS), Isfahan, Iran, between September 2015 and May 2016. NDS is a referral Center in Natanz where all diabetic patients are registered.

Eligible participants were selected based on inclusion criteria: patients with T2D mellitus (fasting plasma glucose levels of ≥ 126 mg/dL), aged 40–65 years, body mass index (BMI) 18.5–30 kg/m². Patients who smoked, were using insulin or medications rather than common used diabetes medications including a determined doses of metformin (up to 1.5 gr) or glibenclamide (10 mg), those with uncontrolled blood glucose (fasting blood sugar [FBS] >170 mg/dl), high physical activity, and patients with recent experience of hospitalization as well as subjects with frequent use of herbal medications, pregnant, or lactating women and those who had planned for pregnancy were excluded from the study. Finally, 54 patients were included in the current study. All participants signed an informed

written consent after receiving the explanations for study purposes and design. The study protocol was approved by the Tehran University of Medical Sciences' Ethics Committee (ir.tums.rec. 1394.9211468004-143703; research.tums.ac.ir). The trial was registered at Iranian Registry of Clinical Trials as IRCT2015082623776N1.

Study design

Totally, 54 patients (12 males and 42 females, age 54.59 ± 7.09 years) were randomly divided into two similar groups ($n = 27$) to receive either placebo or saffron extract capsules twice a day (at the morning and evening) for 8 weeks. The sample size was determined using suggested formulas for parallel clinical trials by considering type I (a) and type II errors (b) as 0.05 and 0.20 (study power = 80%). Randomization was performed with the use of computer-generated random numbers. The randomization was blinded from all project investigators, participants and data analyzers, except for the trained physician of the NDS who did the random allocation and assigned participants to the placebo or saffron capsules. Before random assignment, participants were stratified based on sex (male or female) and age (<50 or ≥ 50 years). Each capsule contained 15 mg placebo or saffron hydroalcoholic extracts. In this study, we used commercially available Safrotin. Safrotin contains 15 mg saffron hydroalcoholic extract. All safrotin and placebo capsules were provided by Green Plants of Life Co., (IMPIRAN; Tehran, Iran). Placebo capsules were similar to Safrotin capsules in the appearance, color, and size. The content of placebo capsules was starch, lactose, magnesium stearate, gelatin, and saffron essence.

Participants were asked not to change their diet, physical activity or medications during the intervention. Subjects were also asked to attend the clinic every 2 weeks (2nd, 4th, 6th, and 8th weeks) to take their capsules. To assess participants' compliance, they were requested to bring their capsules' boxes at each visit to determine a total number of capsules remaining. To increase the compliance, all patients were receiving short messages on their cell phones to remind taking supplements each day.

Biochemical tests

At the beginning and at the end of the intervention, all participants referred to central laboratory of Natanz, Isfahan, Iran. After 12 h fasting, participants' blood samples were taken, then serum was isolated and kept at -70°C . Serum concentration of triacylglycerol (TG) and total cholesterol (TC) were measured using enzymatic methods (Pars Azmoun.co kit, Tehran, Iran). FBS was measured by autoanalyzer (Hitachi 911, Japan) using enzymatic and colorimetric method (Pars Azmoun.co kit, Tehran, Iran). Glucose tolerance of participants was estimated by measuring

serum 2 h Plasma Glucose (2 hPG). For this purpose, all participants received oral 82.5 g glucose monohydrate solution (equivalent to 75 g dehydrated glucose) and their blood samples were taken after 2 h. In addition, serum concentration of hemoglobin A1C (HbA1C) was measured using Elisa kit (Bioassay Technology Laboratory, Elisa kit). Measurement of high-density lipoprotein (HDL)-cholesterol was done by auto-analyzer, using cholesterol oxidase method. Moreover, serum low-density lipoprotein (LDL)-cholesterol was estimated using Friedewalds' formula.

Assessment of other variables

At the study beginning, general characteristics of participants were obtained using a questionnaire. In addition, a skilled nutritionist measured weight, height, and waist circumference (WC). Weight was measured by a digital scale (Sega 707, Hamburg, Germany) to the nearest 100 g using light clothes and without shoes; height by a stadiometer (Seca, Hamburg, Germany) without shoes to the nearest 0.1 cm, and WC at the narrowest level by a nonstretchable tape to the nearest 0.1 cm. BMI was calculated as weight (kg) divided by height squared (m^2). Systolic and diastolic blood pressure were also measured twice by a standard barometer that was calibrated by Institute of Standard and Industrial Research of Iran in the right arm of the patients who were at sitting position for at least 10 min. All these measures were also examined at the periodical visits and at the end of the intervention. Three 24-hour dietary recalls were taken from all of the participants at the beginning, 4th week, and the end of the study, by a skilled nutritionist. Dietary intakes of energy and macronutrients were determined using nutritionist IV (N-IV) software (First Databank, San Bruno, CA, USA) modified for Iranian foods. In addition, physical activity of subjects was assessed by a valid and reliable (Alpha coefficient = 0.7) Persian version of the International physical activity questionnaire.^[18] This assessment was repeated at the end of the study. Data on physical activity were expressed as metabolic Equivalents using available publications.^[19,20]

