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Effects of Saffron Supplementation on Glycolipid Metabolism and Blood Pressure in Patients With Metabolic Syndrome and Related Disorders: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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ABSTRACT

Saffron is a traditional herbal medicine used to treat conditions associated with metabolic syndrome (MetS). However, the conclusions of relevant clinical studies have been inconsistent. This study aimed to assess the impact of saffron supplementation on the metabolism of glycolipids and blood pressure in individuals with MetS and related disorders. Web of Science, PubMed, Cochrane Library, Scopus, and Embase were comprehensively searched for studies investigating saffron supplementation for MetS and related disorders up to February 2024. Stata 17.0 was used to conduct the Meta-analysis. Twenty-five randomized controlled trials (RCTs) were included in this study, involving 1486 participants with MetS and related conditions. Compared to placebo, saffron supplementation triggered significant reductions in fasting blood glucose (FBG) (WMD: −6.67 mg/dL; 95% CI: −10.55, −2.78; $p = 0.001$; $I^2 = 50.0\%$), glycosylated hemoglobin A1c (HbA1c) (WMD: −0.25%; 95% CI: −0.35, −0.14; $p < 0.001$; $I^2 = 0.0\%$), total cholesterol (TC) (WMD: −4.77 mg/dL; 95% CI: −8.83, −0.71; $p = 0.021$; $I^2 = 31.8\%$), systolic blood pressure (SBP) (WMD: −1.15 mmHg; 95% CI: −1.66, −0.64; $p < 0.001$; $I^2 = 41.8\%$), and diastolic blood pressure (DBP) (WMD: −1.61 mmHg; 95% CI: −1.88, −1.34; $p < 0.001$; $I^2 = 7.0\%$). However, no significant changes were observed for homeostatic model assessment for insulin resistance (HOMA-IR), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), body mass index (BMI), and waist circumference (WC). Saffron supplementation has an improving effect on FBG, HbA1c, TC, DBP, and SBP in patients with MetS and related disorders. Nonetheless, additional high-quality RCTs involving diverse ethnic populations are necessary to validate this effect.

1 | Introduction

Metabolic syndrome (MetS) is a condition characterized by a group of clinical symptoms, such as insulin resistance, hyperglycemia, hyperlipidemia, hypertension, and obesity (Engin 2017). The assessment and diagnosis of Mets by international organizations is primarily based on the presence of five indicators: (a) central obesity with increased waist

Abbreviations: BMI, body mass index; CI, confidence interval; DBP, diastolic blood pressure; FBG, fasting blood glucose; HbA1c, glycosylated hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment for insulin resistance; LDL-C, low-density lipoprotein cholesterol; MetS, metabolic syndrome; NAFLD, non-alcoholic fatty liver disease; RCTs, randomized controlled trials; SBP, systolic blood pressure; SD, standard deviation; SE, standard error; T2DM, type 2 diabetes mellitus; TC, total cholesterol; TG, triglyceride; WC, waist circumference; WMD, weighted mean difference.

circumference (WC) and body mass index (BMI), (b) high fasting blood glucose (FBG) levels, (c) high blood pressure, (d) a low level of high-density lipoprotein cholesterol (HDL-C), and (e) high triglyceride (TG) levels (Z. Lin and Sun 2024). MetS significantly increases the risk of developing type 2 diabetes mellitus (T2DM), chronic kidney disease, and cardiovascular disease (CVD) (Bovolini et al. 2021). Although the pathophysiological mechanisms of the MetS are not fully elucidated, neurohormonal activation, chronic inflammation, and insulin resistance are considered important players in the progression of MetS and its subsequent transition to T2DM and CVD (Fahed et al. 2022). The global prevalence of MetS has been estimated to range from 12.5% to 31.4%, with estimates varying based on diagnostic criteria (Noubiap et al. 2022). MetS impacts approximately 20% of the US population and around 25% in Europe (Rochlani et al. 2017). Treatment of MetS is mainly based on a combination of lifestyle changes and pharmacological interventions (Rochlani et al. 2017). However, pharmaceutical drugs are frequently costly, exhibit poor patient compliance, and are associated with a multitude of adverse effects upon prolonged administration (Nyakudya et al. 2020). Therefore, there is a need to explore safe and effective complementary and alternative therapies for managing MetS. Herbal therapies play an important role in treating MetS as a complementary and alternative approach (Abdulghani and Al-Fayyadh 2024). As a traditional herb, saffron has been shown to possess the potential to treat MetS (Marrone et al. 2024).

As a functional food and spice, saffron (*Crocus sativus* L.) is widely utilized in Indian, European, Arab, and Central Asian cuisines (Butnariu et al. 2022; Maqbool et al. 2022). The traditional medicine systems of various nations employ saffron extensively for treating multiple diseases, including gastrointestinal ailments, central nervous system disorders, cardiovascular diseases, and respiratory disorders (Hosseinzadeh and Nassiri-Asl 2013). Furthermore, saffron is utilized in Ayurvedic medicine to treat diabetes mellitus (Mousavi and Bathaie 2011). The principal components of saffron responsible for its pharmacological activities are crocin, crocetin, and safranal (Shafiee et al. 2017). Modern pharmacological studies have demonstrated that saffron and its constituents exert diverse pharmacological activities, including antidepressant, hypolipidemic, anti-inflammatory, hypoglycemic, antioxidant, and memory-enhancing (Asdaq and Inamdar 2010; Ayati et al. 2020; Hatziagapiou et al. 2019; Lin et al. 2021; Pashirzad et al. 2019; Yaribeygi et al. 2019). Multiple studies have demonstrated the therapeutic potential of saffron and its active ingredients for treating various components of MetS, including diabetes, hypertension, obesity, and hyperlipidemia (Asdaq et al. 2024; Imenshahidi, Hosseinzadeh, and Javadpour 2010; Mohaqiq et al. 2020; Razavi and Hosseinzadeh 2017).

The improvement effect of saffron on the components of MetS and related diseases has been explored through various clinical trials, yielding inconsistent findings. Kermani, Zebarjadi, et al. (2017) demonstrated a remarkable reduction in HDL-C, TG, TC, and FBG levels in MetS patients after a 12-week intervention with saffron (100 mg/day) (Kermani, Zebarjadi, et al. 2017). Conversely, Zilaee et al. (2018) found no significant impact of saffron on TC, TG, and HDL-C among MetS patients (Zilaee et al. 2018). Recent research highlighted the beneficial effects of consuming saffron on plasma glycemic status and lipid profile in individuals with T2DM (Tajaddini et al. 2023), contrasting with findings from another study that observed no significant effects (Ebrahimi, Sahebkar, et al. 2019). Furthermore, previous meta-analyses have examined the influence of saffron on blood glucose and lipid profiles, encompassing diverse populations of healthy adults and patients with various conditions, with inconsistent results (Asbaghi et al. 2019; Pourmasoumi et al. 2019; Zamani et al. 2022). The inconsistency in the results of these studies may be attributed to differences in study design, intervention dose, intervention duration, sample size, and race. In summary, comprehensive systematic evaluations and meta-analyses are necessary to ascertain whether saffron can benefit patients with MetS and related disorders. Therefore, in the current systemic review and meta-analysis, we aimed to synthesize data from relevant randomized controlled trials (RCTs) to quantify the effects of saffron on blood glucose, lipid levels, and blood pressure in individuals with MetS and associated conditions.

2 | Methods

This meta-analysis was performed in compliance with the statement of Preferred Reporting Items of Systematic Reviews and Meta-Analysis (PRISMA) 2020 (Page et al. 2021). The registered ID of this study in PROSPERO is CRD42023462534.

2.1 | Search Strategy

Two independent reviewers systematically searched for relevant published RCTs from the inception of the five online databases—Embase, Web of Science, Cochrane Library, Scopus, and PubMed—until February 2024. The search was performed with specific keywords: "saffron," "Crocus," "*Crocus sativus*," "crocin," "metabolic syndrome," "fasting Blood glucose," "FBG," "blood glucose," "insulin resistance," "triglycerides," "HDL-C," "cholesterol, hdl," "LDL-C," "cholesterol, ldl," "blood pressure," "SBP," "DBP," "waist circumference," "WC," in combination with "clinical trial," "clinical trials," "randomized controlled trial," "randomized controlled trials," "controlled clinical trial," "random," "random allocation," "placebo," and "placebos" (Table S1). No language limitations were imposed during the process. The references of relevant articles and included studies were also reviewed to avoid missing any pertinent studies.

2.2 | Study Selection

The retrieved studies were independently screened by two reviewers (XL.Z. and JX.M.) to identify eligible studies based on the screening criteria. A third reviewer (YG.S.) would resolve the disagreements that arose between them. For inclusion, studies must meet the following criteria: (a) they were original RCTs performed on adults (age > 18 years) with MetS or related disorders, including T2DM, hypertension, NAFLD, and obesity; (b) they investigated saffron (or saffron extract or crocin) supplementation versus placebo; and (c) they reported one or more of the following outcomes pre- and post-treatment: FBG, HbA1c, homeostatic model assessment for insulin resistance (HOMA-IR), BMI, WC, TG, TC, LDL-C, HDL-C, DBP, and SBP.

The exclusion criteria included studies that (a) involved children, pregnant, or lactating women; (b) assessed saffron (or saffron extract or crocin) supplementation in combination with other herbal components; or (c) were case reports, reviews, conference abstracts, commentaries, letter to editors, or animal studies.

