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Cardioprotective of Saffron (*Crocus sativus* L.) treatment in patients with type 2 diabetes mellitus: a systematic review and meta-analysis

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ABSTRACT

Objective To investigate the cardioprotective effect of Saffron (*Crocus sativus* L.) treatment as a potential supplement on patients with type 2 diabetes mellitus (T2DM).

Methods Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were applied to analyze articles retrieved from PubMed, ScienceDirect, Cochrane Library, Web of Science, China National Knowledge Infrastructure (CNKI), and China Biology Medicine (CBM) with a publication time span from January 15, 2015 to March 20, 2023. The articles were published in English only, including randomized controlled trials (RCTs) on adult patients who were diagnosed with T2DM, and received either Saffron or placebo treatment. Meta-analysis was performed using Review Manager 5.4 software. The present study was registered on the International Prospective Register of Systematic Reviews (PROSPERO) with a registration number as CRD42023443180.

Results Seven RCTs with 455 patients were included in the study. The data revealed that Saffron treatment significantly reduced tumor necrosis factor (TNF)-α (P = 0.008) and fasting blood glucose (FBG) (P = 0.04) levels compared with what placebo did in T2DM patients. No significant differences were shown in the levels of interleukin (IL)-6, malondialdehyde (MDA), high serum C-reactive protein (hs-CRP), lipid profile, blood pressure, and body mass index (BMI) between Saffron and placebo (P > 0.05) .

Conclusion Saffron treatment has a cardioprotective effect in T2DM patients by reducing TNF-α and FBG levels. However, the potential anti-oxidant, anti-hypertensive, and anti-dyslipidaemia effects of the phytochemical need to be further investigated.

1 Introduction

Type 2 diabetes mellitus (T2DM) is a metabolic disorder characterized by β-cell pancreatic function failure and insulin resistance. T2DM is one of the most common chronic diseases in the world. It is estimated that the incidence of diabetes will reach 300 million in 2025 [1, 2]. Based on World Health Organization (WHO) 2022 report,

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diabetes causes 2 million of deaths from non-communicable disease (NCDs) [2]. This disease's prevalence rate is now increasing in adults, children, and adolescents.

T2DM predisposes to cardiovascular diseases (CVDs) and is an equivalent risk for coronary artery disease and diabetic cardiomyopathy [3]. Impaired insulin secretion and hyperglycemia are causal risk factors for macrovascular complications in diabetic and non-diabetic patients. Insulin resistance occurs when nutrient storage pathways are exposed to chronic energy overload. Ectopic lipid accumulation in the liver and skeletal muscle triggers signaling pathways that impair insulin signaling, resulting in decreased muscle glucose uptake and reduced hepatic glycogen synthesis [4, 5]. Consequently, the pancreas pumps out more insulin to transport blood sugar into cells. Over time, cells become unresponsive to all insulin (resistance) [6]. Insulin resistance leads to a decrease in glucose-stimulated insulin secretion, resulting in the occurrence of glucose toxicity, which consequently produces and secretes pro-inflammatory cytokines, including interleukin (IL)-6 and tumour necrosis factor (TNF)-α, especially in pancreatic β cells and cardiac muscle cells (cardiomyocytes) [4]. Pro-inflammatory cytokines can activate life-threatening cellular signaling pathways, including thrombosis, the induction of adhesion molecules, and recruitment of neutrophils, which subsequently result in the occlusion of blood vessels, ultimately leading to conditions such as myocardial infarction, apoptosis or tissue necrosis [5, 6]. In addition, T2DM patients commonly exhibit obesity and dyslipidemia, contributing to the increasing of atherogenesis and atherosclerosis. Inflammation also affects the endothelium through mitochondrial dysfunction and endothelial nitric oxide synthase (eNOS) secretion, affecting vascular relaxation and causing arterial stiffness. Because this stage of inflammation was chronic, angiotensin II (Ang II) consistently increased in blood pressure [6]. Insulin and oral antidiabetic drugs are essential for managing T2DM, but complications including congestive heart failure, coronary heart disease, cardiomyopathy, and peripheral arterial disease have been persistently reported. Due to the high prevalence of diabetes and its complications, health providers are looking for supplementation and/or phytochemical treatments, such as Saffron (*Crocus sativus* L.) [7].

Saffron has been used worldwide as a traditional spice or food coloring. Since ancient times, people have believed the health benefits of Saffron, and recently this plant has begun to be widely studied for the identification of its beneficial properties and mechanisms. Saffron contains four main primary metabolites, encompassing picrocrocin, crocin, as well as safranal and crocetin [8], and also some secondary metabolites such as carotenoids, monoterpenes, and flavonoids. In T2DM patients, Saffron treatment demonstrated a robust improvement in glucose uptake, accompanied by enhanced phosphorylation of adenosine monophosphate-activated protein kinase (AMPK) and glucose transporter 4 (GLUT4). It also significantly reduced the blood hemoglobin A1c (HbA1c) levels and markedly elevated insulin levels in the blood of diabetic rats [7]. Building on prior evidence, Saffron can reduce the production of pro-inflammatory proteins such as TNF-α, IL-1β, and IL-6 both *in vitro* and *in vivo,* and has shown cardioprotective effects such as antihypertensive, anti-ischemic, hypolipidemic, anti-oxidant, and anti-inflammatory properties [9, 10].