Statistical analysis

Normal distribution of data was investigated using Kolmogorov–Smirnov test. Data were expressed as mean \pm standard deviation (SD). Baseline characteristics of study participants, as well as their dietary intakes throughout the study were compared using student's *t*-test for continuous variables and Chi-square test for categorical variables. To examine time and time \times group effects, we applied repeated measure of analysis of variance, and adjusted our findings for the potential confounders including participants' physical activity, total energy intake, and BMI. $P < 0.05$ was considered statistically

significant. All statistical analyses were done using the Statistical Package for Social Sciences for Windows version 18 (SPSS Inc., Chicago, IL, USA).

RESULTS

Fifty-two patients completed the study. One person from the placebo and one from the saffron group voluntarily left the study during the intervention due to complications of the capsules, especially headache. Flowchart of the study has been indicated in Figure 1.

Baseline characteristics of participants are shown in Table 1. There were no significant differences between the two groups with regard to basic characteristics. Mean (\pm SD) age and BMI of participants were 55.00 ± 7.22 and 25.87 ± 7.29 , respectively.

Dietary intake of participants is indicated in Table 2. There were no significant differences in dietary intakes between the two groups at the baseline. Moreover, differences in dietary intakes remained nonsignificant throughout the intervention.

In addition, participants' physical activity did not change significantly throughout the intervention. Significant reduction was found in serum concentration of FBS in the saffron group as compared to the controls (saffron group = 128.84 ± 31.86 mg/dL; placebo group = 153.76 ± 41.23 mg/dL, $P < 0.001$). This reduction remained significant after controlling for the potential confounders including physical activity, total energy intake, and BMI ($P < 0.001$). Changes in serum concentration of HbA1C ($P = 0.90$), 2 hPG ($P = 0.81$), TC ($P = 0.11$), TG ($P = 0.10$), LDL ($P = 0.08$), HDL ($P = 0.11$) were not significant after consumption of saffron than placebo; and remained unchanged after controlling for the potential confounders [Table 3].

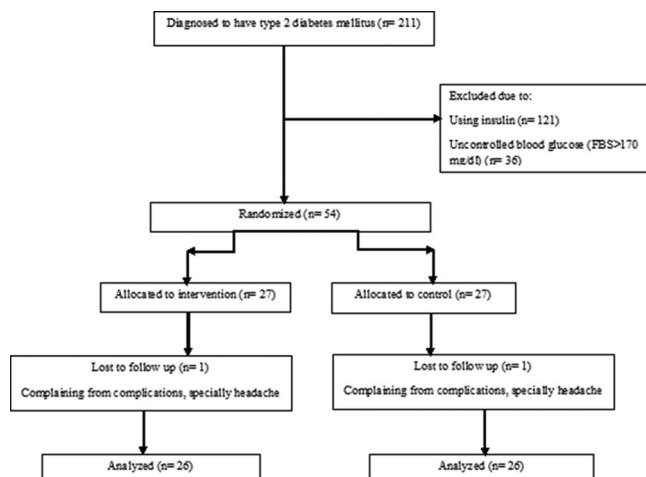


Figure 1: Flowchart of the study

Table 1: Baseline characteristics of participants

Variables	Saffron group (n=26)	Placebo group (n=6)	P ^a
Age, year (mean±SD)	54.57±6.96	55.42±7.58	0.67*
BMI, kg/cm ² (mean±SD)	23.84±11.89	28.30±3.24	0.29*
Weight, kg (mean±SD)	63.10±31.64	66.34±9.01	0.71*
WC, cm (mean±SD)	98.25±10.08	96.51±8.13	0.60*
Family numbers (mean±SD)	3.46±1.27	3.00±1.25	0.19*
Sex (n)			
Male	6	6	1.00*
Female	20	20	
Job (n)	0	0	0.18**
Workless employee	0	1	
Self-employment	1	3	
Farmer	0	0	
Housewife	18	20	
Retired	7	2	
Disabled	0	0	
Drug (n)			
Metformin	9	5	0.40**
Glibenclamide	7	7	
Metformin + glibenclamide	10	14	
Marriage (n)			
Single	0	0	0.68**
Married	22	23	
Widow	4	3	
Divorced	0	0	
Education illiterate (n)	2	9	
Primary education	14	13	0.16**
High school diploma	6	3	
University degree	4	1	
Income (n)			
Low	11	16	0.22**
Medium	15	9	
High	0	1	

