Effects of dietary polyphenol curcumin supplementation on metabolic, inflammatory, and oxidative stress indices in patients with metabolic syndrome: a systematic review and meta-analysis of randomized controlled trials

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Objective: The aim was to conduct a systematic review and meta-analysis for assessing the effectiveness and safety of dietary polyphenol curcumin supplement on metabolic, inflammatory, and oxidative stress indices in patients with metabolic syndrome (MetS).

Methods: A comprehensive search for clinical trials was conducted in the following scientific databases: PubMed, SCOPUS, Cochrane Library, EMBASE, Web of Science, and China Biological Medicine. Randomized controlled trials (RCTs) evaluating the efficacy and safety of curcumin supplement for MetS were identified. A random-effects meta-analysis was performed using inverse variance, and efficacy was expressed as mean difference (MD) with 95% confidence interval (CI). The metabolic syndrome markers that were evaluated in the present study included waist circumference (WC), fasting blood sugar (FBS), systolic blood pressure (SBP), diastolic blood pressure (DBP), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), tumor necrosis factor-a (TNF-a), interleukin 6 (IL-6), C-reactive protein (CRP), ultrasensitive c-reactive protein (hsCRP), and malondialdehyde (MDA). By employing the Cochrane tool, RCTs were assessed for bias risk.

Results: A total of 785 participants from 13 RCTs were included, with intervention durations ranging from 4 to 12 weeks. Compared with the control group, the curcumin group had positive effects on WC (MD = -2.16, 95% CI: -3.78 to -0.54, p = 0.009, seven studies), FBS (MD = -8.6, 95% CI: -15.45 to -1.75, p = 0.01, nine studies), DBP (MD = -2.8, 95% CI: -4.53 to -1.06, p = 0.002, five studies), HDL-C (MD = 4.98, 95% CI: 2.58 to 7.38, p < 0.0001, eight studies), TNF-a (MD = -12.97, 95% CI: -18.37 to -7.57, p < 0.00001, two studies), CRP (MD = -1.24, 95% CI: -1.71 to -0.77, p < 0.00001, two studies), and MDA (MD = -2.35, 95% CI: -4.47 to -0.24,

p = 0.03, three studies). These improvements were statistically significant. Meanwhile, there was no significant improvement in SBP (MD = -4.82, 95% CI: -9.98 to 0.35, p = 0.07, six studies), TG (MD = 1.28, 95% CI: -3.75 to 6.30, p = 0.62, eight studies), IL-6 (MD = -1.5, 95% CI: -3.97 to 0.97, p = 0.23, two studies), or hsCRP (MD = -1.10, 95% CI: -4.35 to 2.16, p < 0.51, two studies). FBS, SBP, HDL-C, IL-6, CRP, hsCRP, and MDA had a relatively high heterogeneity.

Conclusion: Curcumin exhibited promising potential in enhancing markers associated with metabolic syndrome, including inflammation. However, additional studies are required to confirm such findings since the included evidence is limited and has a relatively high heterogeneity.

Systematic review registration: https://www.crd.york.ac.uk/prospero, identifier CRD42022362553.

KEYWORDS

curcumin, turmeric, metabolic syndrome, inflammation, meta-analysis

1 Introduction

Metabolic syndrome (MetS) is a metabolic disease. The National Cholesterol Education Program Adult Treatment Panel III (NCEP: ATPIII) and the International Diabetes Federation (IDF) are prominent organizations dedicated to addressing issues related to cholesterol and diabetes. At present, the two most extensively adopted definitions are those of the IDF and NCEP: ATP III (1). The criteria of both organizations for assessing MetS include waist circumference (WC), blood pressure (for assessing MetS BP), fasting blood sugar (FBS), triglycerides (TG), and high-density lipoprotein cholesterol (HDL-C) (2). As a novel non-communicable disease, metabolic syndrome has emerged as a global problem. MetS, although challenging to measure epidemiologically, is estimated to be approximately three times more prevalent than diabetes. Therefore, it is believed to affect around one-fourth of the global population already (3). Moreover, MetS can lead to an increased risk of diabetes and coronary heart disease and is associated with a number of malignancies, including colon, liver, and pancreatic cancers (4, 5).