Although Saffron has been reported to be beneficial, its actual dosage for T2DM patients is still arguable in comparison with placebo. The cardioprotective effects of Saffron and its constituents, particularly crocin, have been investigated in several clinical trials [9]. However, only a handful of studies have been conducted on the cardioprotective effects of Saffron with T2DM patients as the subjects, with inconclusive and arguable findings produced. Among the handful studies, some of them were carried out using data only from a single center, with a relatively small sample size. Hence, this meta-analysis study was designed to determine the cardioprotective effect of Saffron vs. placebo as a supplementing treatment for T2DM patients to hopefully provide evidence for clinicians on the use of Saffron treatment in T2DM patients.

2 Data and methods

A systematic review of the literature and subsequent meta-analysis were performed in adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [11]. To increase the transparency of the research process and mitigate the risk of errors in reports, this study was registered on the International Prospective Register of Systematic Reviews (PROSPERO) [12], under the registration number CRD42023443180.

2.1 Literature retrieval and screening

Databases such as PubMed, ScienceDirect, Cochrane Library, Web of Science, China National Knowledge Infrastructure (CNKI), and China Biology Medicine (CBM) were searched exhaustively to collect data. The Medical Subject Headings (MeSH)-registered terms were used as part of the search strategy in PubMed, with the following searching terms and formula applied as well, such as "Saffron" or "crocus sativus" or "crocin" or "safranal", and "cardioprotective" or "cardiovascular disease(s)" and "type 2 diabetes mellitus" and "randomized control trials". Articles about randomized control trials (RCTs) published in English from January 15, 2015 to March 20, 2023 were also included.

To enhance search sensitivity, the articles listed in the

selected references were checked reversely (meaning citation tracking). Two reviewers of the study worked independently on reviewing all titles, abstracts, and journal information of the articles. A systematic review was subsequently conducted using several articles that met the inclusion criteria, and separately assessed based on their full text. In the screening process, articles with irrelevant titles and abstracts were excluded. Duplicate papers in different databases were removed to remain only one by cross checking. The full text of the articles that met the inclusion criteria were read for extracting useful information. In case of disagreements between the two independent reviewers regarding inclusion or exclusion, final decisions were made by a third reviewer, adhering to the predetermined inclusion and exclusion criteria mentioned earlier.

2.2 Inclusion and exclusion criteria

Papers were included if they (i) were about RCTs; (ii) were published in English; (iii) compared Saffron with placebo; (iv) enrolled subjects aged between 18 and 55; (v) examined patients whose T2DM were confirmed using HbA1c and/or fasting blood glucose (FBG) parameters; (vi) reported changes in any of the following parameters, such as IL-6, TNF-α, malondialdehyde (MDA), high serum C-reactive protein (hs-CRP), lipid profile low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides (TG), total cholesterol (TC), systolic blood pressure (SBP), diastolic blood pressure (DBP), body mass index (BMI), and FBG.

Papers were excluded if they (i) exhibited unclear primary outcomes that were mentioned in the inclusion criteria, or even not reported them at all, or insufficient data in their full text; (ii) demonstrated unextractable or incalculable data, such as images or graphics without mean and standard deviation details; (iii) showed conflicts of interest; (iv) were about non-RCTs or unpublished studies; (v) investigated drugs in addition to Saffron in the experimental group; (vi) only included an abstract or table of contents.

2.3 Outcomes and study quality

The inflammatory markers such as TNF-α and IL-6, oxidant markers such as MDA and hs-CRP, and lipid profiles such as TG, LDL, HDL, TC, SBP, DBP, FBG, and BMI, were assessed. Jadad score was used to assess the quality of the RCTs, with a scale ranging from 0 to 5. Studies with scores higher than 4 were classified as high-quality and included in the meta-analysis; those with scores ranging between 3 and 4 were considered moderate in quality; those with scores below 3 were categorized as low-quality and excluded from the meta-analysis [13]. The level of evidence for each study was assessed using the Oxford Center for Evidence-Based Medicine. If a study held a level of 1b (individual RCT with narrow confidence intervals) with a recommendation grade of A (strong recommendation), it was considered for inclusion [14].

2.4 Statistical analysis

The statistical analysis was performed with the use of Review Manager version 5.4. For each parameter, the choice of statistical analysis method relied on the nature of data [15]. The odd ratio (OR) was employed when dealing with dichotomous or categorical data, whereas mean difference (MD) with a 95% confidence interval (CI) was used for continuous data. The Cochrane Chi-square test and inconsistency (I^2) were for heterogeneity examination between the studies. $P < 0.05$ was considered statistically significant. Heterogeneity, measured by I^2, was observed in a range from 0% to 100%, with classifications of low for $I^2 < 25\%$, modest for 25% – 50%, and large for > 50%. Heterogeneity was significant when $I^2 > 50\%$, and a sensitivity analysis was conducted to detect the influence of individual studies on the overall estimate [16]. This involved systematically excluding one study at a time, and then repeating the analysis to assess the robustness of the results. If the included research demonstrated homogeneity, the fixed-effect model would be employed. Conversely, if heterogeneity were observed, the random-effect model would be employed [17].

3 Results

3.1 Baseline characteristic

A total of 57 articles were retrieved. Among them, 9 were identified in Cochrane, 28 in ScienceDirect, 14 in PubMed, 2 in Web of Science, 1 in CBM, and 3 in CNKI. A total of 16 articles were removed for duplication and another 32 articles were excluded because they were reviews (8 articles), clinical trials (9 articles), irrelevant study design (14 articles), and consist of abstract only (1 article). In addition, two articles were removed because the data could not be analyzed. Furthermore, additional one article was identified through citation searches but was subsequently excluded because it did not meet eligibility requirements. Finally, seven articles were obtained in the end (Figure 1).