^aP value for variable comparing between the two groups ($P < 0.05$); Calculated by *Independent t-test and **Fisher exact test. BMI = Body mass index; WC = Waist circumference; SD = Standard deviation

Changes in anthropometric measures and blood pressure throughout the study in both saffron and placebo groups are indicated in Figure 2. Although an increase was seen in systolic and diastolic blood pressures during the intervention, it was nonsignificant. In addition, differences in anthropometric measures between two groups were also not statistically significant ($P = 0.46$).

DISCUSSION

Our study showed that hydroalcoholic extract of saffron significantly decreases the serum levels of FBS in T2D patients comparing to the controls.

Based on the best of our knowledge, there was no study investigated the effect of saffron on metabolic control including serum lipid profile and glucose concentrations in T2D mellitus. However, Azimi *et al.* have shown a

significant decrease in TC and LDL and increase in HDL among T2D patients after drinking daily three glasses of saffron tea (containing 1 g saffron) for 8 weeks. However, no significant effect was seen on blood glucose profiles.^[16] However, this effect may be due to tea instead of saffron. In another study by Fadai *et al.*, 12 weeks consumption of saffron (30 mg/day) in patients with schizophrenia who suffered from metabolic syndrome induced significant reduction only in FBS.^[21] In an animal study by Samarghandian *et al.* on diabetic rats suffered from encephalopathy, saffron at doses of 40 and 80 mg/kg significantly reduced TC, TG, LDL, and blood glucose and increased HDL after 28 days.^[17]

We could not found significant changes in TG and HDL serum concentrations throughout the intervention. In addition, we also failed to find a significant effect of saffron on the blood pressure. This finding is in a line with Azimi *et al.* study in which daily consumption of three glasses saffron tea (containing 1 g saffron) for 8 weeks did not effect on blood pressure in T2D patients.^[22] In an animal model study, 5 weeks administration of three doses saffron aqueous extract (10, 20, and 40 mg/Kg/day) did not change blood pressure in normotensive rats.^[23]

The mechanisms through which dietary saffron extract might influence the metabolic control in T2D mellitus are lacking. Saffron is considered as a natural source of dietary antioxidants. Antioxidants are hypothesized to modulate diabetes by reducing its complications. Such that, antioxidants may improve endothelial function, reduce platelet aggregation, lower blood glucose, and might induce anti-inflammatory effects.^[24,25] It becomes so important when we know systemic inflammation as a risk factor in multiple aspects of diabetes etiology and pathology.^[26]

This study is the first randomized clinical trial investigating effect of saffron hydroalcoholic extract on metabolic control in T2D mellitus. Several other strengths of the current study need to be highlighted; including having detailed data on diet and physical activity. In addition, matching subjects for age and sex and controlling medications using by the participants improved our conclusions. Given these strengths, some limitations must also be taken into account. We measured some serum glucose and lipid indicators in this study. Assessment of insulin resistance, serum concentration of insulin, and important serum indicators of inflammation might improve our conclusions. In addition, as there was no human study available in this area, we took a saffron daily dose and our study sample size and duration similar to the clinical trials investigated the effect of saffron on depression.^[25-29] Therefore, further studies by using different doses of saffron, with larger

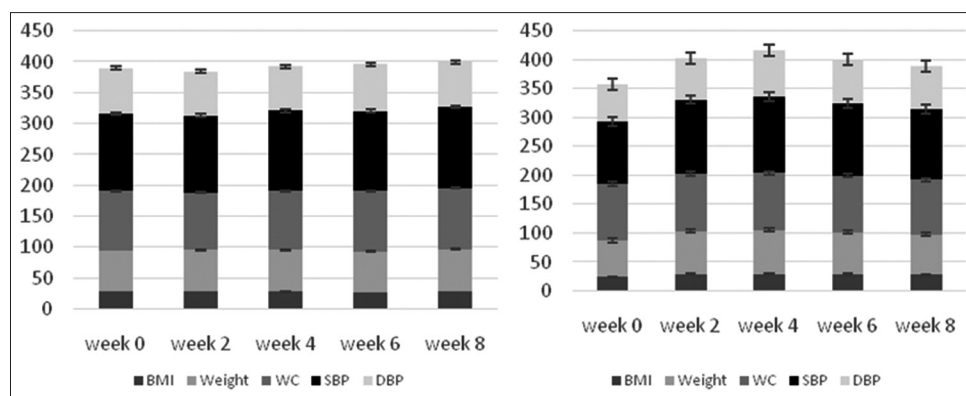


Figure 2: Changes in anthropometric measures and blood pressure parameters throughout the study in the saffron (right) and placebo (left) groups. *Calculated by the analysis of variance repeated measure. Anthropometric measures and systolic and diastolic blood pressure did not change significantly during the study. BMI = Body mass index; WC = Waist circumference; SBP = Systolic blood pressure; DBP: Diastolic blood pressure