Abdominal adiposity is highly correlated to increased morbidity and mortality (6). Additionally, it serves as an indicator of "dysfunctional adipose tissue," which is a key factor in the clinical diagnosis of MetS (7). MetS is a growing global public health concern. To effectively manage the condition, new and efficient treatments with minimal adverse effects are urgently needed.

Curcumin, a natural plant-based dietary polyphenol, is an active ingredient derived from turmeric from the ginger family. Curcumin has anti-inflammatory, anti-oxidant, anti-diabetic, and anti-atherosclerotic properties (8–10), which can improve the metabolic parameters and symptoms of polycystic ovarian syndrome, MetS, non-alcoholic fatty liver, and cardiovascular disease (11). As suggested by a recent study, curcumin is a potential drug for dealing with MetS (12).

In previous research, curcumin supplementation has been reported to improve obesity-related indices, fasting glucose, and lipids in metabolic diseases such as obesity, fatty liver, and MetS (13–18). A previous meta-analysis also revealed that curcumin supplementation improved certain components of MetS, including FBS, TG, diastolic blood pressure (DBP), and HDL-C, but there were no significant changes in systolic blood pressure (SBP) and WC (19). Another study reported similar results (20). However, four (21–24) newly randomized controlled trials on metabolic indices were missed in the aforementioned meta-analysis. Notably, pro-inflammatory state and oxidative stress are significant factors of MetS and play an important role in the development process of MetS (25, 26). In a previous meta-analysis, it was found that curcumin did not have a significant effect in reducing inflammatory markers associated with chronic inflammatory diseases (27). However, a randomized controlled trial demonstrated that curcumin supplementation improved the indicators of inflammation and oxidative stress in patients with critical sepsis (28). Furthermore, in one study, oxidative stress and inflammatory markers in conditions such as obesity, diabetes, and non-alcoholic fatty liver disease (NAFLD) were systematically reviewed (29). However, there has been no systematic review conducted specifically on inflammatory and oxidative stress markers in patients with metabolic syndrome (MetS). As such, the aim of the present study was to perform a meta-analysis of published randomized controlled clinical trials to further evaluate the effects of curcumin on metabolic, inflammatory, and oxidative stress markers in patients with MetS.

2 Methods

The Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) 2020 (30) standards were followed in

the execution of the current meta-analysis, which was registered with PROSPERO under ID number CRD42022362553.

2.1 Literature search strategy

From the outset through June 2022, six electronic databases—PubMed, SCOPUS, Cochrane Library, EMBASE, Web of Science, and China Biological Medicine (CBM)—were thoroughly searched. The terms used included the following: "curcumin" or "turmeric yellow" or "yellow, turmeric" or "curcumin phytosome" or "curcuminoid" or "curcuma" or "curcuminoid supplement" or "curcumin extract" and "metabolic syndrome" or "metabolic syndromes" or "syndrome, metabolic" or "syndromes, metabolic" or "metabolic syndrome X" or "insulin resistance syndrome X" or "syndrome X, metabolic" or "syndrome X, insulin resistance" or "metabolic X syndrome" or "syndrome, metabolic X" or "X Syndrome, metabolic" or "dysmetabolic syndrome X" or "Reaven syndrome X" or "syndrome X, Reaven" or "metabolic cardiovascular syndrome" or "cardiovascular syndrome, metabolic" or "syndrome, metabolic cardiovascular" or "cardiometabolic syndrome" or "cardiometabolic syndromes" or "syndrome, cardiometabolic" or "insulin resistance syndrome x" or "insulin resistance" or "metabolic diseases" or "plurimetabolic syndrome" or "syndrome x plus", and "randomized controlled trial" or "randomized" or "placebo" or "RCTs". In order to include any relevant studies that may not have been captured in the initial database search, a thorough examination of the reference lists of potentially eligible literature was conducted.

2.2 Research selection

The studies included in the present analysis met the following inclusion criteria (1): participants of both genders aged 18 years or older, (2) diagnosed with metabolic syndrome according to either NCEP-ATP III or IDF guidelines (31), (3) evaluated the effects of curcumin on at least one metabolic, inflammatory, or oxidative stress marker, and (4) provided data on the baseline and endpoint measurements for both intervention and control groups or reported changes within each group. When there were numerous reports regarding the identical population under study, the most comprehensive dataset was examined. There were no exclusions based on the individuals' race or sexual orientation (Table 1).