2.3 | Data Extraction

Independent reviewers XL.Z. and JX.M. used a structured data collection table to extract data from eligible studies. To ensure consistency, a third reviewer (YG.S.) would solve any discrepancies between them. The extracted data consisted of basic information on articles and patients, as well as pre-and post-treatment levels of FBG, HbA1c, HOMA-IR, BMI, WC, TG, TC, LDL-C, HDL-C, DBP, and SBP.

2.4 | Quality Assessment

Two independent reviewers, XL.Z. and JX.M., evaluated the risk of bias for included studies using the Cochrane risk-of-bias tool (Higgins et al. 2011). The quality of evidence was evaluated by employing the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) criteria (Guyatt et al. 2011), which classified evidence into four qualities, ranging from high quality to very low quality. Any different opinions between the two reviewers were resolved by discussing with a third reviewer.

2.5 | Statistical Analysis

Stata 17.0 was used to perform the meta-analysis. The quantitative analysis of FBG, HbA1c, HOMA-IR, BMI, WC, TG, TC, LDL-C, HDL-C, DBP, and SBP was performed with the mean change and standard deviation (SD) of pre- and post-treatment. If the SD of mean change was not reported, the following formula was used to calculate this parameter (Borenstein et al. 2009): $SD_{change}{}^2 = (SD_{pre\text{-}intervention}{}^2 + SD_{after\text{-}intervention}{}^2) - (2R \times SD_{pre\text{-}intervention} \times SD_{after\text{-}intervention})$, assuming $R = 0.5$. If a standard error was reported instead of SD, the equation $SD = SE \times \sqrt{N}$ was utilized to calculate SD (Hozo, Djulbegovic, and Hozo 2005). The pooled effect size, calculated through either a random-effects or fixed-effects model, was reported as a weighted mean difference (WMD) along with its associated 95% confidence interval (CI). A p value of <0.05 was deemed statistically significant. The heterogeneity among the included studies was assessed through the Higgins I^2 statistic. The statistical significance of heterogeneity was determined according to $I^2 \geq 50\%$ and p value <0.05 (Higgins et al. 2003). A fixed-effects model was chosen only when $I^2 < 50\%$, otherwise, a random-effects model was utilized. The TG, TC, LDL-C, HDL-C, and FBG units were converted from mmol/L to mg/dL. Subgroup analyses were carried out categorizing by intervention type, duration, dose, and health status to pinpoint potential sources of heterogeneity. Evaluation of publication bias was executed using Egger's and Begg's tests. Sensitivity analysis was conducted to evaluate each study's impact on the pooling results. Funnel plots were employed for parameters with at least 10 included studies to identify publication bias (Egger et al. 1997).

3 | Results

3.1 | Study Selection

During the initial search, 554 studies were identified (Figure 1). Of these, 252 duplicates were removed initially. From the remaining 302 studies, 269 were excluded based on title and abstract screening, resulting in 33 for full-text review. Eight of these studies were not included due to the lack of outcomes of interest ($n = 6$), non-RCT study ($n = 1$), and repeated publication study ($n = 1$). Ultimately, 25 studies were selected for the meta-analysis, with no additional studies included during the literature review.

3.2 | Studies Characteristics

Table 1 outlines the key characteristics of the studies included in this analysis. The 25 studies used in this analysis were published between 2014 and 2023 (Azimi et al. 2014, 2016; Behrouz et al. 2020; Ebrahimi, Aryaeian, et al. 2019; Ebrahimi, Sahebkar, et al. 2019; Hooshmand-Moghadam et al. 2021; Hooshmand Moghadam et al. 2022; Jaafarinia et al. 2022; Javandoost et al. 2017; Karimi-Nazari et al. 2019; Kermani, Kazemi, et al. 2017; Kermani, Zebarjadi, et al. 2017; Milajerdi et al. 2018; Mobasseri et al. 2020; Mojtahedi et al. 2022; Moravej Aleali et al. 2019; Nikbakht-Jam et al. 2016; Parsi et al. 2020; Pour et al. 2020; Saberi-Karimian et al. 2021; Sepahi et al. 2022; Shahbazian et al. 2019; Tajaddini et al. 2023; Zilaee et al. 2018). Nineteen studies were randomized double-blind trials (Behrouz et al. 2020; Behrouz et al. 2021; Ebrahimi, Sahebkar, et al. 2019; Hooshmand-Moghadam et al. 2021; Hooshmand Moghadam et al. 2022; Karimi-Nazari et al. 2019; Mobasseri et al. 2020; Moravej Aleali et al. 2019; Parsi et al. 2020; Pour et al. 2020; Rajaei et al. 2013; Saberi-Karimian et al. 2021; Shahbazian et al. 2019; Tajaddini et al. 2023), and three were randomized triple-blind trials (Jaafarinia et al. 2022; Milajerdi et al. 2018; Sepahi et al. 2022). Two studies were randomized single-blind trials (Azimi et al. 2014; Azimi et al. 2016), while one did not report blinding (Mojtahedi et al. 2022). All these RCTs were conducted in Iran. This study included 1486 participants, with the smallest and largest sample sizes being 24 (Mojtahedi et al. 2022) and 150 (Sepahi et al. 2022), respectively. These studies involved male and female participants with MetS, T2DM, hypertension, NAFLD, or obesity, with a mean age range of 33.1–62.7 years. Among 26 studies, because Sepahi's study included two intervention arms and a placebo arm, we defined this study as Sepahi et al. 2022a and Sepahi et al. 2022b, respectively. The interventions used were saffron and crocin. Saffron was administered from 15 to 1000 mg/day, while crocin was given daily doses from 15 to 30 mg. The intervention duration was from 8 to 12 weeks.

3.3 | Risk of Bias Assessment

The comprehensive risk of bias was evaluated as low (Figure 2). Among the studies, two did not provide details on their random sequence generation methods (Nikbakht-Jam et al. 2016; Pour et al. 2020). Additionally, two studies had inadequate information on allocation concealment (Mojtahedi et al. 2022; Zilaee et al. 2018), with two more not following allocation concealment

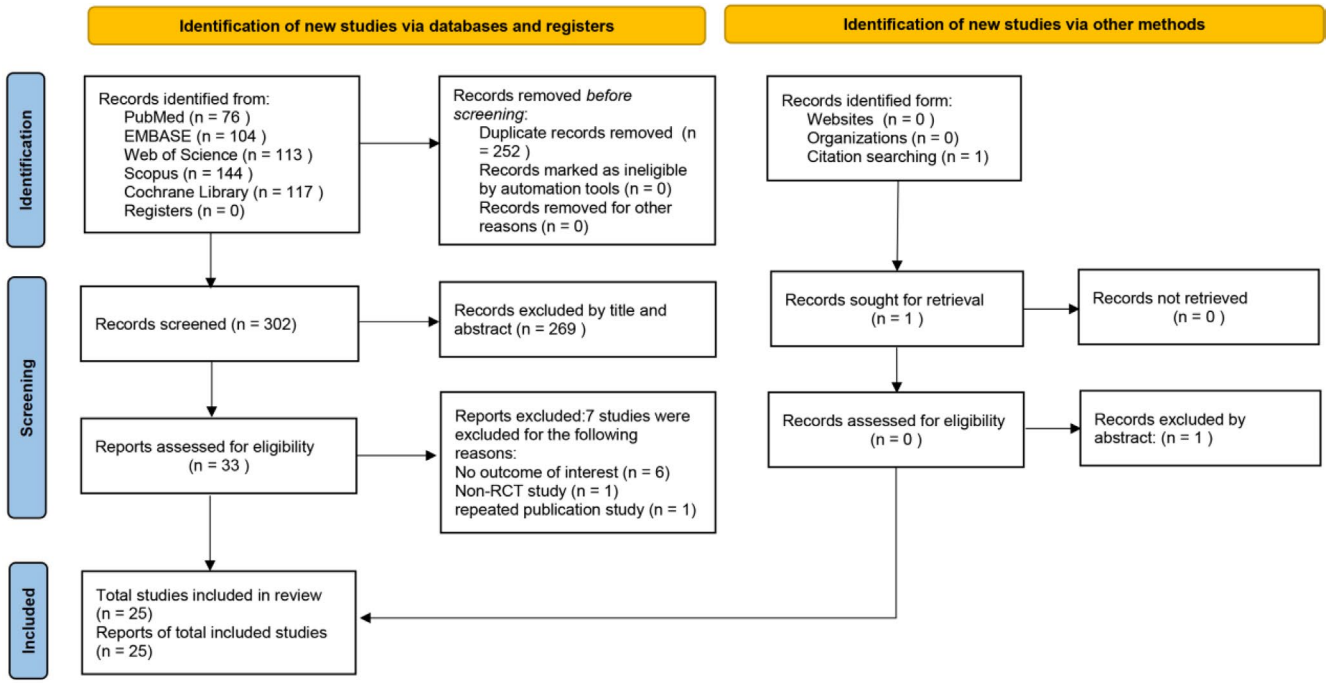

FIGURE 1 | Flowchart of included studies selection.

procedures (Azimi et al. 2014; Azimi et al. 2016). Two studies were identified as high risk due to the absence of blinding of researchers (Azimi et al. 2014; Azimi et al. 2016), while two other trials lacked relevant information on blinding protocols (Mojtahedi et al. 2022; Nikbakht-Jam et al. 2016). Moreover, two studies were deemed high risk due to only blinding the subjects (Azimi et al. 2014; Azimi et al. 2016), and four studies lacked details on blinding outcome assessment (Hooshmand-Moghadam et al. 2021; Hooshmand Moghadam et al. 2022; Mojtahedi et al. 2022; Nikbakht-Jam et al. 2016). Notably, five studies were deemed high-risk due to issues with selective reporting (Ebrahimi, Aryaeian, et al. 2019; Ebrahimi, Sahebkar, et al. 2019; Javandoost et al. 2017; Nikbakht-Jam et al. 2016; Shahbazian et al. 2019), while the risk assessment for two studies was not feasible due to insufficient information (Behrouz et al. 2021; Zilaee et al. 2018). Concerning attrition bias and other biases, all studies were evaluated as low.

