Complementary Therapies in Medicine 47 (2019) 102158

Contents lists available at ScienceDirect

Complementary Therapies in Medicine

journal homepage: www.elsevier.com/locate/ctim

The effect of saffron supplementation on blood glucose and lipid profile: A systematic review and meta-analysis of randomized controlled trials

Omid Asbaghi[a], Sepideh Soltani[b], Noushin Norouzi[a], Alireza Milajerdi[c,d], Saeed Choobkar[e], Zatollah Asemi[f,*]

[a] Student Research Committee, Lorestan University of Medical Sciences, Khorramabad, Iran
[b] Prevention of Metabolic Disorders Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[c] Department of Community Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, Tehran, Iran
[d] Students' Scientific Research Center (SSRC), Tehran University of Medical Sciences (TUMS), Tehran, Iran
[e] Lorestan University of Medical Sciences, Khorramabad, Iran
[f] Research Center for Biochemistry and Nutrition in Metabolic Diseases, Kashan University of Medical Sciences, Kashan, Iran

ARTICLE INFO

Keywords:
Saffron
Glucose
Lipid profile
Meta-analysis

ABSTRACT

Background: Despite several studies about the effects of saffron supplementation on serum concentrations of lipid and glucose profiles, no systematic study had summarized the findings. Therefore, we conduct current study to systematically summarize findings from studies about the effect of saffron supplementation on serum levels of glucose and lipid profiles and to do a meta-analysis, if possible.

Methods: A systematic literature search was conducted for clinical trials published in PubMed, SCOPUS, EMBASE, Cochrane's Library and ISI Web of Science from the beginning to 22 February 2019. All randomized clinical trials on the effect of saffron supplementation on serum concentrations of lipid and glucose profiles were included.

Results: In overall, six studies were included in the current study. Pooled analysis of six studies for the effect of saffron on serum TG, TC and FBG concentrations and of five studies for LDL and HDL, showed a significant reduction in TG (WMD: -8.93 mg/dl; 95% CI: -16.49 to -1.37, P = 0.02) and TC levels (WMD: -5.72 mg/dl; 95% CI: -11.10 to -0.34, P = 0.03), a significant increase in HDL levels (WMD: 2.7 mg/dl; 95% CI: 0.22 to 5.18, P = 0.03), and no significant effect on LDL (WMD: -2.30 mg/dl; 95% CI: -11.73 to 7.13, P = 0.63) and FBG levels (WMD: -5.30 mg/dl; 95% CI: -14.20 to 3.60, P = 0.51).

Conclusion: We found a significant reduction in serum concentrations of TC and TG and a significant increase in serum levels of HDL following supplementation with saffron. Saffron supplementation had no significant influence on serum FPG and LDL concentrations.

1. Introduction

Prevalence of chronic diseases is increasing worldwide. Cardiovascular disease (CVDs) and diabetes mellitus are among the most prevalent chronic diseases, which are known to be responsible for million deaths annually. It is estimated that annual CVD mortality will be increased to 25 million per year by 2020.[1,2] On the other hand, prevalence of diabetes has been increased worldwide. In 2017, about 451 million people had diabetes, and about 5 million deaths were occurred due to diabetes.[3] Therefore, control of complications of these chronic conditions is a health priority.

Different classes of lipid-modulating and anti-diabetic agents are used to modulate serum concentrations of glucose and lipids.[4,5] However, several possible complications have been reported. Therefore, recent efforts have been made to find herbal medicines for this purpose. For instance, previous studies have shown significant effects of ginger,[6,7] cinnamon,[8,9] turmeric,[10] and ginseng [11] on modulation of serum glucose and lipid profiles. In addition, additional single nutraceuticals and nutraceutical combinations such as berberine, phytosterols, policosanol, soy products and red yeast rice have demonstrated both lipid- and glucose-lowering effects.[12,13] Saffron (Crocus sativus L.) is a popular Iranian additive [14] which its beneficial effects on several diseases have been found in previous studies. Although several studies have investigated the effect of saffron supplementation on serum glucose and lipids concentrations, findings are inconsistent. Saffron supplementation has significantly reduced blood glucose and

* Corresponding author.
E-mail address: asemi_z@Kaums.ac.ir (Z. Asemi).

https://doi.org/10.1016/j.ctim.2019.07.017
Received 2 June 2019; Received in revised form 22 July 2019; Accepted 24 July 2019
Available online 25 July 2019
0965-2299/

lipid profiles in some studies. However, some other studies failed to find such the significant effects.[14–19] Findings from a recent systematic review and meta-analysis showed no significant effect of saffron supplementation on lipid and glucose profiles.[20] However, data from studies that used each forms of saffron or its constituents were pooled in that study. Due to the different influence of these interventions, findings from that study are prone to bias.

Despite above mentioned controversies between available studies, no earlier study has summarized findings from studies on the effects of saffron alone on serum glucose and lipid profiles. Therefore, we conduct current study to systematically summarize findings from studies about the effect of saffron supplementation on serum levels of glucose and lipid profiles and to do a meta-analysis, if possible.