The studies consisted of 455 patients in the two groups, with 229 in the Saffron group and 226 in the placebo group. Table 1 shows the characteristics of the included studies. The evidence base level was 1b for RCTs with a recommendation grade of A for all seven articles [14]; all studies were regarded as high-quality, with Jadad scores between 4 and 5 (Table 2).

3.2 Effects of Saffron on pro-inflammatory cytokines

3.2.1 TNF-α The reduction in TNF-α levels in T2DM patients was evaluated in three articles [3, 18, 19]. Saffron

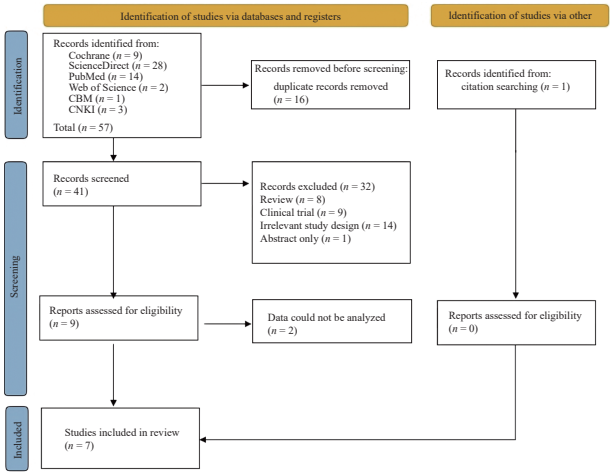

Figure 1 PRISMA flow chart of the record screening process for articles

treatment significantly reduced TNF-α levels (MD = – 0.75; 95% CI, – 1.30 to – 0.19; P = 0.008). Heterogeneity in the study groups were moderate (I^2 = 66%). The data distribution is shown in Figure 2.

3.2.2 IL-6 Three articles [3, 18, 19] involving 84 samples in the Saffron treatment group and 81 in the placebo group reported a decrease in IL-6 levels in T2DM patients. The analysis indicated that Saffron treatment did not significantly reduce IL-6 levels (MD = – 0.10; 95% CI, – 0.40 to 0.21; P = 0.54). Moderate heterogeneity was observed (I^2 = 57%), suggesting a moderate level of variability in the data (Figure 3).

3.3 Effects of Saffron on anti-oxidant levels

3.3.1 MDA Decreased MDA levels were observed in three studies [3, 4, 19]. As depicted in Figure 4, the reduction in MDA levels in T2DM patients undergoing Saffron treatment was found to be statistically insignificant (MD = 0.01; 95% CI, – 0.28 to 0.30; P = 0.95). Low heterogeneity was identified (I^2 = 18%), indicating low variability in the data.

3.3.2 Hs-CRP In three studies [3, 4, 19], researchers reported reduced hs-CRP levels in T2DM patients (Figure 5), yet no significant difference was observed (MD = 0.03; 95% CI, – 0.54 to 0.60; P = 0.91). Large heterogeneity was identified (I^2 = 73%) in T2DM patients treated with Saffron vs. placebo, indicating large variability in the data. SHAHBAZIAN et al. [3] reported the highest heterogeneity in

Table 1 Characteristics and quality and articles of included studies

Study	Intervention	Preparation and dosage	Mean age (years)	Study design	LE	Jadad score	Follow-up time	Case (n)	
								Saffron	Placebo
MOBASSERI M, 2020 [18]	Saffron	Powder 100 mg/d, QD	50.57 ± 9.88	RCT	1b	5	8 weeks	30	27
	Placebo	Capsule (starch) 1 capsule, QD	51.63 ± 11.30						
BEHROUZ V, 2021 [19]	Saffron	Tablet (extract of Saffron) 15 mg/d, BID	57.08 ± 7.41	RCT	1b	5	12 weeks	22	22
	Placebo	Tablet (starch) 1 tablet, BID	59.86 ± 9.46						
MORAVEJ ALEALI A, 2019 [20]	Saffron	Capsule (extract of Saffron) 15 mg/d, BID	53.50 ± 9.90	RCT	1b	5	3 months	38	38
	Placebo	Capsule (lactose, magnesium stearate, & starch) 1 capsule, BID	52.40 ± 13.00						
EBRAHIMI F, 2019 (A) [4]	Saffron	Tablet (Saffron) 100 mg/d, QD	55.20 ± 7.30	RCT	1b	5	12 weeks	40	40
	Placebo	Maltodextrin	53.00 ± 10.60						
EBRAHIMI F, 2019 (B) [21]	Saffron	Powder (Saffron) 100 mg/d, QD	55.20 ± 7.30	RCT	1b	4	12 weeks	40	40
	Placebo	Powder (maltodextrin)	53.00 ± 10.60						
MILAJERDI A, 2017 [7]	Saffron	Capsule (extract of Saffron) 30 mg/d, QD	54.57 ± 6.96	RCT	1b	4	8 weeks	27	27
	Placebo	Capsule (starch, lactose, magnesium stearate, gelatin, & Saffron essence) 1 capsule, BID	55.42 ± 7.58						
SHAHBAZIAN H, 2019 [3]	Saffron	Capsule (extract of Saffron) 30 mg/d, QD	53.50 ± 9.90	RCT	1b	5	3 months	32	32
	Placebo	Capsule (lactose, magnesium stearate and starch) 1 capsule, BID	52.40 ± 13.00						

LE, level of evidence base. 1b, level of evidence RCTs. BID, take the medication twice a day. QD, take the medication once a day.