3.4 | Findings From the Systematic Review

Eighteen studies assessed FBG levels, of which nine demonstrated a significant decrease consequent to saffron supplementation (Behrouz et al. 2020; Hooshmand Moghadam et al. 2022; Karimi-Nazari et al. 2019; Milajerdi et al. 2018; Mobasseri et al. 2020; Moravej Aleali et al. 2019; Sepahi et al. 2022; Shahbazian et al. 2019; Tajaddini et al. 2023). Among these nine studies, Sepahi's study found that only crocin intervention significantly reduced FBG levels, with no significant impact attributed to saffron. Five studies indicated a remarkable reduction in HbA1c after saffron treatment (Behrouz et al. 2020; Hooshmand Moghadam et al. 2022; Karimi-Nazari et al. 2019; Sepahi et al. 2022; Tajaddini et al. 2023), while six studies did not show a significant effect (Azimi et al. 2014; Ebrahimi, Sahebkar, et al. 2019; Jaafarinia et al. 2022; Milajerdi et al. 2018; Moravej Aleali et al. 2019; Shahbazian et al. 2019). Regarding HOMA-IR, three studies observed a significant decline (Behrouz et al. 2020; Hooshmand Moghadam et al. 2022; Tajaddini et al. 2023), whereas Sepahi's study revealed a remarkable increase in HOMA-IR after crocin intervention (Sepahi et al. 2022). Four studies indicated a significant decrease in TC levels (Kermani, Zebarjadi, et al. 2017; Mojtahedi et al. 2022; Moravej Aleali et al. 2019; Tajaddini et al. 2023), while one showed a significant increase (Azimi et al. 2014). Regarding TG levels, three studies indicated a significant reduction (Hooshmand-Moghadam et al. 2021; Jaafarinia et al. 2022; Tajaddini et al. 2023). One study reported a dramatically increased effect of saffron on HDL-C levels (Mojtahedi et al. 2022). Two studies showed a remarkable decrease in LDL-C post-saffron intervention (Mojtahedi et al. 2022; Tajaddini et al. 2023). Additionally, one study revealed a remarkable decrease in WC post-saffron treatment (Ebrahimi, Sahebkar, et al. 2019). Ten studies assessed the effects of saffron or crocin on BMI (Azimi et al. 2016; Behrouz et al. 2021; Ebrahimi, Sahebkar, et al. 2019; Hooshmand-Moghadam et al. 2021; Hooshmand Moghadam et al. 2022; Jaafarinia et al. 2022; Kermani, Kazemi, et al. 2017; Pour et al. 2020; Saberi-Karimian et al. 2021; Tajaddini et al. 2023), with none showing a significant change.

3.5 | Effects of Saffron Supplementation on Glycemic Parameters

Seventeen studies (18 arms with 1030 participants) assessed the impact of saffron supplementation on FBG. The results revealed a remarkable decrease in FBG after saffron supplementation intake (WMD: −6.67 mg/dL; 95% CI: −10.55, −2.78; $p = 0.001$), with high heterogeneity ($I^2 = 50.0\%$, $p = 0.008$) (Figure 3A). Subgroup analysis did not identify the potential sources of heterogeneity (Table 2). Nevertheless, the heterogeneity was

TABLE 1 | Characteristics of the included studies.

Author	Year	Country	Study design	Participants gender	Health status	Mean age (years)	Sample size for analysis	Intervention type	Intervention dose (mg/day)	Intervention duration (weeks)	Control group
						I/C	I/C				
Tajaddini et al.	2023	Iran	RCTs, DB	M/F	T2DM	50.75/51.83	30/30	Saffron	100	8	Placebo
Sepahi et al.	2022a	Iran	RCTs, TB	M/F	T2DM	57.58/56.92	50/25	Crocin	30	12	Placebo
Sepahi et al.	2022b	Iran	RCTs, TB	M/F	T2DM	57.58/56.92	50/25	Saffron	30	12	Placebo
Mojtahedi et al.	2022	Iran	RCTs, NR	M/F	Hypertension	63.1/62.5	12/12	Saffron	200	12	Placebo
Jaafarinia et al.	2022	Iran	RCTs, TB	M//F	T2DM	63.86/62.68	21/19	Crocin	15	12	Placebo
Hooshmand Moghadam et al.	2021	Iran	RCTs, DB	M	T2DM	NR	13/13	Saffron	100	12	Placebo
Saberi-Karimian et al.	2021	Iran	RCTs, DB	M//F	MetS	38.97/43.46	21/22	Crocin	30	8	Placebo
Hooshmand-Moghadam et al.	2021	Iran	RCTs, DB	M	Hypertension	63.1/62.5	12/12	Saffron	200	12	Placebo
Behrouz et al.	2021	Iran	RCTs, DB	M/F	T2DM	57.08/59.86	23/22	Crocin	30	12	Placebo
Pour et al.	2020	Iran	RCTs, DB	M/F	NAFLD	43.42/42.05	36/36	Saffron	100	12	Placebo
Parsi et al.	2020	Iran	RCTs, DB	M/F	NAFLD	33.08/36.1	30/30	Crocin	15	8	Placebo
Mobasseri et al.	2020	Iran	RCTs, DB	M/F	T2DM	50.57/51.63	30/27	Saffron	100	8	Placebo
Behrouz et al.	2020	Iran	RCTs, DB	M/F	T2DM	57.08/59.86	23/22	Crocin	60	12	Placebo
Shahbazian et al.	2019	Iran	RCTs, DB	M/F	T2DM	53.5/52.4	32/32	Saffron	30	12	Placebo
Moravej Aleali et al.	2019	Iran	RCTs, DB	M/F	T2DM	53.5/52.4	32/32	Saffron	30	12	Placebo
Karimi-Nazari et al.	2019	Iran	RCTs, DB	M/F	Obesity	57.95/57.9	36/39	Saffron	15	8	Placebo
Ebrahimi, Sahebkar, et al.	2019	Iran	RCTs, DB	M/F	T2DM	55.2/53	40/40	Saffron	100	12	Placebo

(Continues)

TABLE 1 | (Continued)

Author	Year	Country	Study design	Participants gender	Health status	Mean age (years)	Sample size for analysis	Intervention type	Intervention dose (mg/day)	Intervention duration (weeks)	Control group
						I/C	I/C				
Ebrahimi, Aryaeian, et al.	2019	Iran	RCTs, DB	M/F	T2DM	55.2/53	40/40	Saffron	100	12	Placebo
Zilaee et al.	2018	Iran	RCTs, DB	M/F	MetS	42.19/43.6	35/35	Saffron	100	12	Placebo
Milajerdi et al.	2018	Iran	RCTs, DB	M/F	T2DM	54.57/55.42	26/26	Saffron	30	8	Placebo
Kermani, Zebarjadi, et al.	2017	Iran	RCTs, DB	M/F	MetS	43.64/42.59	22/22	Saffron	100	12	Placebo
Kermani, Kazemi, et al.	2017	Iran	RCTs, DB	M/F	MetS	53.8/50.9	24/24	Crocin	100	6	Placebo
Javandoost et al.	2017	Iran	RCTs, DB	M/F	MetS	36.59/40.04	21/22	Crocin	30	8	Placebo
Azimi et al.	2016	Iran	RCTs, SB	M/F	T2DM	57.02/53.64	42/39	Saffron	1000	8	Placebo
Nikbakht-Jam et al.	2016	Iran	RCTs, DB	M/F	MetS	38.97/43.46	29/29	Crocin	30	8	Placebo
Azimi et al.	2014	Iran	RCTs, SB	M/F	T2DM	57.02/53.64	42/39	Saffron	1000	8	Placebo

Abbreviations: C, control; DB, double-blinded; F, female; I, intervention; M, male; MetS, metabolic syndrome; NAFLD, non-alcoholic fatty liver disease; RCTs, randomized controlled trials; SB, single-blinded; T2DM, type 2 diabetes mellitus; TB, triple-blinded.