The following exclusion criteria were applied: (1) trials without specific restrictions, (2) studies with a duration of less than 4 weeks, (3) participants taking antihypertensive, antidyslipidemic, or antidiabetic medications, (4) insufficient data reported in the included studies, and (5) participants with malignancies or other systemic or chronic diseases unrelated to diabetes.

2.3 Data extraction and quality assessment

After removing any duplicate entries, two reviewers individually evaluated the remaining records for qualification using the titles and abstracts. Subsequently, the reviewers individually selected potentially eligible literature in full text for inclusion in the present study. The title of the initial author, the publishing year, the location, the number of participants (in the intervention and placebo arms), the MetS diagnostic criteria, the participants' ages and genders, the intervention dose, the length of the study, the reported side effects, and the results were all extracted by two reviewers.

Using the method suggested by the Cochrane Handbook V.5.1.0 (32), two writers independently evaluated the included randomized controlled trials' (RCTs) risk of bias. Seven categories were considered during the evaluation, including the blinding of participants and staff, the blinding of the result evaluation, bad outcome data, selective reporting, and other biases. According to the recommendations in the Cochrane Handbook, each item was awarded a risk-of-bias score that ranged from moderate to high to unclear. In addition, STATA 15.1 software was used to plot funnel plots for determining the presence of publication bias.

2.4 Statistical analysis

Review Manager was used for every analysis (RevMan 5.4; Cochrane Collaboration, Copenhagen, Denmark) (33). In comparison to the controls, curcumin's effects on metabolic indices and inflammatory marker results were expressed as mean differences (MD) and reported with corresponding 95% confidence intervals (CI). For all data, a p-value less than 0.05 was regarded as statistically significant. The heterogeneity was assessed by inconsistency(I^2) and chi-square tests. High heterogeneity between studies was considered when the heterogeneity $p < 0.1$ and $I^2 \geq 50\%$. Conversely, low heterogeneity was considered when

TABLE 1 Eligibility criteria.

Inclusion criteria	
Participants	Patients with a diagnosis MetS
Interventions	The intervention group was given curcumin supplementation (unlimited dose, dosage form, or duration)
Comparisons	The control group was treated with placebo or blank
Outcomes	WC, FBS, SBP, DBP, TG, HDL-C, TNF-a, IL-6, CRP, hsCRP, and MDA
Study type	RCTs assessing the effects of curcumin supplementation on MetS

these criteria were not met. By removing one study at a time and redoing the analysis, a sensitivity analysis was performed. Subgroup analyses were also conducted by sample size and intervention duration based on the features of the included studies.

3 Results

3.1 Selection of trials

The explicit research screening process is shown in Figure 1. The preliminary database retrieval and the additional retrieval yielded a total of 691 records, with 434 articles being excluded for duplicated records. A total of 241 items were eliminated after reading the titles and abstracts in accordance with the inclusion and exclusion criteria. After reading the full texts of 16 studies, two studies were excluded due to non-compliant outcome indicators, and one study had missing data. This resulted in the inclusion of 13 randomized controlled studies with 785 patients (21–24, 34–42).

3.2 Research characteristics

Table 2 provides an overview of the trials that were taken into consideration. All 13 studies included in the analysis were parallel RCTs conducted between 2014 and 2022. Iran ($n = 10$) accounted for the majority of the trials, followed by Pakistan ($n = 1$), China ($n = 1$), and Italy (n = 1). The total sample size included 785 MetS participants (373/412, male/female). Two cohorts contained exclusively male (34, 36) participants, and two cohorts consisted of only female (24, 35) participants. The trials ranged in length from 4 to 12 weeks, with two lasting 4 weeks (21, 38), three lasting 6 weeks (24, 35, 41), four lasting 8 weeks (34, 36, 39, 40), and four lasting 12 weeks (22, 23, 37, 42).

3.3 Risk of bias

Figure 2 demonstrates that three studies were assigned a low risk of bias due to extensive reporting of information on each item, while 10 trials were given an uncertain risk of bias due to insufficient reporting. Among the included studies, 10 RCTs had insufficient information regarding the random sequence generation method (21, 22, 24, 34, 35, 38–42), and 10 RCTs had imperfect allocation concealment information (21, 22, 24, 34, 35, 38–42). The design and blinding implementation of three RCTs were not clear (21, 34, 38).