Table 2 Jadad scores of the included studies

Study	Randomization	Blinding	Withdrawal	Jadad score
MOBASSERI M, 2020 [18]	2	2	1	5
BEHROUZ V, 2021 [19]	2	2	1	5
MORAVEJ ALEALI A, 2018 [20]	2	2	1	5
EBRAHIMI F, 2019 (A) [4]	2	2	0	4
EBRAHIMI F, 2019 (B) [21]	2	2	1	5
MILAJERDI A, 2017 [7]	2	2	0	4
SHAHBAZIAN H, 2019 [3]	2	2	1	5

Randomization: 1 point, and additional 1 point would be given if the randomization method was appropriate (e.g. computer generated). Blinding: 1 point, and additional 1 point would be given if the blinding method was appropriate (e.g. indentical placebo). Withdrawal: 0 was the score point for studies that did not meet the Jadad score criteria, and additional 1 point would be given if the number of withdrawal was clear and the reasons stated.

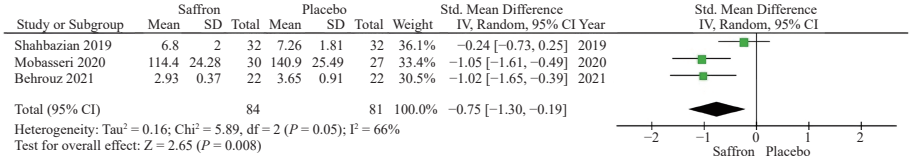

Figure 2 Forest plot of effect of Saffron on TNF-α

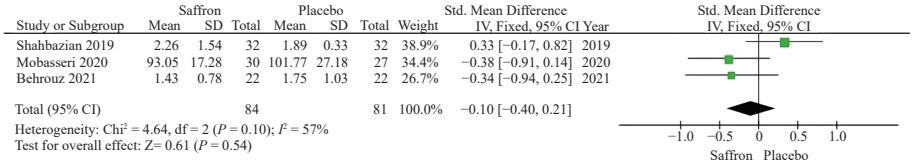

Figure 3 Forest plot of effect of Saffron on IL-6

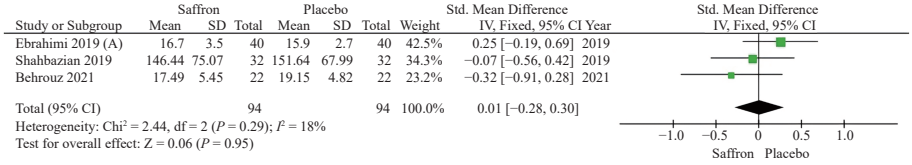

Figure 4 Forest plot of effect of Saffron on MDA

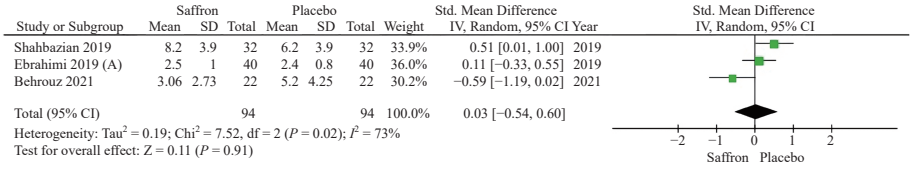

Figure 5 Forest plot of effect of Saffron on hs-CRP

comparison within the Saffron group, and a similar observation presented in the placebo group.

3.4 Effects of Saffron on lipid profile

An analysis of lipid profile levels, TG, HDL, LDL, and TC, was carried out (Table 3). It has been reported that Saffron treatment for T2DM patients is statistically insignificant in reducing LDL, TG, and TC levels, and also statistically insignificant in increasing HDL ($P > 0.05$). Heterogeneity was found only in the TG and HDL levels, with $I^2 = 82\%$, suggesting high variability in the TG and HDL levels, while in LDL level, low heterogeneity was observed ($I^2 = 0\%$), indicating consistent effectiveness of Saffron in reducing LDL across all studies.

3.5 Effect of Saffron on blood pressure

Four articles [3, 18, 20, 21] reported SBP and DBP. Based on pooled analysis, Saffron treatment was not found to have significantly reduced blood pressure; both SBP (MD = 0.74; 95% CI, – 4.54 to 6.02; $P = 0.78$) and DBP (MD = 3.71; 95% CI, – 3.82 to 11.24; $P = 0.33$) demonstrated large heterogeneity (I^2 = 74% and 66%, respectively), meaning large variability in the data (Figure 6).

Table 3 Summarized pooled analysis of lipid profile

Lipid profile	Sample size		Sum of study	Pooled MD (inverse variance)	*P* value	I^2 (%)	Favour
	Saffron	Placebo					
LDL	104	104	3	MD – 7.93; 95% CI, – 24.90 to 9.03	0.36	0	Saffron
TG	105	107	3	MD – 2.32; 95% CI, – 7.76 to 3.12	0.40	82	Saffron
HDL	105	105	3	MD – 2.32; 95% CI, – 7.76 to 3.12	0.40	82	Saffron
TC	105	105	3	MD 0.12; 95% CI, – 0.15 to 0.39	0.38	46	Placebo

LDL, low density lipoprotein. TG, triglyceride. HDL, high density lipoprotein. TC, total cholesterol. MD, mean difference. I^2, heterogeneity.