2. Materials and methods

This systematic review has been conducted according to the PRISMA statement.[21]

2.1. Search strategy

Relevant papers published until february 2019 were searched through the international scientific literature databases, including PubMed, SCOPUS, EMBASE, Cochrane's Library and ISI Web of Science without restriction of time or publication language. For this purpose, we used the following keywords: ((("Crocus sativus Linn "[Title/Abstract] OR "Safranal "[Title/Abstract] OR "saffron "[Title/Abstract]) AND ("Diabetic"[Title/Abstract] OR "glucose"[Title/Abstract] OR "fasting blood glucose"[Title/Abstract] OR "FBG"[Title/Abstract] OR ("hemoglobin A1c"[Title/Abstract] OR "HbA1c"[Title/Abstract] OR "HOMA-IR"[Title/Abstract] OR "homeostatic model assessment"[Title/Abstract] OR "Insulin"[Title/Abstract] OR "fasting blood sugar"[Title/Abstract] OR "glycemia"[Title/Abstract] OR "glycaemia"[Title/Abstract] OR "hyperglycaemia"[Title/Abstract] OR "FBS"[Title/Abstract]) OR "triglyceride"[Title/Abstract] OR "Triacylglycerol"[Title/Abstract] OR "cholesterol"[Title/Abstract] OR Lipoprotein"[Title/Abstract] OR "very low density lipoprotein"[Title/Abstract] OR "VLDL"[Title/Abstract] OR "low density lipoprotein"[Title/Abstract] OR "LDL"[Title/Abstract] OR "LDL-C"[Title/Abstract] OR "high density lipoprotein"[Title/Abstract] OR "HDL"[Title/Abstract] OR "HDL-C"[Title/Abstract] OR "lipid"[Title/Abstract])). In addition, to avoid missing of any other relevant publication, we also searched the reference lists of relevant articles.

2.2. Inclusion criteria

All randomized clinical trials (RCTs) that investigated the effect of saffron on blood glucose or lipid profile in adults were included.

2.3. Exclusion criteria

Studies with the following properties were excluded: 1) had observational design or were conducted in animal models; 2) conducted on children (< 18 years); 3) did not perform randomized allocation; 4) had no placebo-control group; 5) examined the effect of another intervention along with saffron; 6) acute intervention, or 7) used an specific type of saffron or its constituents.

2.4. Data extraction

Two researchers (NN, OA) independently extracted necessary information from the studies. Controversies were resolved by the third researcher (AM). Following data were extracted: first author's name, country, publication's year, study design, health condition of participants, study sample size in intervention and control groups, participants' sex, participants' mean age and body mass index, dosage of saffron supplementation, duration of study, and means ± Standard Deviation (SD) of biochemical profiles before and after intervention or their changes throughout the intervention.

2.5. Quality assessment

Methodological quality of included studies was evaluated using the Jadad scoring system. This scoring system contained five questions about: 1) presence of randomization; 2) application of an appropriate method for randomization; 3) presence of double-blinding; 4) application of an appropriate method for double-blinding; and 5) providing reasonable explanations for the withdrawals and dropouts. A score of 0 or 1 was given to each question. The scores were then summed up and a total score of 0–5 was yielded.[22] Studies with a total score of equal or greater than 3 were considered as high-quality, while those with a total score of less than 3 were considered as low-quality studies.[22]

2.6. Data synthesis and statistical analysis

Overall effect size was calculated using mean ± SD of changes in serum concentrations of glucose and lipids within intervention and control groups by the random-effect model,[23] and was expressed as weighted mean difference (WMD) and 95% CI. Evaluation of between-study heterogeneity was performed using I-square (I^2) and test Q test. Subgroup analysis based on saffron dosage and duration of intervention, baseline FBG, and blood lipids level, mean age, and study quality was conducted to detect potential sources of heterogeneity.[24] All other statistics were converted to mean ± SD using proper formula. Median and 95% confidence intervals were converted to mean and SD using the method introduced by Hozo et al.[25] Standard errors of mean (SEM) were converted to SDs by S.D═S.E.M × √n (n is the number of participants in each group). If serum concentrations of a glucose or lipid profile were reported in different units, we converted them into the most frequently used unit. All analyses were done using the STATA version 12 (Stata Corporation, College Station, TX, USA).

3. Results

Overall, 903 publications were found in the initial search through Pubmed (n = 136), Scopus (n = 267), Web of science (n = 256), Embase (n = 222) and Cochrane (n = 22). Overall, Overall, 903 publications were found in the initial search through Pubmed (n = 136), Scopus (n = 267), Web of science (n = 256), Embase (n = 222) and Cochrane (n = 22). Overall [14,15,17–19,26] were included in this meta-analysis. The flow-diagram of study selection is presented in Fig. 1.

4. Study characteristics

The characteristics of included articles are summarized in the Table 1. All papers were Randomized Clinical Trials (RCTs), published between 2011 and 2018, which were done in Iran.[14,15,17–19,26] The duration of the intervention varied from 4 to 12 weeks. Saffron supplements were used in dosages between 30 and 1000 mg. A total of 147 participants in intervention group and 144 participants in control group were enrolled.[14,15,17–19,26] Participants of these studies had sexual dysfunction,[15] type 2 diabetes,[14,26] schizophrenia,[17] coronary artery disease [18] and metabolic syndrome.[19] One study was done exclusively in men,[17] while the other studies recruited both genders.[14,15,18,19,26] As measured by the Jadad scoring system, the quality of all included studies was moderate [26] or high.[14,15,17–19]

5. Meta-Analysis

Results of pooled fix or random-effect size (according to significant or non-significant heterogeneity) analysis of six studies [14,15,17–19,26] for TG, TC and FBG, and also five studies [14,17–19,26] for LDL and HDL