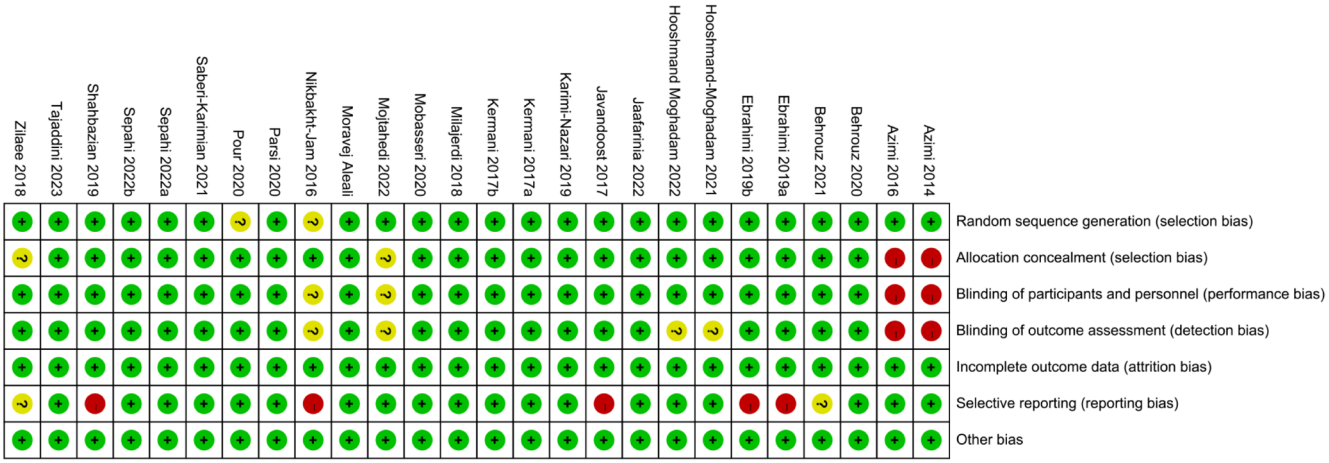

FIGURE 2 | Risk of bias assessment of included studies. A green dot accompanied by a plus sign signifies a low risk of bias, whereas a yellow dot with a question mark indicates an unclear risk of bias, and a red dot with a minus sign denotes a high risk of bias.

significantly reduced ($I^2 = 33.9\%$; $p = 0.085$) after excluding the study of Sepahi et al. (2022b). Further subgroup analysis unveiled a significant reduction in FBG levels in cases involving saffron or crocin treatment, duration < 12 weeks, dose > 100 mg/day, and T2DM patients. Sensitivity analysis demonstrated that removing any single study did not alter the overall effect on FBG levels (Figure S1).

Eleven studies (12 arms with 737 individuals) assessed the impact of saffron supplementation on HbA1c, revealing a notable decrease following saffron supplementation (WMD: −0.25%; 95% CI: −0.35, −0.14; $p < 0.001$), with high heterogeneity ($I^2 = 51.4\%$, $p = 0.020$) (Figure 3B). The intervention type and duration were identified as the potential sources of heterogeneity according to subgroup analysis (Table 2). Moreover, the heterogeneity was markedly reduced ($I^2 = 3.8\%$; $p = 0.406$) after excluding the study of Sepahi et al. (2022a). All subgroups showed a notable decrease in HbA1c. Pooled results remained robust through the sensitivity analysis (Figure S1).

Six studies (7 arms involving 425 participants) investigated the impact of saffron supplementation on HOMA-IR. The findings revealed no significant difference compared to a placebo (WMD: 0.08; 95% CI: −0.65, 0.80; $p = 0.833$) (Figure 3C). Despite a high heterogeneity among the studies ($I^2 = 97.3\%$, $p < 0.001$), no potential sources of heterogeneity were identified through subgroup analysis (Table 2). However, the overall effect size remained consistent after sensitivity analysis (Figure S1).

3.6 | Effects of Saffron Supplementation on Lipid Profile

Fifteen studies (16 arms with 406 participants) evaluated TG. The overall effect size showed no notable alterations in TG (WMD: −11.15 mg/dL; 95% CI: −25.56, 3.27; $p = 0.130$). Although there was considerable heterogeneity ($I^2 = 89.8\%$, $p < 0.001$) (Figure 4A), subgroup analysis did not pinpoint the source of heterogeneity. However, when the study by Parsi et al. (2020) was excluded, heterogeneity notably decreased ($I^2 = 6.6\%$; $p = 0.379$). Additionally, subgroup analysis indicated a remarkable decrease in TG with saffron intervention (WMD: −6.67 mg/dL; 95% CI: −11.67, −1.66; $p = 0.009$). Sensitivity analysis indicated the robustness of pooling results (Figure S1).

Sixteen studies (17 arms involving 463 participants) assessed TC. The combined findings demonstrated that saffron supplementation notably decreased TC levels (WMD: −4.77 mg/dL; 95% CI: −8.83, −0.71; $p = 0.021$), with no considerable heterogeneity observed across the studies ($I^2 = 31.8\%$, $p = 0.102$) (Figure 4B). Subgroup analysis indicated a remarkable decrease in TC levels under specific conditions: when the intervention type involved saffron, the intervention period lasted < 12 weeks, the intervention dose was ≥ 100 mg/day, and the disease types were T2DM and MetS. The sensitivity analysis demonstrated that individual studies did not significantly influence the combined results (Figure S1).

Seven studies involving 392 individuals assessed LDL-C and HDL-C. The findings suggested no remarkable impact of saffron supplementation on LDL-C (WMD: −1.52 mg/dL; 95% CI: −5.66, 2.62; $p = 0.472$) and HDL-C levels (WMD: 0.44 mg/dL; 95% CI: −1.17, 2.04; $p = 0.595$) (Figure 4C,D). No heterogeneity were observed in LDL-C ($I^2 = 0.0\%$; $p = 0.510$) and HDL-C ($I^2 = 0.0\%$; $p = 0.977$). Based on subgroup analysis, no subgroup had a notable impact on LDL-C and HDL-C (Table 2). The pooling results were not dramatically altered by the omission of any individual study, according to the sensitivity analysis (Figure S1).

3.7 | Effects of Saffron Supplementation on Blood Pressure

Nine studies involving 462 individuals assessed SBP and DBP. The pooling results showed that SBP levels (WMD: −1.15 mmHg; 95% CI: −1.66, −0.64; $p < 0.001$) and DBP levels (WMD: −1.61 mmHg; 95% CI: −1.88, −1.34; $p < 0.001$) were notably decreased. No remarkable heterogeneity was observed in SBP ($I^2 = 41.8\%$; $p = 0.089$) or DBP ($I^2 = 7.0\%$; $p = 0.377$) (Figure 5). According to subgroup analysis, under the condition that the intervention period was ≤ 12 weeks and the intervention dose was ≥ 100 mg/day, dramatically decreased SBP and DBP levels. However, crocin only had a reducing effect on DBP (Table 2). Additionally, saffron and crocin effectively reduced SBP and

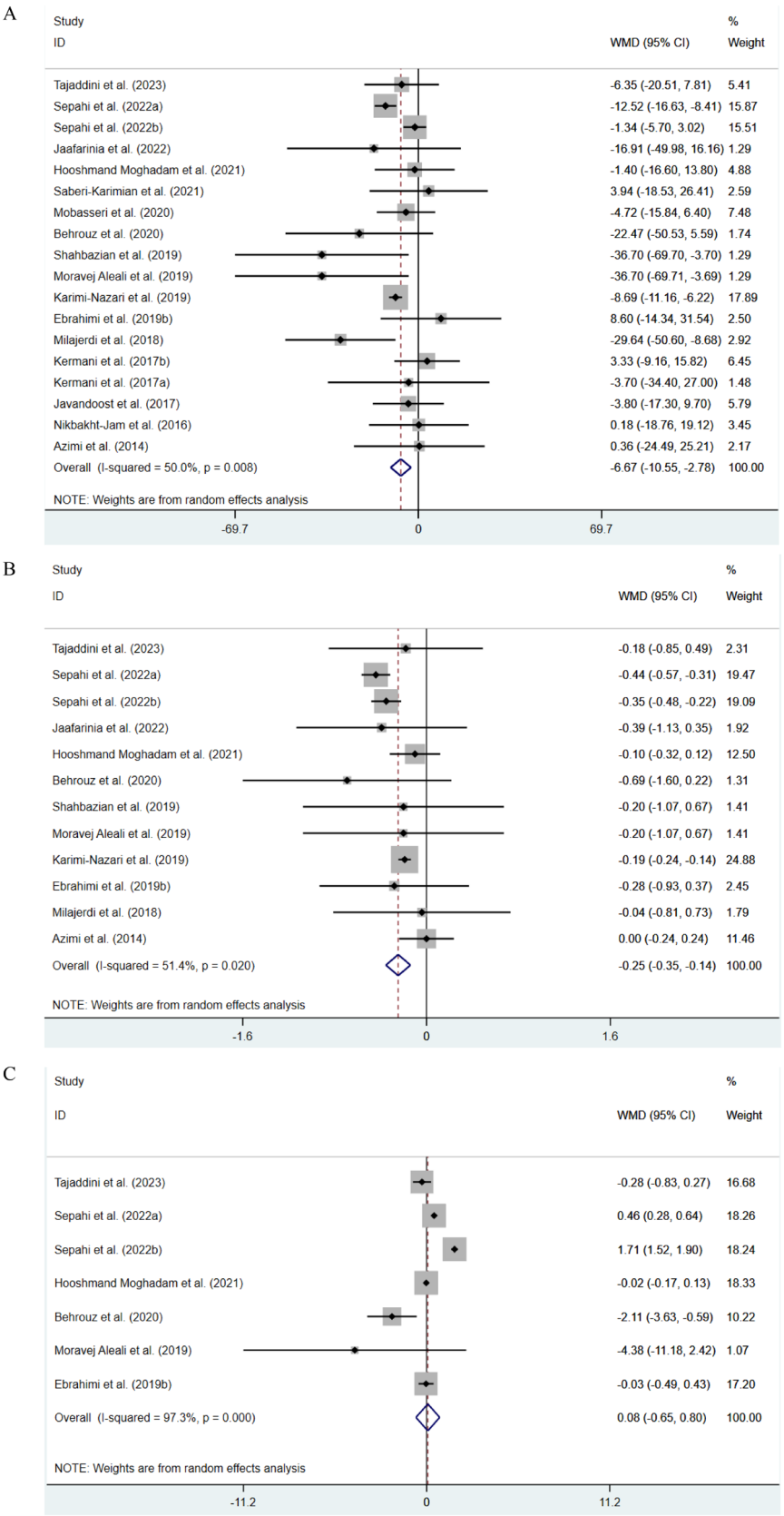

FIGURE 3 | Forest plot of the effects of saffron supplementation on FBG (A), HbA1c (B), and HOMA-IR (C).