3.6 Effect of Saffron on FBG

Decreased FBG levels were observed in three studies [3, 7, 20]. The decrease in FBG levels in T2DM patients receiving Saffron treatment was found to be statistically significant (MD = – 16.01; 95% CI, – 31.22 to – 0.81; $P = 0.04$). No difference in heterogeneity was observed ($I^2 = 0\%$) (Figure 7), indicating consistent effectiveness of Saffron in reducing FBG across all studies.

3.7 Effect of Saffron on BMI

Five articles [4, 7, 18, 20, 21] reported statistically insignificant BMI (MD = 0.86; 95% CI, – 1.09 to 2.81; $P = 0.39$). No differences were observed in heterogeneity ($I^2 = 0\%$), suggesting consistent effectiveness of Saffron for BMI across all studies (Figure 8).

3.8 Sensitivity analysis

A pre-defined subgroup analysis became necessary to identify the source of heterogeneity. If statistical heterogeneity ($I^2 > 50\%$ or $P < 0.10$) was identified, the samples would be segmented based on predetermined subgroup criteria, and the meta-analysis rerun to calculate the effect values for each subgroup.

Sensitivity analysis was conducted by systematically removing each RCTs one by one to estimate the

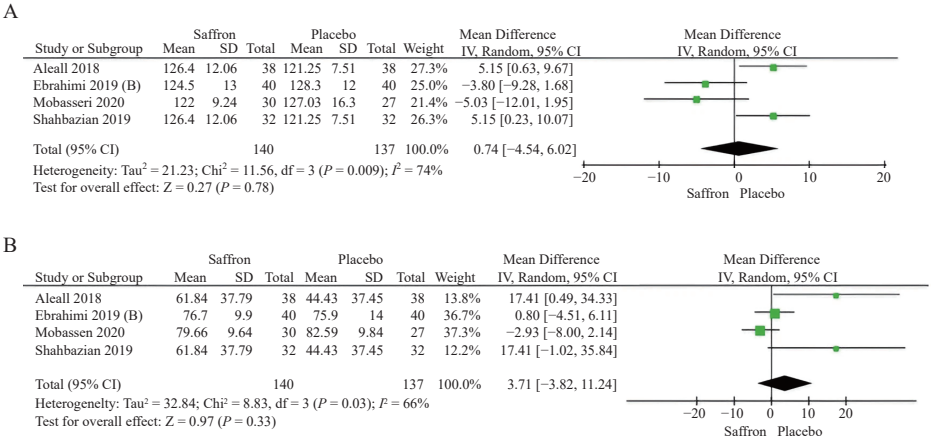

Figure 6 Forest plots of effects of Saffron on SBP (A) and DBP (B)

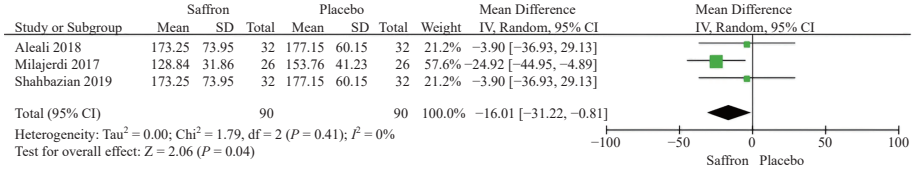

Figure 7 Forest plot of effect of Saffron on FBG

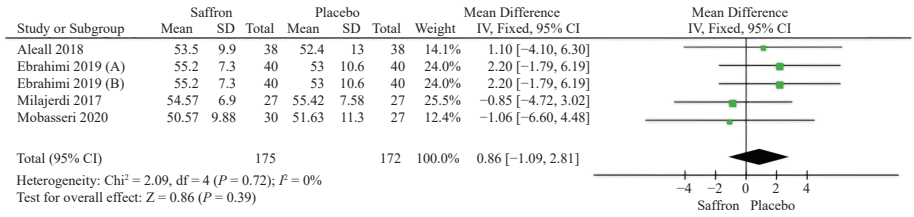

Figure 8 Forest plot of effect of Saffron on BMI

effectiveness of individual studies on the pooled effect size [17]. The sensitivity analysis results revealed that, after excluding the study by SHAHBAZIAN et al. [3], the IL-6 result became significant (MD = – 0.37; 95% CI, – 0.76 to 0.03; P = 0.07; I^2 = 0%), and there was a reduction in heterogeneity in TNF-α, with significant result remained (MD = – 1.04; 95% CI, – 1.45 to – 0.62; P < 0.000 01; I^2 = 0%). This suggests that the inclusion of SHAHBAZIAN's study may have influenced the overall findings, and its exclusion led to changes in significance and hetergeneity of the outcomes. In addition, after excluding the studies by MORAVEJ ALEALI et al. [20] and SHAHBAZIAN et al. [3], the pooled effect for SBP (MD = – 4.27; 95% CI, – 8.58 to 0.04; P = 0.05; I^2 = 0%) changed to be significant, and a reduction was observed in the heterogeneity in DBP (MD = – 1.15; 95% CI, – 4.82 to 2.51; P = 0.54; I^2 = 0%), with insignificant result remained. The observed heterogeneity may stem from factors such as insufficient sample sizes or variation in methods/interventions in the included articles.