Table 2: Dietary intake of participants

Variables	Saffron group (mean±SD) (n=26)			P_a	Placebo group (mean±SD) (n=26)			P_a	P_b	P_c
	Time 1 ^a	Time 2 ^b	Time 3 ^c		Time 1	Time 2	Time 3			
Energy (C)	1363.40±424.07	1321.20±384.00	1456.40±497.28	0.87	1488.80±503.70	1303.80±390.34	1652.40±468.48	0.14	0.35	0.33
Carbohydrate (g)	216.60±74.85	189.98±62.69	223.05±90.54	0.76	237.75±92.89	196.37±51.61	248.76±74.62	0.75	0.38	0.62
Protein (g)	56.67±18.52	54.99±15.40	63.78±31.12	0.47	58.91±20.97	55.22±20.35	66.54±19.74	0.13	0.69	0.93
Fat (g)	35.29±16.22	36.35±17.45	35.86±16.94	0.90	36.93±21.69	37.19±18.77	45.07±17.77	0.27	0.76	0.08

^aStudy beginning; ^bMidst study; ^cEnd of study. P_a = P value for variable changes throughout the intervention intragroup. Calculated by ANOVA repeated measure; P_b = P value for variable comparing between the two groups at the beginning of the intervention. Calculated by independent t -test; P_c = P value for variable comparing between the two groups at the end of the intervention after adjusting for basal values. Calculated by ANOVA analysis of covariance; SD = Standard deviation; ANOVA = Analysis of variance

Table 3: Serum concentration of glucose and lipids and physical activity of the study participants[#]

Variables	Mean±SD				P_a	P_b	P_c
	Saffron group (n=26)		Placebo group (n=26)				
	Time 1 [^]	Time 2 [^]	Time 1	Time 2			
HbA1C (%)	6.37±1.30	6.75±1.28	6.83±1.36	7.25±1.65	0.01	0.90	0.99
FBS (mg/dL)	164.36±40.88	128.84±31.86	159.64±38.38	153.76±41.23	<0.001	<0.001	<0.001
2hPG (mg/dL)	248.62±91.24	210.21±75.64	240.50±100.68	207.62±74.69	<0.01	0.81	0.83
TC (mg/dL)	179.04±35.29	166.96±25.80	181.44±33.19	169.28±25.57	0.20	0.11	0.11
TG (mg/dL)	146.54±41.86	127.00±37.61	137.96±40.71	128.20±38.50	<0.01	0.10	0.17
LDL (mg/dL)	83.79±29.48	85.90±32.04	95.90±36.16	82.94±26.95	0.21	0.08	0.08
HDL (mg/dL)	58.83±8.47	63.33±5.11	60.95±7.17	61.17±7.08	0.08	0.11	0.16
Physical activity (METs)	1193.80±621.21	1181.50±555.17	942.33±435.49	872.89±341.42	0.48	0.62	0.65

[#]Analyzed using repeated measure of ANOVA test; [^]Beginning intervention; [^]End intervention. P_a = P value for time effect; P_b = P value for intervention effect; P_c = Adjusted P value for time×intervention effect. Adjusted for BMI, physical activity, and total energy intake (METs adjusted for all of these factors, except for physical activity); BMI = Body mass index; HbA1c = Hemoglobin A1c; FBS = Fasting blood sugar; 2hPG = 2 h plasma glucose; TC = Total cholesterol; TG = Triacylglycerol; LDL = Low density lipoprotein; HDL = High-density lipoprotein; METs = Metabolic equivalents; SD = Standard deviation; ANOVA = Analysis of variance

sample sizes and longer durations are recommended for the future.

CONCLUSIONS

Given together, it should be said that saffron hydroalcoholic extract may considerably improve blood glucose control by reducing FBS serum concentrations in T2D patients. However, saffron extract have no significant effect on lipids serum concentrations and blood pressure among patients with T2D. Further studies with different dosages of saffron extract and duration and larger sample size are required to confirm these findings.

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Conflicts of interest

There are no conflicts of interest.

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