DBP in individuals with T2DM, while no notable decrease was observed in individuals with MetS. Sensitivity analysis indicated the robustness of the overall results of DBP, while the combined results of SBP (WMD: −2.47 mmHg; 95% CI: −5.22, 0.29; $p = 0.079$) became insignificant after omitting the study of Azimi et al. (2016) (Figure S1).

TABLE 2 | Subgroup analysis of the effects of saffron supplementation on glycolipid metabolism and blood pressure.

	Meta-analysis			Heterogeneity		
Study group	**Number of studies**	**WMD (95%Cl)**	***P*-effect**	I^2 (%)	***P*-within group**	***P*-between group**
FBS (mg/dL)						
Intervention type						0.504
Saffron	11	−5.92 (−11.15, −0.69)	0.026	58.9	0.007	
Crocin	7	−11.03 (−14.74, −7.33)	<0.001	0.0	0.465	
Intervention duration (weeks)						0.541
<12	9	−8.21 (−10.49, −5.93)	<0.001	0.0	0.491	
≥12	9	−7.44 (−15.00, 0.12)	0.054	69.3	0.001	
Intervention dose (mg/day)						0.057
<100	11	−9.21 (−14.19, −4.23)	<0.001	63.2	0.002	
≥100	7	−1.46 (−7.40, 4.47)	0.629	0.0	0.907	
Health status						0.204
T2DM	12	−9.04 (−15.28, −2.80)	0.005	61.1	0.003	
MetS	5	0.28 (−7.24, 7.79)	0.943	0.0	0.945	
Other	1	−8.69 (−11.16, −6.22)	0.001	—	—	
HbA1c (%)						
Intervention type						0.281
Saffron	9	−0.20 (−0.27, −0.13)	<0.001	11.4	0.340	
Crocin	3	−0.44 (−0.57, −0.32)	<0.001	0.0	0.858	
Intervention duration (weeks)						0.415
<12	4	−0.18 (−0.23, −0.13)	<0.001	0.0	0.482	
≥12	8	−0.34 (−0.44, −0.25)	<0.001	10.2	0.351	
Intervention dose (mg/day)						0.124
<100	8	−0.31 (−0.45, −0.18)	<0.001	59.2	0.016	
≥100	4	−0.07 (−0.23, −0.08)	0.348	0.0	0.823	
Health status						0.887

(Continues)

TABLE 2 | (Continued)

Study group	Meta-analysis			Heterogeneity		
	Number of studies	WMD (95%Cl)	*P*-effect	I^2 (%)	*P*-within group	*P*-between group
T2DM	11	−0.26 (−0.39, −0.14)	<0.001	37.7	0.098	
MetS	0	—	—	—	—	
Other	1	−0.19 (−0.24, −0.14)	<0.001	—	—	
HOMA-IR						
Intervention type						0.409
Saffron	5	0.25 (−0.83, 1.33)	0.650	98.1	<0.001	
Crocin	2	−0.71 (−3.22, 1.80)	0.579	90.8	0.001	
Intervention duration (weeks)						0.898
<12	1	−0.28 (−0.83, 0.27)	0.321	—	—	
≥12	6	0.15 (−0.66, 0.95)	0.722	97.6	<0.001	
Intervention dose (mg/day)						0.566
<100	4	0.21 (−0.93, 1.36)	0.715	97.1	<0.001	
≥100	3	−0.04 (−0.18, 0.10)	0.599	0.0	0.674	
Health status						—
T2DM	7	0.08 (−0.65, 0.80)	0.833	97.3	<0.001	
MetS	0	—	—	—	—	
Other	0	—	—	—	—	
TG (mg/dL)						
Intervention type						0.608
Saffron	9	−6.67 (−11.67, −1.66)	0.009	0.0	0.594	
Crocin	7	−14.77 (−49.11, 19.56)	0.399	95.1	<0.001	
Intervention duration (weeks)						0.740
<12	9	−9.94 (−36.36, 16.48)	0.461	93.0	<0.001	
≥12	7	−7.50 (−17.32, 2.33)	0.135	45.0	0.091	
Intervention dose (mg/day)						0.870

(Continues)

TABLE 2 | (Continued)

Study group	Meta-analysis			Heterogeneity		
	Number of studies	WMD (95%Cl)	*P*-effect	I^2 (%)	*P*-within group	*P*-between group
< 100	10	−13.53 (−32.3, 5.24)	0.158	93.7	< 0.001	
≥ 100	6	−5.74 (−19.83, 8.35)	0.425	0.0	0.827	
Health status						0.423
T2DM	9	−7.09 (−15.96, 1.78)	0.117	41.9	0.099	
MetS	6	−2.87 (−19.40, 13.65)	0.733	0.0	0.905	
Other	2	−32.35 (−95.49, 30.79)	0.315	99.0	< 0.001	
TC (mg/dL)						
Intervention type						0.370
Saffron	9	−5.90 (−10.37, −1.45)	0.009	49.9	0.036	
Crocin	7	0.76 (−9.08, 10.60)	0.880	0.0	0.673	
Intervention duration (weeks)						0.357
< 12	8	−2.02 (−7.40, 3.36)	0.461	0.0	0.915	
≥ 12	9	−8.42 (−14.62, −2.22)	0.008	56.6	0.018	
Intervention dose (mg/day)						0.597
< 100	10	−2.75 (−7.67, 2.18)	0.274	29.2	0.176	
≥ 100	7	−9.08 (−16.26, −1.89)	0.013	31.1	0.191	
Health status						0.444
T2DM	9	−3.42 (−9.24, 2.40)	0.250	39.1	0.107	
MetS	6	−15.65 (−25.08, −6.23)	0.001	0.0	0.635	
Other	2	−0.61 (−7.70, 6.49)	0.866	0.0	0.622	
LDL-C (mg/dL)						
Intervention type						0.423
Saffron	5	−1.40 (−5.62, 2.83)	0.517	0.0	0.407	
Crocin	2	−4.47 (−25.25, 16.31)	0.674	16.0	0.275	
Intervention duration (weeks)						0.400

(Continues)

TABLE 2 | (Continued)

Study group	Meta-analysis			Heterogeneity		
	Number of studies	WMD (95%Cl)	*P*-effect	I^2 (%)	*P*-within group	*P*-between group
< 12	3	−0.55 (−5.73, 4.63)	0.835	28.4	0.248	
≥ 12	4	−3.24 (−10.14, 3.66)	0.358	0.0	0.552	
Intervention dose (mg/day)						0.278
< 100	3	0.98 (−4.51, 6.47)	0.726	0.0	0.478	
≥ 100	4	−4.81 (−11.11, 1.50)	0.135	0.0	0.583	
Health status						0.595
T2DM	3	−2.37 (−10.89, 6.15)	0.586	0.0	0.504	
MetS	2	−11.13 (−22.59, 0.33)	0.057	0.0	0.708	
Other	2	0.78 (−4.42, 5.98)	0.769	0.0	0.605	
HDL-C (mg/dL)						
Intervention type						0.874
Saffron	5	0.57 (−1.12, 2.26)	0.507	0.0	0.963	
Crocin	2	−0.86 (−6.07, 4.35)	0.747	0.0	0.567	
Intervention duration (weeks)						0.869
< 12	3	0.42 (−2.12, 2.96)	0.744	0.0	0.717	
≥ 12	4	0.44 (−1.63, 2.52)	0.675	0.0	0.913	
Intervention dose (mg/day)						0.861
< 100	3	−0.13 (−3.63, 3.38)	0.944	0.0	0.792	
≥ 100	4	0.59 (−1.22, 2.39)	0.526	0.0	0.896	
Health status						0.837
T2DM	3	0.62 (−1.91, 3.14)	0.631	0.0	0.913	
MetS	2	−0.78 (−4.07, 2.52)	0.644	0.0	0.655	

(Continues)

TABLE 2 | (Continued)

Study group	Meta-analysis			Heterogeneity		
	Number of studies	WMD (95%Cl)	*P*-effect	I^2 (%)	*P*-within group	*P*-between group
Other	2	1.04 (−1.65, 3.72)	0.449	0.0	0.780	
SBP (mmHg)						
Intervention type						0.716
Saffron	5	−1.11 (−1.63, −0.60)	<0.001	62.3	0.031	
Crocin	4	−4.85 (−10.15, 0.45)	0.073	0.0	0.743	
Intervention duration (weeks)						0.409
<12	4	−1.12 (−1.63, −0.60)	<0.001	0.0	0.956	
≥12	5	−2.48 (−5.80, 0.83)	0.142	68.7	0.012	
Intervention dose (mg/day)						0.974
<100	3	−5.57 (−11.99, 0.84)	0.088	0.0	0.580	
≥100	6	−1.12 (−1.63, −0.61)	<0.001	53.8	0.055	
Health status						0.791
T2DM	5	−1.17 (−1.69, −0.65)	<0.001	47.4	0.107	
MetS	3	0.99 (−2.63, 4.62)	0.591	0.0	0.410	
Other	1	−12.00 (−24.24, 0.24)	0.055	—	—	
DBP (mmHg)						
Intervention type						0.390
Saffron	5	−1.60 (−1.88, −1.33)	<0.001	31.7	0.210	
Crocin	4	−3.12 (−6.86, 0.61)	0.101	0.0	0.549	
Intervention duration (weeks)						0.321
<12	4	−1.60 (−1.88, −1.33)	<0.001	0.0	0.790	
≥12	5	−2.04 (−4.51, 0.43)	0.105	46.3	0.114	
Intervention dose (mg/day)						0.251
<100	3	−3.90 (−7.99, 0.20)	0.062	0.0	0.523	
≥100	6	−1.60 (−1.88, −1.33)	<0.001	18.1	0.296	