3.9 Publication bias in the studies

No publication bias was observed via Egger's test in TNF-α (P = 0.05), IL-6 (P = 0.10), MDA (P = 0.29), LDL (P = 0.61), TG (P = 0.61), TC (P = 0.13), FBG (P = 0.41), or BMI (P = 0.72). However, biased data were found in the hs-CRP (P = 0.02), HDL (P = 0.04), SBP (P = 0.009), and DBP (P = 0.03) parameters. All parameters showed symmetrical funnel plots, indicating low heterogeneity (Figure 9). Nonetheless, it's essential to consider that variations in interventions, drug preparation, and time variation in follow-up could contribute to increased heterogeneity in studies.

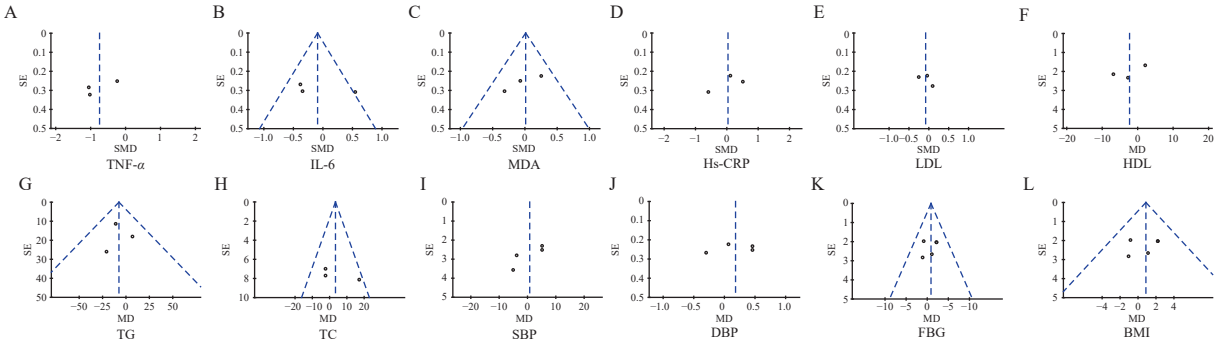

Figure 9 Funnel plots of publication bias in the studies reporting effects of Saffron

A, TNF-α. B, IL-6, C, MDA. D, hs-CRP. E, LDL. F, HDL. G, TG. H, TC. I, SBP. J, DBP. K, FBG. L, BMI. SE, standard error. MD, mean difference. SMD, standardized mean difference.

4 Discussion

T2DM together with dyslipidemia and hypertension create an imbalance in the body's anti-inflammatory and anti-oxidant levels, thereby escalating the risk of developing CVDs, such as congestive heart failure, coronary heart disease, cardiomyopathy, stroke, and peripheral arterial disease [22, 23]. This meta-analysis study represents the first comprehensive summary of clinical evidence from seven RCTs aiming to determine the cardioprotective role of Saffron treatment compared with placebo in T2DM patients.

4.1 Anti-inflammatory activity of Saffron in T2DM patients

From this meta-analysis, Saffron treatment demonstrated a significant reduction in TNF-α levels, while there was no significant effect in IL-6 and hs-CRP. These results aligned with previous studies that suggested Saffron intervention led to a reduction in TNF-α levels, yet did not show significant effects on IL-6 and hs-CRP [24]. Another conflicting study suggested that Saffron supplementation was not proven to significantly decrease the levels of the three inflammatory markers, hs-CRP, TNF-α, and IL-6, in T2DM patients [1, 4, 9]. The significant reduction could be attributed to higher threshold values (TNF-α $\geqslant$ 15 pg/mL and hs-CRP $\geqslant$ 3 mg/L) coupled with lower supplementation doses ($\leqslant$ 30 mg/d) [1]. This insignificant result might be a consequence of a relatively small sample size. The limited number of trials in association with Saffron on IL-6 and hs-CRP levels has hindered the application of subgroup analysis on IL-6 and hs-CRP. A moderate heterogeneity in the study data might be attributed to the differences in drug preparation (capsule/tablet/powder), duration of intervention, and time variation in follow-ups.

High threshold for inflammatory biomarkers heighten the sensitivity of cytokines to anti-oxidants [25]. T2DM is associated with subclinical systemic inflammation due to the increased levels of pro-inflammatory cytokines such as IL-6, hs-CRP, and TNF-α. These cytokines are implicated in insulin resistance alnd endothelial dysfunction [3, 26]. T2DM, insulin resistance, and atherosclerosis are all

characterized by chronic inflammation. The pro-inflammatory cytokine TNF-α plays a pivotal role as a key mediator in the pathophysiology of these interconnected conditions. TNF-α can activate macrophages within intact pancreatic islets, leading to the secretion of IL-1β. This mechanism may contribute to the cytotoxic effects on β cells induced by TNF-α. TNF-α disrupts the phosphorylation cascades of the insulin receptor β and insulin receptor substrate-1, thereby modifying the transmembrane signaling pathways crucial for insulin action in various insulin-sensitive tissues [22, 23]. TNF-α also activates nuclear factor kappa B (NF-κB) and induces apoptotic cell death. These findings suggest that reducing TNF-α levels could be a potential therapeutic approach for treating T2DM. TNF-α antagonists have also been associalted with a reduced risk of myocalrdial infarction and the development of acute coronary syndromes [26, 27]. Saffron contains potential bioactive components such as flavonoids, tannins, anthocyanins, alkaloids, and saponins, contributing to its anti-inflammatory effects on rats [9, 28]. Therefore it would be favorable for diabetes treatment if anti-diabetic agents also exhibit anti-TNF-α activities. In addition, Saffron also down-regulates pro-inflammatory markers and enzymes such as interferon gamma (IFN-g), NF-κB, inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), myeloperoxidase (MPO), prostanoids, and phospholipase A2 [1, 29].