3.4 Results of the meta-analysis

3.4.1 Waist circumference
Seven trials (22–24, 34, 36, 38, 41) gave waist circumference data without heterogeneity ($p = 0.97$, $I2 = 0\%$); hence, a fixed-effects model

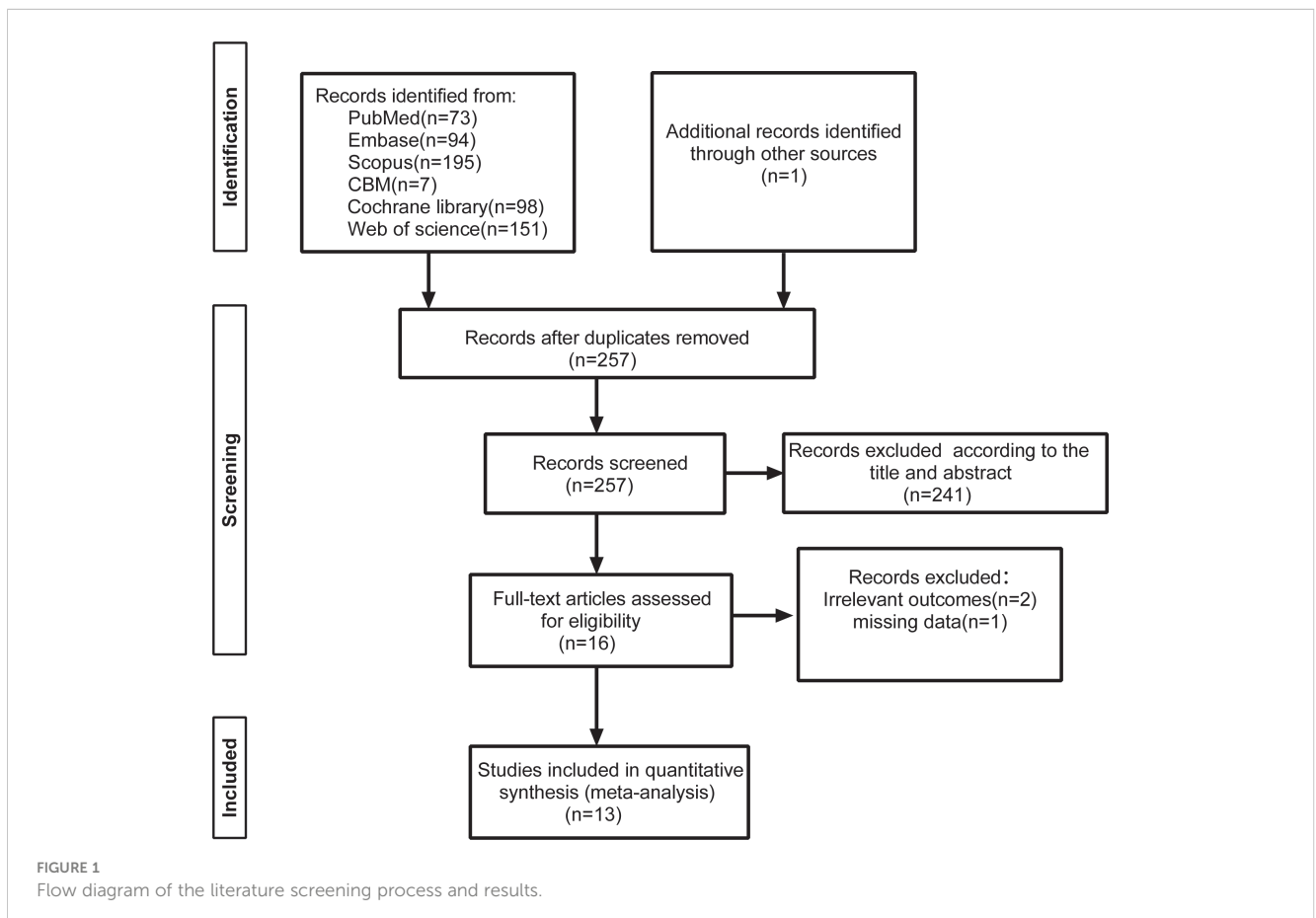**FIGURE 1**
Flow diagram of the literature screening process and results.

TABLE 2 Characteristics of the trials included in the meta-analysis.