(Continues)

TABLE 2 | (Continued)

Study group	Meta-analysis			Heterogeneity		
	Number of studies	WMD (95%Cl)	*P*-effect	I^2 (%)	*P*-within group	*P*-between group
Health status						0.167
T2DM	5	−1.60 (−1.88, −1.33)	<0.001	0.0	0.554	
MetS	3	−0.85 (−4.24, 2.54)	0.624	0.0	0.491	
Other	1	−6.90 (−12.11, −1.34)	0.009	—	—	
BMI (kg/m^2)						
Intervention type						0.635
Saffron	6	−0.02 (−0.40, 0.37)	0.936	0.0	0.866	
Crocin	4	−0.07 (−1.15, 1.30)	0.906	0.0	0.958	
Intervention duration (weeks)						0.384
< 12	4	0.17 (−0.32, 0.66)	0.489	0.0	0.881	
≥ 12	6	−0.25 (−0.81, 0.32)	0.391	0.0	0.997	
Intervention dose (mg/day)						0.690
< 100	3	−0.12 (−1.52, 1.28)	0.867	0.0	0.999	
≥ 100	7	0.00 (−0.38, 0.38)	0.997	0.0	0.903	
Health status						0.748
T2DM	6	0.00 (−0.38, 0.38)	0.998	0.0	0.911	
MetS	2	0.33 (−1.53, 2.19)	0.731	0.0	0.667	
Other	2	−0.50 (−0.38, 0.36)	0.588	0.0	0.759	
WC (cm)						
Intervention type						0.652
Saffron	7	−1.13 (−2.60, 0.33)	0.130	32.1	0.183	
Crocin	2	−2.16 (−6.13, 1.82)	0.287	17.3	0.272	
Intervention duration (weeks)						0.872
< 12	4	−0.53 (−2.41, 1.35)	0.581	0.0	0.565	
≥ 12	5	−2.09 (−4.11, −0.08)	0.042	42.8	0.136	

(Continues)

TABLE 2 | (Continued)

Study group	Meta-analysis			Heterogeneity		
	Number of studies	WMD (95%CI)	*P*-effect	I^2 (%)	*P*-within group	*P*-between group
Intervention dose (mg/day)						0.677
< 100	2	−0.28 (−2.50, 1.95)	0.807	0.0	0.933	
≥ 100	7	−1.86 (−3.61, −0.11)	0.037	33.8	0.170	
Health status						0.735
T2DM	4	−2.28 (−4.37, −0.18)	0.033	53.8	0.090	
MetS	3	−1.59 (−4.99, 1.81)	0.359	0.0	0.474	
Other	3	−0.03 (−2.19, 2.13)	0.977	0.0	0.752	

3.8 | Effects of Saffron Supplementation on Anthropometric Parameters

Ten studies involving 519 participants assessed BMI, while nine studies comprising 575 individuals assessed WC. The findings indicated that supplementation with saffron did not have a notable impact on BMI (WMD: −0.01 kg/m^2; 95% CI: −0.38, 0.36; $p = 0.968$) and WC (WMD: −1.25 cm; 95% CI: −2.63, 0.12; $p = 0.074$) (Figure 6). There was no significant heterogeneity noted in BMI ($I^2 = 0.0\%$; $p = 0.988$) or WC ($I^2 = 22.1\%$; $p = 0.246$). However, unveiled a remarkable reduction in WC among individuals with T2DM under intervention duration ≥ 12 weeks and dose ≥ 100 mg/day (Table 2). Sensitivity analysis demonstrated that excluding individual studies did not alter the overall results (Figure S1).

3.9 | Quality of Evidence Assessment

Using five criteria including risk of bias, inconsistency, indirectness, imprecision, and publication bias, the evidence quality for FBG, HbA1c, HOMA-IR, TG, and HDL-C was deemed "moderate" due to inconsistencies or imprecision. The "high" quality assessment was conducted for LDL-C, TC, SBP, DBP, BMI, and WC (Table S2).

3.10 | Publication Bias

The results of Egger's and Begg's tests indicated that the *p* values of FBG, HbA1c, HOMA-IR, TG, TC, LDL-C, HDL-C, DBP, SBP, BMI, and WC were 0.449, 0.888; 0.583, 0.751; 1.000, 0.601; 0.344, 0.876; 0.902, 0.633; 0.548, 0.222; 0.368, 0.238; 0.466, 0.523; 0.118, 0.132; 0.721, 0.954; and 0.348, 0.996, respectively. The results suggested no remarkable publication bias. The funnel plots showed the same result (Figure S2).

4 | Discussion

Based on the included studies of RCTs, our findings indicated that saffron supplementation resulted in notable decreases in FBG, HbA1c, TC, DBP, and SBP levels in populations with MetS and related disorders. Nevertheless, saffron supplementation did not significantly change HOMA-IR, TG, LDL-C, and HDL-C levels. Subgroup analysis revealed that saffron dramatically reduced FBG, HbA1c, TC, SBP, and DBP levels, while crocin showed reductions only in FBG and HbA1c. Specifically, saffron significantly decreased FBG, HbA1c, TC, TG, SBP, and DBP levels, whereas crocin demonstrated significant reductions solely in FBG and HbA1c levels. Notably, saffron decreased FBG, HbA1c, SBP, and DBP levels in an intervention duration of less than 12 weeks. Furthermore, saffron significantly reduced FBG and HbA1c levels when the daily dosage was below 100 mg, while doses exceeding 100 mg/day caused remarkable reductions in HbA1c, TC, DBP, and SBP levels.

In terms of heterogeneity, a study by Sepahi et al. (2022) caused a high heterogeneity of FBG. Study Sepahi et al. (2022a), intervention type, and intervention duration were the possible sources of heterogeneity of HbA1c. A study by Parsi et al. (2020) resulted

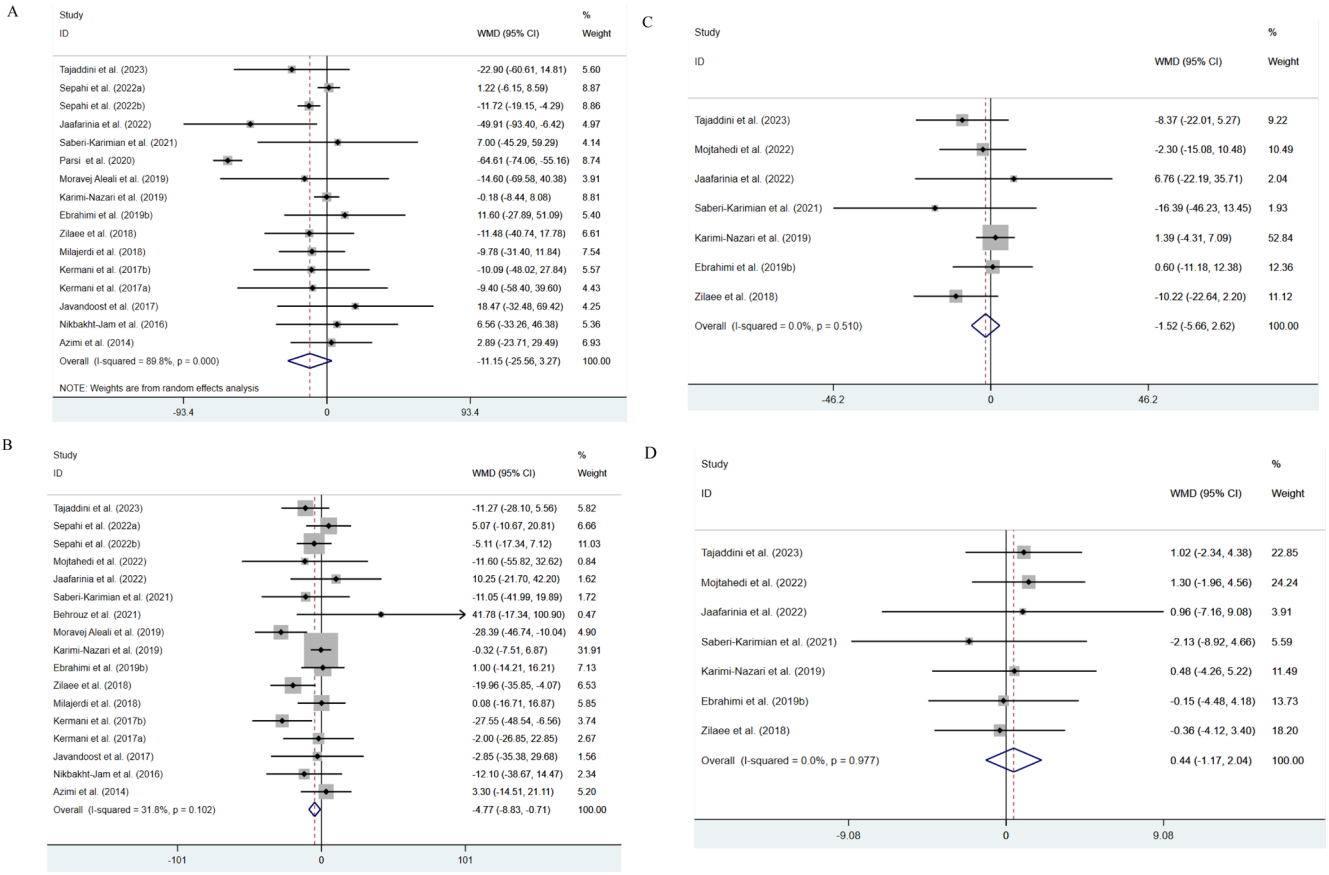

FIGURE 4 | Forest plot of the effects of saffron supplementation on TG (A), TC (B), LDL-C (C), and HDL-C (D).

in a high heterogeneity of TG. No potential sources of heterogeneity were identified through subgroup analyses in HOMA-IR. The observed heterogeneity may be attributed to discrepancies in study design, intervention duration, intervention dose, and sample size across the included studies.