4.2 Anti-oxidant activity of Saffron in T2DM patients

Oxidative stress causes damage to lipids, proteins, and DNA, and is also associated with various pathological conditions. Among the highly oxidative products are reactive oxygen species (ROS) and MDA [30, 31]. The results of our study found that Saffron supplementation was not suggested to have significantly reduced MDA levels in T2DM patients compared with patients receiving placebo. These results align with previous studies, indicating that daily crocin/Saffron supplementation for T2DM patients did not affect plasma MDA levels, a marker of oxidative stress [3, 19, 32]. However, contradictory findings exist, as other studies indicated that Saffron could indeed reduce serum MDA levels in both humans and experimental animals [1, 9, 33]. In a study by EBRAHIMI et al. [4], MDA was significantly reduced compared with baseline values but did not reach statistical significance when compared with the placebo group. Several potential reasons might account for the failure to achieve significant changes in MDA levels, including low supplementation doses, initially low MDA levels in subjects, a brief duration of intervention, a limited number of samples, and homogeneity in the origin of the articles. Additionally, various confounding factors such as smoking habits, physical activity, and diet could also contribute to these outcomes [4, 19]. It is important to note that while certain positive effects of Saffron on anti-oxidant status have been confirmed through *in vitro* or *in vivo* animal studies, the extent to which these effects are replicated in humans remains uncertain. The mechanism by which Saffron influences oxidative stress is associated with increased glutathione reductase levels [1, 9]. *In vitro* studies suggested that crocetin reduced ROS levels, mitigated free radical-mediated lipid peroxidation, and enhanced radical scavenging activity [9, 33].

4.3 Anti-hyperlipidemia effect of Saffron in T2DM patients

The findings of our study demonstrated that Saffron supplementation did not significantly impact the reduction of LDL, TG, and TC levels, nor did it show a notable increase in HDL among T2DM patients. These results conformed to previous research findings, indicating that Saffron supplementation was unable to reduce lipid profiles [1, 34, 35]. However, a significant decrease in cholesterol deposits within atherosclerotic lesions, foam cells, aortal, and atheroma was observed in the treatment group in this study [36, 37]. It was reported that TG, TC, and LDL levels were markedly reduced without observed increase in HDL level after Saffron supplementation. SADIGI et al. [38] in 2019 also reported similar results concerning LDL, TG, and TC levels, with significant findings observed for HDL levels [25]. In contrast to our findings, several animal demonstrated significant reductions in blood lipids. The doses prescribed in these studies were notably higher than those used in most clinical trials, ranging between 25 and 100 mg/kg [1]. These results may explain the absence of the hypolipidemic effect of Saffron in human subjects. The doses of Saffron used in animal studies, where a significant decrease in blood lipids was observed, were substantially higher than those included in the RCTs. A significant decrease in LDL, TG, and TC levels would likely be observed in individuals with BMI $\geqslant$ 30 (obese) [36]. The mechalnism by which Saffron can reduce blood lipids in animal models involves inhibiting lymphatic cholesterol absorption and acting as competitive inhibitor for pancreatic lipase activity [20, 39]. Plasma LDL level is also correlated with a broader pulse pressure and blood pressure. By regulating cholesterol levels, blood pressure is indirectly controlled [40].

4.4 Anti-hypertension effect of Saffron in T2DM patients

Based on SBP and DBP values, it was revealed that Saffron supplementation was ineffective in significantly reducing blood pressure. These results were consistent with studies by MILAJERDI et al. [7] and ZAMANI et al. [1], which similarly reported that Saffron administration did not result in a statistically significant difference in blood

pressure. However, an increase in SBP and DBP was observed during the intervention. AZIMI et al. [9] also reported that three cups of Saffron tea (equivalent to 1 g of Saffron) over eight weeks had no significant influence on blood pressure in T2DM patients. In animal models, a five-week administration of Saffron with three doses of aqueous extract [10, 20, and 40 mg/(kg·d)] did not alter blood pressure in normotensive rats. Meanwhile, other contradictory studies suggested that the administration of high dose of Saffron (400 mg) was able to reduce SBP and MAP [4, 27]. However, this study did not reveal any significant difference in disease progression compared with patients undergoing standard therapy [27]. These contrasting results may be attributed to the use of different doses, varying crocin content in the supplements administered, distinct thresholds, and differences in the duration of follow-up evaluation. Today, the specific mechanism that explains the effect of Saffron on blood pressure is still unknown. However, the significant effect of supplementation may be explalined by the high content of crocetin, which can reduce the expression of soluble intercellular adhesion molecule-1 (sICAM-1) and potentialy lower arterial stiffness and blood pressure [41, 42].