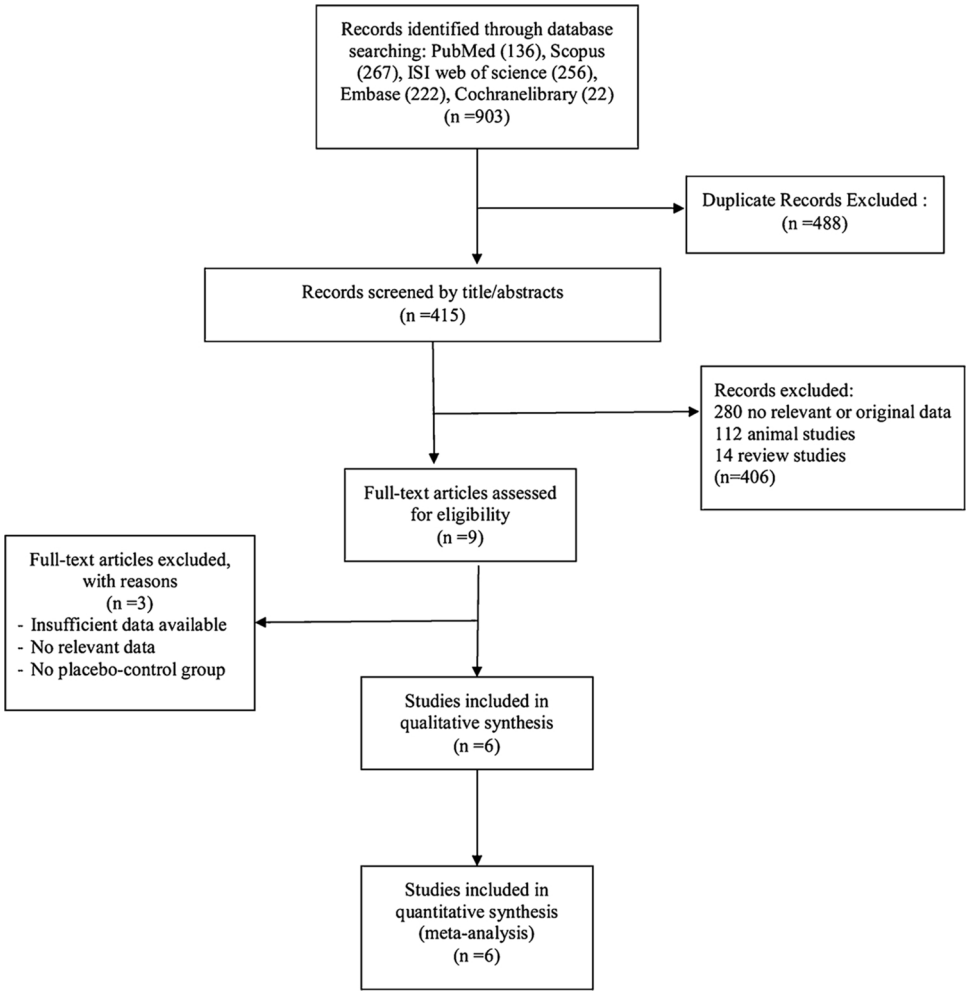

Fig. 1. Flowchart of study selection for inclusion trials in the systematic review.

showed significant decreasing effects of saffron supplementation on TG (WMD: -8.93 mg/dl; 95% CI: -16.49 to -1.37, P = 0.02) without no significant heterogeneity shown within the studies (I^2 = 42.8%, P = 0.120) and TC levels (WMD: -5.72 mg/dl; 95% CI: -11.10 to -0.34, P = 0.03) without significant heterogeneity shown within the studies (I^2 = 42.8%, P = 0.120), a significant effect on HDL level (WMD: 2.7 mg/dl; 95% CI: 0.22 to 5.18, P = 0.03) with significant heterogeneity (I^2 = 69.8%, P = 0.01), However, supplementation with saffron did not have a significant effects on LDL (WMD: -2.30 mg/dl; 95% CI: -11.73 to 7.13, P = 0.63) and FBG levels (WMD: -5.30 mg/dl; 95% CI: -14.20 to 3.60, P = 0.51). The forest plots for the effects of saffron supplementation on FBG, TG, TC, LDL and HDL are shown in Figs. 2–6 , respectively. Subgroup analyses were performed to find probable explanations for the between-study heterogeneities and to reach the best conclusion:

6. Subgroup analyses

Subgroup analysis of the effect of saffron on serum concentrations of FBG, LDL and HDL by the baseline values, trial duration, saffron dosage and participants' health condition was done due to significant heterogeneity ($p < 0.05$).

6.1. Subgroup analysis for the effects of saffron on FBG

After subgroup analysis heterogeneity was disappeared in studies that, saffron dosages was > 30 mg (I^2 = 0.0%, P = 0.786). However, saffron supplementation did not effect on serum concentrations of FBG in all of the subgroups. (Table 2).

6.2. Subgroup analysis for the effects of saffron on LDL

Our subgroup analyses indicated no significant heterogeneity in studies conducted on subjects without type 2 diabetes (I^2 = 2.5%, P = 0.359) and studies with duration equal to 12 weeks (I^2 47.8%, P = 0.166). However, subgroup analysis shown that the effect of saffron supplementation could reduce LDL concentration in non-type 2 diabetes subjects (WMD: -8.39 mg/ dl; 95% CI: -15.19 to -1.59, P 0.016) (Table 2).