Due to the absence of strict regulation, nutraceutical manufacturers have less stringent requirements than the pharmaceutical industry to prove the efficacy, safety, and quality of marketed products. As a result, many existing products may be ineffective (Williamson, Liu, and Izzo 2020). The hypoglycemic mechanisms of saffron and its constituents include: (a) Improve β-cell function. Saffron can prevent the deterioration of β-cell function through its antioxidant effect, promoting islet regeneration (Elgazar, Rezq, and Bukhari 2013). Crocin inhibits diabetes-induced pancreatic β-cell apoptosis by down-regulating p53 protein levels in pancreatic tissues (Ghorbanzadeh et al. 2017). (b) Enhance insulin sensitivity. Saffron enhances insulin sensitivity by activating mitogen-activated protein kinases (MAPKs) and AMP-activated protein kinase (AMPK)/acetyl-CoA carboxylase (ACC) in skeletal muscle cells (Kang et al. 2012). Additionally, saffron can reduce the levels of inflammatory cytokines such as interferon-γ (IFN-γ) and tumor necrosis factor-α (TNF-α) in pancreatic tissue and plasma interleukin-1β (IL-1β), contributing to enhancing insulin sensitivity (Hazman, Aksoy, and Büyükben 2016). (c) Induces glucose transporter protein 4 (GLUT-4) localization. Saffron promotes glucose uptake by facilitating the translocation of GLUT-4 to the plasma membrane through the AMPK/ACC pathway (Kang et al. 2012). Likewise, safranal enhances glucose uptake by promoting GLUT-4 translocation (Hazman, Aksoy, and Büyükben 2016). Furthermore, saffron stimulates insulin secretion and enhances β-cell functionality, facilitating GLUT-4 translocation (Shirali, Zahra Bathaie, and Nakhjavani 2013). (d) Prevent oxidative stress. Saffron can prevent oxidative stress by increasing the levels of antioxidant enzymes such as superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT), thus preventing insulin resistance and β-cell dysfunction caused by oxidative stress (Rajaei et al. 2013; Talebanzadeh et al. 2018). Crocin inhibits the mRNA expression levels of SOD, GPx, and CAT to prevent oxidative stress (Altınöz et al. 2016). (e) Inhibit inflammatory response. Saffron and Crocin prevent inflammation-induced insulin resistance by down-regulating inflammatory mediators involved in insulin resistance-related inflammation, such as TNF-α, high-sensitivity C-responsive protein (hs-CRP), and interleukin-6 (IL-6) (Behrouz et al. 2021; Samarghandian, Azimi-Nezhad, and Farkhondeh 2016). Crocin also exerts hypoglycemic effects by preventing β-cell damage caused by inflammation (Samarghandian, Azimi-Nezhad, and Farkhondeh 2016). Our findings revealed a considerable decrease in FBG and HbA1c levels following saffron supplementation, aligning with prior meta-analytical findings (Amatto et al. 2024; Zamani et al. 2022). However, our results diverged from other meta-analyses (Pourmasoumi et al. 2019; Rahmani et al. 2020).

Research indicated that saffron and crocin could reduce elevated lipid levels during hyperlipidemic stress (Asdaq and

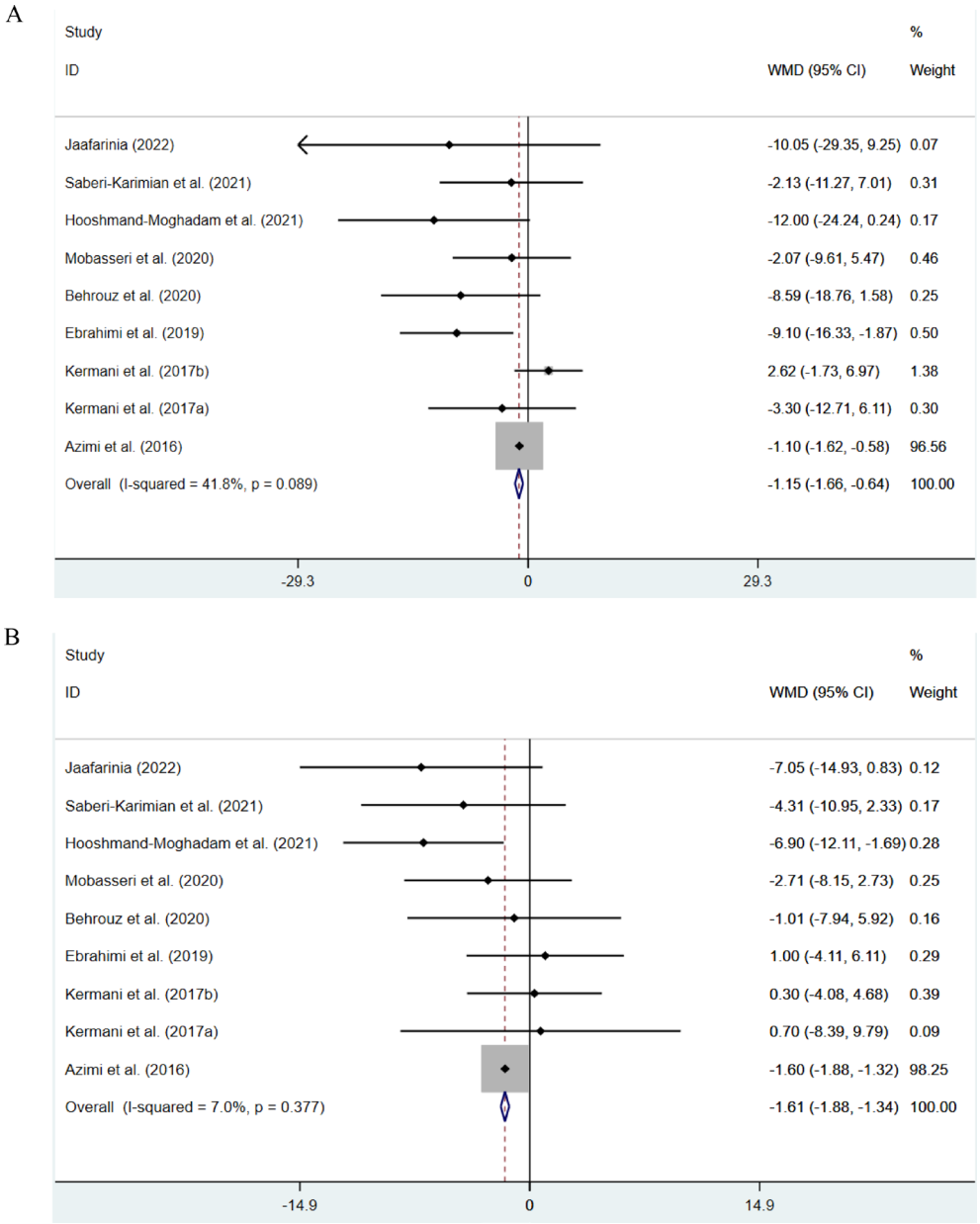

FIGURE 5 | Forest plot of the effects of saffron supplementation on SBP (A) and DBP (B).

Inamdar 2010; Shirali, Zahra Bathaie, and Nakhjavani 2013). The lipid-lowering mechanisms of saffron and its constituents encompass preventing oxidative stress, activating peroxisome proliferator-activated receptor alpha (PPAR-α), inhibiting lipase, and increasing lipocalin levels (Alavizadeh and Hosseinzadeh 2014). Saffron prevents oxidative stress by decreasing the lipid peroxidation malondialdehyde (MDA) and the production of reactive oxygen species through the up-regulation of antioxidant enzymes such as superoxide dismutase and glutathione reductase (Nasimi Doost Azgomi et al. 2022). Crocin reduces the gene expression of adipogenic lipocalin (aP2), peroxisome proliferator-activated receptor-γ (PPAR-γ), fatty acid synthase (FAS), sterol regulatory element-binding protein-1c (SREBP-1c), CCAAT/enhancer-binding protein α (CEBPα), CEBPβ, diacylglycerol acyltransferase (DGAT), stearoyl coenzyme A desaturase 1 (SCD1), and up-regulates PPARα, hormone-sensitive lipase (HSL) and lipoprotein lipase (LPL), thereby inhibiting adipogenesis and lipid accumulation and promoting lipolysis (Yaribeygi et al. 2024). Our results illustrated the lipid-reducing effects of saffron supplementation in TC, with subgroup analysis indicating a reduction in TG. Nonetheless, saffron supplementation did not influence LDL-C, HDL-C, BMI, and WC. Our findings suggested that the active components of saffron might have a synergistic effect in exerting hypolipidemic effects. Therefore, when used clinically to lower blood lipids, saffron should be used in combinations rather than using its single compound, such as crocin. In addition, one study has shown a linear dependence between the intervention dose of saffron and TC and TG (Rahmani et al. 2019). Therefore, the intervention type and dose of saffron should be carefully selected in future relevant clinical studies. These findings were partially in line with some previous meta-analyses (Amatto et al. 2024; Pourmasoumi et al. 2019; Rajaei et al. 2013; Zamani et al. 2022), but differ from the meta-analysis of (Roshanravan et al. 2022).