Author, year	Location	MetS diagnostic criteria	Age (intervention/control)	No. of participant (intervention/control)	Sex (female/male)	Type of intervention/placebo	Dose of intervention (mg/day)	Duration of study (weeks)	Side effects	Outcome
Salimi, 2017	Iran	NCEP-ATP III	Mean age, 48	10/10	20/0	Curcumin/placebo	20 mg/kg	8	None	BMI, weight, WC, FBG, FAT%, BP, HDL-C, TG, TNF-α,
Alidadi, 2021	Iran	IDF	42.84 ± 6.25/ 44.43 ± 5.92	32/28	29/31	Curcumin/placebo	500	12	None	BMI, WC, NC, FM, VFA, weight, FPG, TC, TG, HDL-C, LDL-C, SBP, DBP
Amin, 2015	Pakistan	NCEP-ATP III	42.4 ± 13.7/41.57 ± 12.8	56/52	108/0	Supplement of turmeric powder/ spaghula husk capsule	2,400	8	Dyspepsia	BMI, weight, WC, HC, SBP, DBP, FBG, LDL, HDL, TG, CRP
Bateni, 2021	Iran	NCEP-ATP III	50 ± 9/54 ± 7	22/21	10/33	Nana-micelle curcumin/placebo	80	12	None	BMI, weight, WC, total body fat%, total body muscle%, SBP, DBP, FBS, HbA1c, Insulin, TG, TC, LDL-C, HDL-C
Pierro, 2015	Italy	NCEP-ATP III	39.10 ± 16.8/ 41.85 ± 15.91	22/22	17/27	Curcumin supplement/ phosphatidylserine	800	4	None	BMI, Weight, WC, HC, FAT%
Osali, 2020	Iran	NCEP-ATP III	Mean age, 62.3 ± 1.23	11/11	0/22	Nano-curcumin/ placebo	80	6	None	BMI, Weight, WC, Glucose, SBP, TG, HDL, body fat%, MDA, CRP, IL-6, IL-10
Panahi, 2015	Iran	NCEP-ATP III	44.80 ± 8.67/ 43.46 ± 9.7	50/50	50/50	Curcuminoids–piperine/placebo	1,000	8	None	hsCRP, MDA, SBP, DBP, FBS, HbA1c
Saberi-Karimian,2018	Iran	IDF	37.52 ± 9.47/ 38.59 ± 10.28	36/36	11/61	Curcumin/placebo	1,000	6	None	Weight, BMI, WC, FBG, hsCRP, FAT%, SBP, DBP, LDL-C, HDL-C, TC, TG, T-Chol, Apo A, Apo B
Yang, 2014	Iran	NCEP-ATP III	59.03 ± 10.1/ 59.61 ± 14.09	30/29	23/36	Curcumin extract/ placebo	1,890	12	Stomach pain, mild diarrhea, nausea	Weight, BMI, TG, T-Chol, FPG, HDL-C, LDL-C, T-Chol, VLDL, HbA1c
Bateni, 2022	Iran	NCEP-ATP III	50 ± 9/54 ± 7	22/21	10/33	Nana-micelle curcumin/placebo	80	12	None	TAC, MDA, hsCRP, NF-kB
Panahi, 2016	Iran	NCEP-ATP III	44.80 ± 8.67/ 43.46 ± 9.7	50/50	50/50	Curcuminoids–piperine/placebo	1,000	8	Gastrointestinal	TNF-α, IL-6, TGF-β, MCP-1
Zhang, 2019	China	NCEP-ATP III	66.9 ± 14.1/68.1 ± 12.3	46/46	45/47	Curcumin/control	1,500	4	None	TC, TG, FPG, LDL-C, HDL-C
Osali, 2018	Iran	NCEP-ATP III	Mean age, 62.3 ± 1.23	11/11	0/22	Nano-curcumin/ placebo	80	6	None	TNF-α