6.3. Subgroup analysis for the effects of saffron on HDL

Subgroup analysis showed no evidence of between-study heterogeneity in studies that, saffron dosages was > 30 mg (I^2 = 0.0%, P = 0.750) and 30mg (I^2 = 0.0%, P = 0.686), and also, conducted on subjects with HDL concentration higher than 50 mg/dl (I^2 = 34.4%, P = 0.218) and non-diabetes subjects (I^2 = 34.4%, P = 0.218). Also, contrary to general analysis, the analysis of subgroups showed that, saffron supplements have led to an increase in HDL concentration in subjects with HDL level higher than 50mg/dl (WMD: 3.54 mg/dl; 95% CI: 0.87 to 6.22, P = 0.009) and non-type 2 diabetes (WMD: 3.54 mg/dl; 95% CI: 0.87 to 6.22, P = 0.009), and also in studies that saffron dosage equal to 30mg (WMD: 4.37 mg/dl; 95% CI: 2.60 to 6.13, P < 0.001) (Table 2).

Table 1
Characteristics of included studies in the meta-analysis of saffron supplementation on glucose level and lipid profile.

Author	year	country	Study design	participants	sex	Mean age (intervention/ control)	Mean BMI (intervention/ control)	Trial duration (week)	Daily dose of saffron (mg)	Sample size (intervention/ control)	Jaded score
P. Mansoori	2011	Iran	R/DB/PL	Sexual Dysfunction	F/M	35/42	NR/NR	4	30	10/10	4
P. Azimi	2015	Iran	R/SB/PL	Type 2 Diabetes Patients	F/M	57.02/63.64	28386/28.40	8	1000	42/39	2
F. Fadai	2014	Iran	R/TB/PL	Patients with Schizophrenia	M	48.1/48.1	NR/NR	12	30	22/22	5
N. Abedimanesh	2017	Iran	R/DB/PL	coronary artery disease	F/M	53.36/56.32	28.64/28.05	8	30	25/25	5
T. Kermani	2018	Iran	R/DB/PL	Metabolic Syndrome	F/M	43.64/42.59	31.02/30.48	12	100	22/22	4
A. Milajerdi	2018	Iran	R/TB/PL	Type 2 Diabetes Patients	F/M	54.57/55.42	23.84/23.30	8	30	26/26	4

Abbreviations: DB, double-blinded; PC, placebo-controlled; R, randomized; NR, not reported; F, Female; M, Male.

7. Publication bias

Assessment of publication bias by the egger's test indicated no evidence of publication bias in the meta-analysis for the effects of saffron supplementation on serum FBG ($p = 0.361$), TG ($p = 0.547$), TC ($p = 0.125$), LDL ($p = 0.548$), and HDL concentrations ($p = 0.670$).

8. Discussion

This meta-analysis showed that saffron supplementation significantly reduced serum concentrations of TG and TC, and increased serum HDL concentrations. However, it had no significant effect on serum levels of FBS and LDL. However, saffron supplementation might have beneficial effects on some plasma lipids, this was not clinically significant. We suggest that higher doses of saffron and longer period of intervention might make results clinically significant. Hypercholesterolemia is one of the major risk factors for the development of CVD. Hypolipidemic agents, including apolipoprotein B-100 antisense oligonucleotides, proprotein convertase subtilisin/kexin type 9 inhibitors, cholesteryl ester transfer protein inhibitors, and microsomal triglyceride transfer protein inhibitors are being used to control dyslipidemia.[27] There is a critical need to identity additional effective hypolipidemic agents that can be used either in combination with statins, or alone, if statins are not tolerated.[27] All of synthetic and naturally-derived hypolipidemic compounds/therapies such as nutraceuticals represent alternative treatment strategies to decrease serum cholesterol levels.[27–30]

Our analysis indicated that saffron supplementation significantly reduced serum concentrations of TG and TC. Rare earlier studies have investigated the effects of saffron or its constituents on serum levels of these biomarkers. However, significant reductions in serum TG and TC have been reported in animal studies.[31] Saffron administration (100 mg/day) in patients with mild to moderate asthma reduced serum concentrations of TG, as compared to placebo.[32] However, intake of saffron alcoholic extract (30 mg/day) in patients with type 2 diabetes mellitus did not affect serum levels of TG.[14] Moreover, changes in serum TG and TC in patients with metabolic syndrome were not significant following intake of crocin (100 mg/day).[33] Administration of crocin in patients with metabolic syndrome also did not change serum concentrations of TC and TG.[34] In the current meta-analysis, the simultaneous reduction of TG and increases of TC and HDL-C, without any impact on LDL-C levels may be due to reduction of the cholesterol content in non-HDL lipoproteins or even apoB. Further studies are needed to confirm these findings.

Our meta-analysis also showed a significant increase in serum levels of HDL following the administration of saffron. Treatment of diabetic rats with saffron extract resulted in a significant increase in serum levels of HDL.[35] It also increased levels of HDL among diabetic encephalopathy-induced rats.[36] As same as for TG and TC, the effects of saffron on serum levels of HDL has been investigated only in rare human studies. Three months supplementation with saffron (30 mg/day) did not affect serum levels of HDL in patients with type 2 diabetes mellitus.[37] Administration of crocin in the same dosages for 8 weeks also did not influence serum HDL concentrations in patients with metabolic syndrome.[34] Similar finding was also reached among patients who were suffering from depression.[38] Lack of adjustment for the baseline values of HDL in that study might be as a cause for the non-significant finding. Most patients with chronic diseases have impairments in their serum levels of HDL at baseline.