4.5 Anti-hyperglycemic effect of Saffron in T2DM patients

In our analysis, it was evident that Saffron significantly reduced FBG levels. These results indicated a hypoglycemic effect of Saffron supplementation, aligning with MILAJERDI et al. [7], where FBG decreased in the Saffron treatment group ($P < 0.000\ 1$). Furthermore, according to AZIMI et al. [9], after eight weeks of giving Saffron tea to T2DM patients, their FBG concentrations weren't significantly affected. There are several mechanisms through which Saffron can play a role in glycemic control, including the reduction of FBG. These mechanisms involve inhibiting glucose re-absorption in the kidneys, diminishing insulin resistance through the stimulation and regeneration of β cells in the islets of Langerhans, and enhancing glucose uptake and insulin sensitivity in skeletal muscle cells. These effects are mediated by mitogen-activated protein kinases (MAPKs) and adenosine monophosphate-activated protein kinase/acetyl-CoA carboxylase (AMPK/ACC) pathways [7]. Glycemic control refers to maintaining optimal serum glucose concentration in diabetic patients. It is imperative to uphold glycemic control for the prevention of complications. Inadequate glycemic control led to uncontrolled diabetes, which resulted in various complications associated with diabetes mellitus [4, 7].

4.6 Effect of Saffron on BMI in T2DM patients

Our study demonstrated that Saffron supplementation was insignificant in mitigating BMI. These results were consistent with previous studies that suggest Saffron consumption did not significantly improve BMI, fasting insulin, lipid profile, and SBP [35]. One possible explanation for the insignificance of our results could be that much of the evidence with satisfactory outcomes was derived from animal studies, which might not provide conclusive evidence of causal effects in human subjects. Furthermore, only a limited number of studies from clinical trials or supported by evidence from RCTs in humans had demonstrable clinical applications. In addition, the mechanisms of action for the therapeutic effects of Saffron were diverse. Saffron components could inhibit the activity of pancreatic lipase and reduce fat absorption. They could also increase lipolysis, energy expenditure, and fat metabolism [30]. Possibly through the following mechanisms, Saffron could affect fat mass and reduce abdominal obesity, thereby addressing risk factors for cardiovascular disease that could be detected in healthy young generation. Engaging in daily physical activity and maintaining a healthy and consistent diet could help reduce risk factors for cardiovascular disease [43-46].

However, there were several limitations to the study. First, all the included studies were focused on Mongoloid ethnicity (native to the Asian region), and the age groups were arguably similar among the studies. The Saffron preparations used varied, as explained in the discussion, although efforts were made to minimize potential bias. We exclusively included RCTs, while various measurements were conducted to ensure quality and minimize potential biases. It was important to note that certain factors such as comorbidities, the treatment of each comorbidity, genetic factors, and socio-demography factor (other than sex and age) could still pose potential influences. Second, our inclusion criteria were limited to studies with sufficient data. The absence of data in some of the included studies, including other specific cardio-parameters such as heart rate, electrocardiogram, troponin, B-type natriuretic peptide (BNP), cardiac index, and ejection fraction, limited the quantitative synthesis of our data. Third, the lack of research on Saffron, differences in drug preparation, duration of intervention, and time variation in follow-up might result in heterogeneity. Statistical heterogeneity in our study was inevitable, and it did not necessarily render our study unacceptable. The observed heterogeneity in our study indicated variability in the data. Identifying several methodological gaps in the included study with the use of Jadad score provided valuable insights for future RCTs. However, to the best of our knowledge, this article represented one of the initial attempts to assess the potential cardioprotective effect of Saffron treatment for the underlying disease. Hence, extensive follow-up investigations are necessary to evaluate other cardio-specific parameters with larger samples, a broader range of dose, and varying intervals of time.

5 Conclusion

From this systematic review and meta-analysis, it is evident that Saffron extract supplementation can significantly decrease FBG and TNF-α levels in T2DM patients when compared with those receiving placebo. This finding highlights the antihyperglycemic and anti-inflammatory effects of Saffron extract, which may be beneficial in mitigating damage to cardiac tissue in these patients.

Competing interests

The authors declare no conflict of interest.

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藏红花对 2 型糖尿病患者的心脏保护作用：一项系统综述和 meta 分析

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【摘要】目的 探讨藏红花作为潜在补充剂在 2 型糖尿病患者治疗过程中的心脏保护作用。**方法** 应用系统综述和 meta 分析优先报告条目（PRISMA）指南对 PubMed、ScienceDirect、Cochrane Library、Web of Science、中国知网（CNKI）和中国生物医学文献数据库（CBM）检索到的文章进行分析，发表时间跨度为 2015 年 1 月 15 日至 2023 年 3 月 20 日。本研究仅纳入英文随机对照试验（RCTs）文献，研究对象为接受藏红花或安慰剂治疗 2 型糖尿病的成年患者。采用 Review Manager 5.4 软件进行 meta 分析。本研究在国际前瞻性系统综述注册数据库（PROSPERO）中注册，注册号为 CRD42023443180。**结果** 本研究纳入了 7 项 RCTs，包括 455 例患者。数据显示，与安慰剂相比，藏红花治疗显著降低了 2 型糖尿病患者的肿瘤坏死因子（TNF-α, $P = 0.008$）和空腹血糖（FBG，$P = 0.04$）水平。藏红花与安慰剂的白细胞介素 6（IL-6）、丙二醛（MDA）、高血清 C 反应蛋白（hs-CRP）、血脂、血压和体重指数水平（BMI）差异均无统计学意义（$P > 0.05$）。**结论** 藏红花治疗通过降低肿瘤坏死因子和空腹血糖水平对 2 型糖尿病患者具有心脏保护作用。然而，这种植物化学物质的潜在抗氧化、抗高血压和抗血脂异常作用有待进一步研究。

【关键词】藏红花；藏红花素；炎性细胞因子；meta 分析；系统综述；2 型糖尿病；心血管疾病