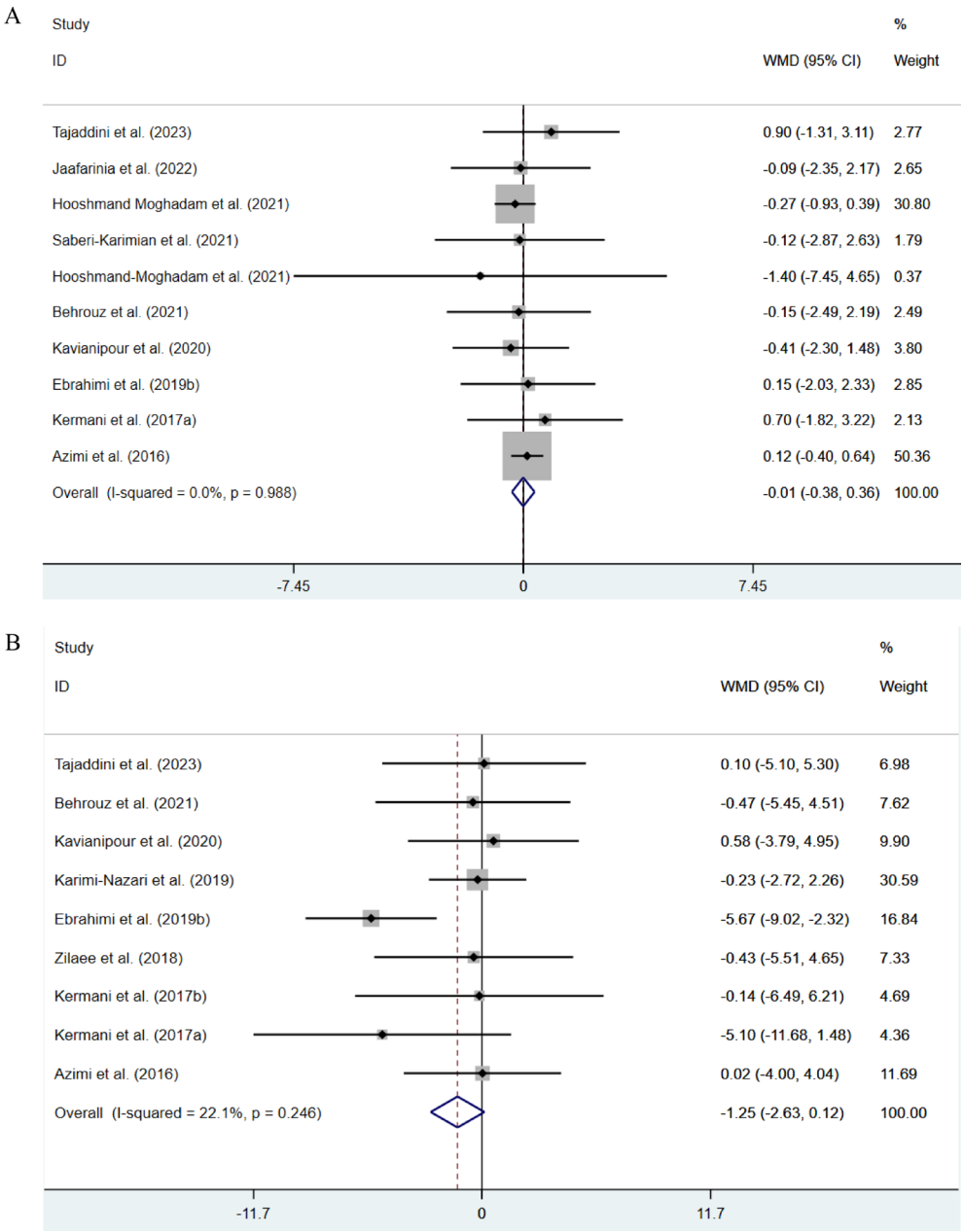

FIGURE 6 | Forest plot of the effects of saffron supplementation on BMI (A) and WC (B).

In chemically induced hypertension animal models, saffron showed a significant anti-hypertensive effect (Imenshahidi et al. 2015; Nasiri et al. 2015). The hypotensive effect of saffron may be related to its antioxidant, anti-inflammatory, and vasomodulation effects. Saffron and corcin can increase nitric oxide (NO) production via the regulation of NO synthase, thereby lowering blood pressure through vasomodulation (Mousavi, Tayarani, and Parsaee 2010; Tang et al. 2006). In addition, Saffron can protect endothelial cells from oxidative damage by enhancing the expression of antioxidant enzymes, thereby regulating blood pressure (Setayesh et al. 2021). Increased expression of intercellular adhesion molecule-1 (ICAM-1) affects the renin-angiotensin system by initiating inflammatory processes, leading to hypertension (Cottone et al. 2007). Crocetin can inhibit hypertension by upregulating the expression of ICAM-1 protein (Xiang et al. 2006). Our results suggested that saffron supplementation decreased DBP and SBP in individuals with MetS-related disorders. Confirming this, a meta-analysis on saffron's effect on blood pressure also highlighted its anti-hypertensive properties (Setayesh et al. 2021).

We used Egger's and Begg's tests to assess publication bias in this study. The results suggested no substantial evidence of publication bias was observed in the meta-analysis (p values ranged from 0.118 to 1.000). However, it is worth noting that publication bias cannot be entirely ruled out because certain studies with null/negative findings may be more difficult to publish than studies with positive findings. If there is potential publication bias, especially the absence of negative results, it may lead to an overestimation of the corresponding results.

Although the included studies were randomized controlled trials, differences in their trial design such as blinding, randomization techniques, and control conditions may lead to variations

in the effects of saffron supplementation on metabolic parameters, which may impact the observed outcomes. The small sample sizes of included studies may lead to overestimating the findings. The duration of the intervention affects participants' physiologic responses, adherence, and retention, thereby influencing the overall outcome of the trial. Although subgroup analyses showed significant reductions in FBG, HbA1c, SBP, and DBP levels at intervention durations of less than 12 weeks, longer interventions may reveal ongoing benefits or potential adaptive effects, warranting further investigation. Regarding the intervention dose of saffron, our subgroup analysis indicated that doses exceeding 100 mg/day yielded remarkable reductions in HbA1c, TC, DBP, and SBP. However, balancing efficacy and safety remains critical as excessive doses may trigger adverse effects, underscoring the necessity for future studies to explore the dose–response relationship of saffron. In addition, some confounding factors such as diet, physical activity, and concomitant medications can also impact participants' metabolic parameters, potentially over- or underestimating the observed results. Hence, it is crucial to interpret these findings with caution.

In addition, none of the included studies found any adverse reactions associated with saffron or crocin after intake. Even doses of saffron up to 1.5 g/d have been reported to be safe (Roshanravan and Ghaffari 2022). Therefore, using saffron as a complementary therapy for managing MetS and related diseases is safe. However, pregnant women should avoid using saffron as high doses may cause miscarriage and embryo abnormalities (Ghaffari and Roshanravan 2019).

Systematic reviews and meta-analyses represent the pinnacle of the hierarchy of clinical evidence (Izzo et al. 2016). This meta-analysis exhibits several strengths. It represents the initial systematic review and meta-analysis examining the potential efficacy of saffron supplementation in addressing MetS and associated disorders, to the best of our knowledge. The study adheres to the PRISMA guidelines to ensure high quality. All the included studies are RCTs with a low overall risk of bias. There are also a few limitations to be considered. First, all included studies were carried out on the Iranian population, necessitating validation of these findings for other ethnic groups through pertinent clinical research. However, these results can provide a reference for clinical research and applications related to saffron. Second, we did not search grey literature, which may result in missing certain studies. Finally, despite conducting subgroup analyses, the reasons for the high heterogeneity of specific parameters remain unidentified, posing a potential threat to the credibility of the results.

5 | Conclusion

The current meta-analysis suggests that saffron supplementation can help reduce FBG, HbA1c, TC, DBP, and SBP in individuals with MetS and related disorders. However, no statistically significant variances were observed between the saffron supplementation and placebo groups concerning insulin resistance (HOMA-IR), serum lipid levels (TG, HDL-C, and LDL-C), as well as anthropometric parameters (BMI and WC). Larger, well-designed RCTs involving diverse ethnic populations are needed to validate the efficacy of saffron supplementation in MetS and related disorders.

Author Contributions

Xiaolei Zhang: conceptualization, data curation, methodology, software, writing – original draft, writing – review and editing. **Jinxin Miao:** data curation, software, writing – original draft, writing – review and editing. **Yagang Song:** data curation, methodology, supervision, writing – review and editing. **Mingsan Miao:** conceptualization, funding acquisition, project administration, supervision, writing – review and editing.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.