We found no significant effects of saffron supplementation on serum LDL and FPG concentrations. Intake of saffron supplements in patients with metabolic syndrome did not change serum levels of fasting plasma glucose.[34] Saffron also had no significant effect on serum LDL concentrations among patients with depression.[38] However, in a RCT on patients with type 2 diabetes mellitus, three months supplementation with saffron resulted in a significant reduction in serum levels of FPG

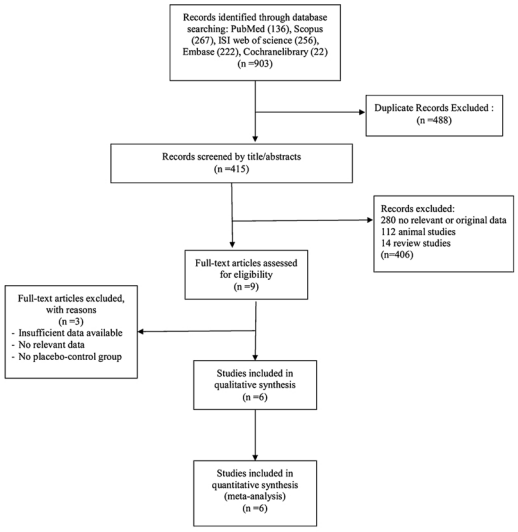

Fig.1

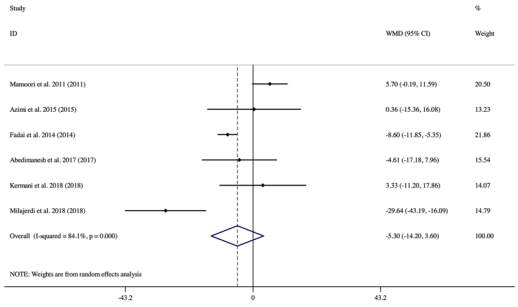

Fig.2

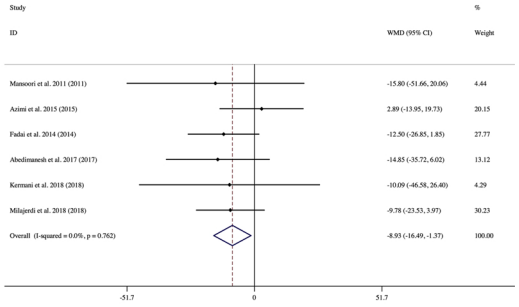

Fig.3

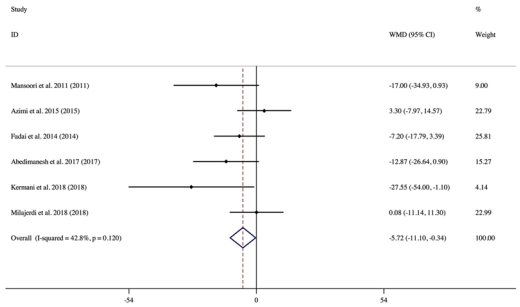

Fig.4

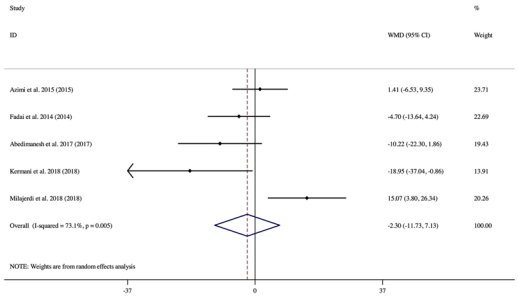

Fig.5

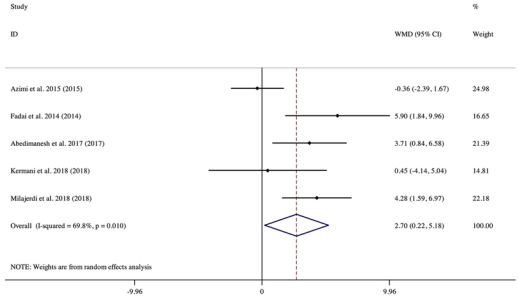

Fig.6

Figs. 2–6. Meta-analysis fasting blood glucose and lipid profile weighted mean difference estimates for 2) FBG, 3) TG, 4) TC, 5) LDL, 6) HDL, in the saffron and placebo groups (CI = 95%).

Table 2
Subgroup analyses of saffron supplementation on glucose level and lipid profile.

	NO	WMD (95%CI)	P within group	P heterogeneity	I^2
Subgroup analyses of saffron supplementation on FBG level.					
Baseline serum FBG (mg/dl)					
< 100	2	−1.67 (-15.67, 12.33)	0.815	< 0.001	94.2%
> 100	4	−7.84 (-22.71, 7.03)	0.301	0.004	77.7%
Trial duration (week)					
< 12	4	−6.59 (-22.04, 8.86)	0.403	< 0.001	86.6%
12	2	−4.82 (-15.70, 6.05)	0.385	0.116	59.4%
saffron dose (mg)					
=30	4	−8.16 (-19.42, 3.10)	0.156	< 0.001	89.8%
> 30	2	1.96 (-8.71, 12.63)	0.719	0.786	0.0%
Health condition					
Non-type 2 diabetes	4	−1.42 (-10.63, 7.79)	0.763	< 0.001	83.9%
type 2 diabetes	2	−14.91 (-44.30, 14.48)	0.320	0.005	87.5%
Subgroup analyses of saffron supplementation on LDL level.					
Baseline serum LDL (mg/dl)					
< 100	3	−4.64 (-13.66, 4.38)	0.314	0.116	53.6%
> 100	2	2.52 (-22.26, 27.30)	0.842	0.003	88.9%
Trial duration (week)					
< 12	3	2.19 (-10.55, 14.94)	0.735	0.010	78.1%
12	2	−9.56 (-22.81, 3.67)	0.157	0.166	47.8%
saffron dose (mg)					
=30	3	0.02 (-14.26, 14.30)	0.998	0.005	81.3%
> 30	2	−7.08 (-26.75, 12.59)	0.481	0.043	75.5%
Health condition					
Non-type 2 diabetes	3	−8.39 (-15.19, -1.59)	**0.016**	0.359	2.5%
type 2 diabetes	2	7.63 (-5.70, 20.96)	0.262	0.052	73.5%
Subgroup analyses of saffron supplementation on HDL level.					
Baseline serum HDL (mg/dl)					
< 50	2	1.87 (-2.67, 6.41)	0.419	0.007	86.3%
> 50	3	3.54 (0.87, 6.22)	**0.009**	0.218	34.4%
Trial duration (week)					
< 12	3	2.42 (-0.71, 5.55)	0.130	0.009	78.5%
12	2	3.28 (-2.05, 8.62)	0.228	0.081	67.1%
saffron dose (mg)					
=30	3	4.37 (2.60, 6.13)	< **0.001**	0.686	0.0%
> 30	2	−0.22 (-2.08, 1.62)	0.810	0.752	0.0%
Health condition					
Non-type 2 diabetes	3	3.54 (0.87, 6.22)	**0.009**	0.218	34.4%
type 2 diabetes	2	1.87 (-2.67, 6.41)	0.419	0.007	86.3%

Abbreviations: CI, confidence interval; FBG, fasting blood glucose; TG, triglycerides; TC, total cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein; WMD, weighted mean differences.

and LDL.[39] In another study, saffron significantly reduced serum levels of FPG in patients with metabolic syndrome.[40] Most participants in those studies were under treatment with common anti-diabetic and anti-hyperlipidemia drugs, however, they did not perform any stratification based on medicines used by the participants. Therefore, further studies are needed to reach a firm conclusion.

Furthermore, a recently published meta-analysis in this regard did not find a significant effect of saffron supplementation on lipid and glucose profiles.[20] However, they combined data from studies that used either saffron or its active constituents. As reported in previous studies, the specific bioactive components of saffron may have different metabolic effects than saffron powder or its extracts.

Although the exact mechanisms through which saffron might influence serum levels of lipids are not clearly determined, the lipid-modifying potency of saffron is attributed to its active constituents, such as crocin. Crocin inhibits activity of pancreatic and gastric lipases and recedes cholesterol and fat absorption.[41] Lipases inhibition by medications such as orlistat has demonstrated both TG and body weight lowering effect.[42] The possible TG-lowering effect of saffron may be mediated by appetite suppressing and body weight reduction.[43] Moreover, crocin can modulate lipid profile disorders through activation of PPAR-α.[44] A significant reduction in cholesteryl ester transfer protein (CETP), one of the most important protein in the modulation of plasma lipids profile and lipoproteins levels, following supplementation with saffron has been reported previously.[34] Inhibition of CETP will increase serum concentrations of HDL-C.[34] In addition, modulation of adiponectin secretion, and antioxidant and anti-inflammatory properties of saffron and its constituents are also among the other probable mechanisms for glucose and lipid-lowering effects of this herbal medicine.[45–48] Finally, saffron supplementation may also increase NO bioavailability,[49] the number of pancreatic beta cells, and insulin secretion.[50] Moreover, modulation of intracellular signaling pathways via increases in AMPK phosphorylation is another potential mechanism in this regard.[51]

The current meta-analysis is among the rare studies summarizing findings from earlier studies on the effects of saffron supplementation,

but not its constituents, on serum lipid and glycemic profiles. However, finding of current study should be interpreted with caution; because of the following limitations. Firstly, the number of included studies for each variable was limited. Moreover, due to the limited duration of intervention in the included studies, we could not determine long-term influence of saffron supplementation on lipid and glucose profiles. In addition, most included studies were done in Iran, therefore, generalization of our findings to other nations should be done with caution. Finally, high between-study heterogeneity is also another concern. We tried to reduce this potential source of bias using different subgroup analyses.

In conclusion, we found a significant reduction in serum concentrations of TC and TG following supplementation with saffron. Saffron supplementation increased serum levels of HDL, but it had no significant influence on serum FPG and LDL concentrations. Further clinical trials with longer follow-up are needed.

References

1. Falko JM. Balancing efficacy and tolerability issues with Statin Therapy—Considerations for the use of Pitavastatin in special patient populations. *US Endocrinol.* 2011;7:30–39.
2. Organization WH. http://www.who. int/mediacentre/factsheets/fs340/en.url http://www who int/mediacentre/factsheets/fs241/en/ < /url. 2014.
3. Cho N, Shaw J, Karuranga S, et al. IDF Diabetes Atlas: Global estimates of diabetes prevalence for 2017 and projections for 2045. *Diabetes Res Clin Pract.* 2018;138:271–281.
4. Derosa G, Sibilla S. Optimizing combination treatment in the management of type 2 diabetes. *Vasc Health Risk Manag.* 2007;3:665.
5. Schuck RN, Mendys PM, Simpson Jr RJ. Beyond statins: Lipid management to reduce cardiovascular risk. *Pharmacotherapy J Human Pharmacol Drug Therapy.* 2013;33:754–764.
6. Elshater A, Salman MM, Moussa MM. Effect of ginger extract consumption on levels of blood glucose, lipid profile and kidney functions in alloxan induced-diabetic rats. *Egypt Acad J Biol Sci.* 2009;2:153–162.
7. Arablou T, Aryaeian N, Valizadeh M, Sharifi F, Hosseini A, Djalali M. The effect of ginger consumption on glycemic status, lipid profile and some inflammatory markers in patients with type 2 diabetes mellitus. *Int J Food Sci Nutr.* 2014;65:515–520.
8. Mang B, Wolters M, Schmitt B, et al. Effects of a cinnamon extract on plasma glucose, HbA1c, and serum lipids in diabetes mellitus type 2. *Eur J Clin Invest.* 2006;36:340–344.
9. Baker WL, Gutierrez-Williams G, White CM, Kluger J, Coleman CI. Effect of cinnamon on glucose control and lipid parameters. *Diabetes Care.* 2008;31:41–43.
10. Babu PS, Srinivasan K. Hypolipidemic action of curcumin, the active principle of turmeric (Curcuma longa) in streptozotocin induced diabetic rats. *Mol Cell Biochem.* 1997;166:169–175.
11. Sotaniemi EA, Haapakoski E, Rautio A. Ginseng Therapy in Non-Insulin-Dependent Diabetic Patients: Effects on psychophysical performance, glucose homeostasis, serum lipids, serum aminoterminalpropeptide concentration, and body weight. *Diabetes Care.* 1995;18:1373–1375.
12. Pirro M, Vetrani C, Bianchi C, Mannarino MR, Bernini F, Rivellese AA. Joint position statement on "Nutraceuticals for the treatment of hypercholesterolemia" of the Italian Society of Diabetology (SID) and of the Italian Society for the Study of Arteriosclerosis (SISA). *Nutr Metab Cardiovasc Dis.* 2017;27:2–17.
13. Pirro M, Mannarino MR, Bianconi V, et al. The effects of a nutraceutical combination on plasma lipids and glucose: A systematic review and meta-analysis of randomized controlled trials. *Pharmacol Res.* 2016;110:76–88.
14. Milajerdi A, Jazayeri S, Hashemzadeh N, et al. The effect of saffron (Crocus sativus L.) hydroalcoholic extract on metabolic control in type 2 diabetes mellitus: A triple-blinded randomized clinical trial. *J Res Medi Sci.* 2018;23.
15. Mansoori P, Akhondzadeh S, Raisi F, et al. A randomized, double-blind, placebo-controlled study of safety of the adjunctive saffron on sexual dysfunction induced by a selective serotonin reuptake inhibitor. *J Medi Plants.* 2011;1:121–130.
16. Azimi P, Ghiasvand R, Feizi A, Hariri M, Abbasi B. Effects of cinnamon, cardamom, saffron, and ginger consumption on markers of glycemic control, lipid profile, oxidative stress, and inflammation in type 2 diabetes patients. *The review of diabetic studies: RDS.* 2014;11:258.
17. Fadai F, Mousavi B, Ashtari Z, et al. Saffron aqueous extract prevents metabolic syndrome in patients with schizophrenia on olanzapine treatment: A randomized triple blind placebo controlled study. *Pharmacopsychiatry.* 2014;47:156–161.
18. Abedimanesh N, Bathaie SZ, Abedimanesh S, Motlagh B, Separham A, Ostadrahimi A. Saffron and crocin improved appetite, dietary intakes and body composition in patients with coronary artery disease. *J Cardiovasc Thorac Res.* 2017;9:200.
19. Kermani T, Zebarjadi M, Mehrad-Majd H, et al. Anti-inflammatory effect of Crocus sativus on serum cytokine levels in subjects with metabolic syndrome: a randomized, double-blind, placebo-controlled trial. *Curr Clin Pharmacol.* 2017;12:122–126.
20. Pourmasoumi M, Hadi A, Najafgholizadeh A, Kafeshani M, Sahebkar A. Clinical evidence on the effects of saffron (crocus sativus L.) on cardiovascular risk factors: A systematic review meta-analysis. *Pharmacol Res.* 2018.
21. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: Explanation and elaboration. *PLoS Med.* 2009;6:e1000100.
22. Moher D, Cook D, Jadad A, et al. *Assessing the quality of reports of randomised trials: Implications for the conduct of meta-analyses.* 1999; 1999.
23. Borenstein M, Hedges LV, Higgins JP, Rothstein HR. *Introduction to meta-analysis.* John Wiley & Sons; 2011.
24. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ: Br Med J.* 2003;327:557.
25. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Med Res Methodol.* 2005;5:13.
26. Azimi P, Ghiasvand R, Feizi A, et al. Effect of cinnamon, cardamom, saffron and ginger consumption on blood pressure and a marker of endothelial function in patients with type 2 diabetes mellitus: A randomized controlled clinical trial. *Blood Press.* 2016;25:133–140.
27. Johnston TP, Korolenko TA, Pirro M, Sahebkar A. Preventing cardiovascular heart disease: Promising nutraceutical and non-nutraceutical treatments for cholesterol management. *Pharmacol Res.* 2017;120:219–225.
28. Patti AM, Al-Rasadi K, Giglio RV, et al. Natural approaches in metabolic syndrome management. *Arch Med Sci.* 2018;14:422–441.
29. Cicero AFG, Colletti A, Bajraktari G, et al. Lipid-lowering nutraceuticals in clinical practice: Position paper from an International Lipid Expert Panel. *Nutr Rev.* 2017;75:731–767.
30. Sahebkar A, Serban MC, Gluba-Brzozka A, et al. Lipid-modifying effects of nutraceuticals: An evidence-based approach. *Nutrition.* 2016;32:1179–1192.
31. Samarghandian S, Azimi-Nezhad M, Farkhondeh T. Immunomodulatory and antioxidant effects of saffron aqueous extract (Crocus sativus L.) on streptozotocin-induced diabetes in rats. *Indian Heart J.* 2017;69:151–159.
32. Zilaee M, Hosseini SA, Jafarirad S, et al. An evaluation of the effects of saffron supplementation on the asthma clinical symptoms and asthma severity in patients with mild and moderate persistent allergic asthma: a double-blind, randomized placebo-controlled trial. *Respir Res.* 2019;20:39.
33. Kermani T, Kazemi T, Molki S, Ilkhani K, Sharifzadeh G, Rajabi O. The efficacy of crocin of saffron (Crocus sativus L.) on the components of metabolic syndrome: A randomized controlled clinical trial. *J Res Pharm Pract.* 2017;6:228.
34. Javandoost A, Afshari A, Nikbakht-Jam I, et al. Effect of crocin, a carotenoid from saffron, on plasma cholesteryl ester transfer protein and lipid profile in subjects with metabolic syndrome: A double blind randomized clinical trial. *ARYA Atheroscler.* 2017;13:245.
35. Hemmati M, Asghari S, Zohoori E, Karamian M. Hypoglycemic effects of three Iranian edible plants; jujube, barberry and saffron: Correlation with serum adiponectin level. *Pak J Pharm Sci.* 2015;28:2095–2099.
36. Samarghandian S, Azimi-Nezhad M, Samini F. Ameliorative effect of saffron aqueous extract on hyperglycemia, hyperlipidemia, and oxidative stress on diabetic encephalopathy in streptozotocin induced experimental diabetes mellitus. *Biomed Res Int.* 2014;2014:920857.
37. Moravej Aleali A, Amani R, Shahbazian H, Namjooyan F, Latifi SM, Cheraghian B. The effect of hydroalcoholic Saffron (Crocus sativus L.) extract on fasting plasma glucose, HbA1c, lipid profile, liver, and renal function tests in patients with type 2 diabetes mellitus: A randomized double-blind clinical trial. *Phytother Res.* 2019.
38. Sahraian A, Jelodar S, Javid Z, Mowla A, Ahmadzadeh L. Study the effects of saffron on depression and lipid profiles: A double blind comparative study. *Asian J Psychiatr.* 2016;22:174–176.
39. Moravej AA, Amani R, Shahbazian H, Namjooyan F, Latifi S, Cheraghian B. The effect of hydroalcoholic Saffron (Crocus sativus L.) extract on fasting plasma glucose, HbA1c, lipid profile, liver, and renal function tests in patients with type 2 diabetes mellitus: A randomized double-blind clinical trial. *Phytotherapy Research: PTR.* 2019.
40. Kermani T, Zebarjadi M, Mehrad-Majd H, et al. Anti-inflammatory effect of Crocus sativus on serum cytokine levels in subjects with metabolic syndrome: A randomized, double-blind, placebo- controlled trial. *Curr Clin Pharmacol.* 2017;12:122–126.
41. Sheng L, Qian Z, Zheng S, Xi L. Mechanism of hypolipidemic effect of crocin in rats: Crocin inhibits pancreatic lipase. *Eur J Pharmacol.* 2006;543:116–122.
42. Sahebkar A, Simental-Mendia LE, Reiner Z, et al. Effect of orlistat on plasma lipids and body weight: A systematic review and meta-analysis of 33 randomized controlled trials. *Pharmacol Res.* 2017;122:53–65.
43. Abedimanesh N, Bathaie SZ, Abedimanesh S, Motlagh B, Separham A, Ostadrahimi A. Saffron and crocin improved appetite, dietary intakes and body composition in patients with coronary artery disease. *J Cardiovasc Thorac Res.* 2017;9:200–208.
44. Luo L, Fang K, Dan X, Gu M. Crocin ameliorates hepatic steatosis through activation of AMPK signaling in db/db mice. *Lipids Health Dis.* 2019;18:11.
45. Schmidt M, Betti G, Hensel A. Saffron in phytotherapy: Pharmacology and clinical uses. *Wiener Med Wochenschr.* 2007;157:315.
46. Liu N, Yang Y, Mo S, Liao J, Jin J. Calcium antagonistic effects of Chinese crude drugs: Preliminary investigation and evaluation by 45Ca. *Appl Radiat Isot.* 2005;63:151–155.
47. Xi L, Qian Z, Xu G, et al. Beneficial impact of crocetin, a carotenoid from saffron, on insulin sensitivity in fructose-fed rats. *J Nutr Biochem.* 2007;18:64–72.
48. Yoshino F, Yoshida A, Umigai N, Kubo K, Masaichi C-i L. Crocetin reduces the oxidative stress induced reactive oxygen species in the stroke-prone spontaneously

hypertensive rats (SHRSPs) brain. *J Clin Biochem Nutr*. 2011;49:182–187.
49. Parizadeh MR, Ghafoori Gharib F, Abbaspour AR, Tavakol Afshar J, Ghayour-Mobarhan M. Effects of aqueous saffron extract on nitric oxide production by two human carcinoma cell lines: Hepatocellular carcinoma (HepG2) and laryngeal carcinoma (Hep2). *Avicenna J Phytomed.* 2011;1:43–50.
50. Dehghan F, Hajiaghaalipour F, Yusof A, et al. Saffron with resistance exercise improves diabetic parameters through the GLUT4/AMPK pathway in-vitro and in-vivo. *Sci Rep.* 2016;6:25139.
51. Kang C, Lee H, Jung E-S, et al. Saffron (Crocus sativus L.) increases glucose uptake and insulin sensitivity in muscle cells via multipathway mechanisms. *Food Chem.* 2012;135:2350–2358.