MetS, metabolic syndrome; BMI, body mass index; WC, waist circumference; FBG, fasting blood glucose; BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TNF, tumor necrosis factor; IL, interleukin; CRP, C-reactive protein; hsCRP, high-sensitivity C-reactive protein; Apo A, apolipoprotein A; Apo B, apolipoprotein B; VLDL, very-low-density lipoprotein; HbA1c, hemoglobin A1c; MDA, malondialdehyde; HC, hip circumference; NC, neck circumference; VFA, visceral fat area; TGF-β, transforming growth factor beta; MCP-1, chemoattractant protein-1.
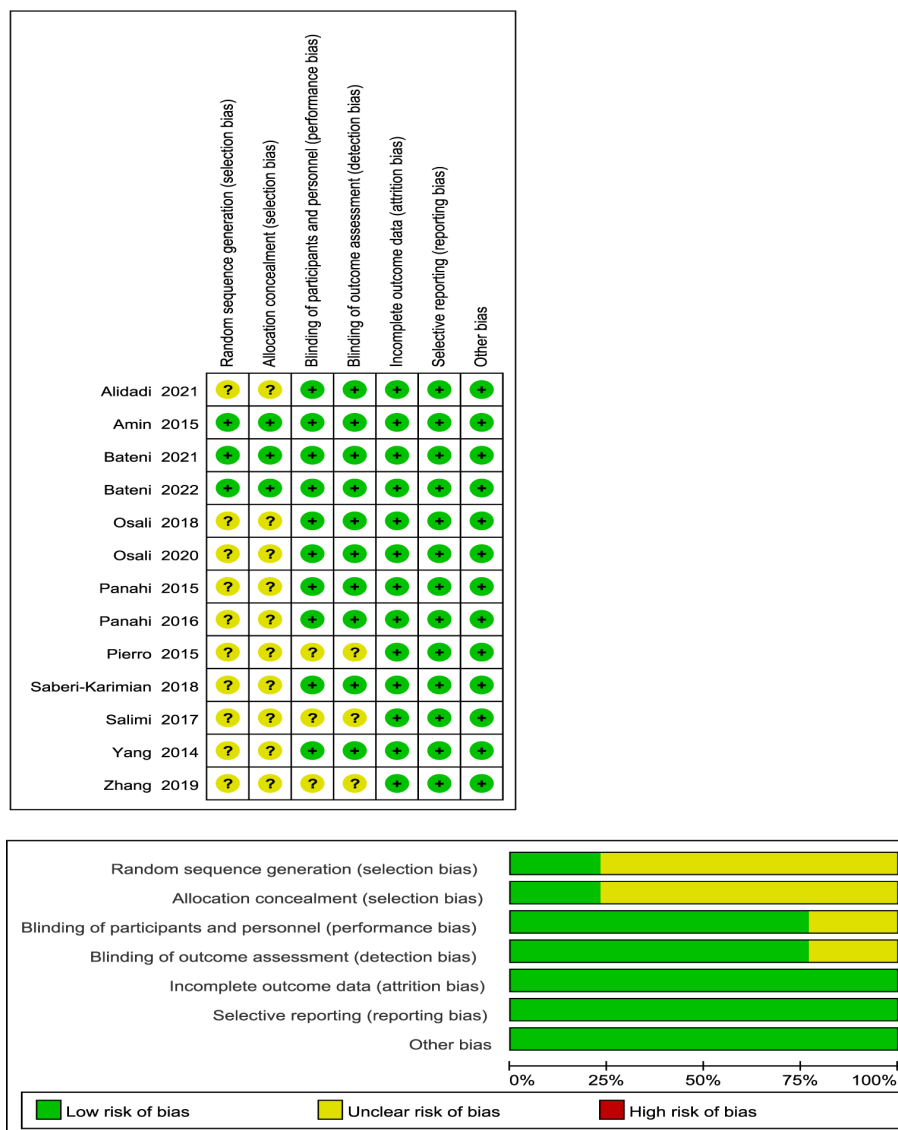
FIGURE 2
Risk assessment of the included studies.

was used. The outcomes demonstrated that, as a consequence of reducing WC, the intervention group surpassed the control group (MD = -2.16, 95% CI: -3.78 to -0.54, p = 0.009) (Figure 3).

3.4.2 Fasting blood sugar

Nine trials (21–24, 34, 36, 39, 41, 42) showed statistically significant heterogeneity in fasting glucose outcomes (p = 0.0005, $I2$ = 71%) and therefore used a random-effects model. The findings demonstrated that the experimental group fared better in decreasing the FBS than the placebo group (MD = -8.6, 95% CI: -15.45 to -1.75, p = 0.01) (Figure 4).

3.4.3 Blood pressure

A fixed-effects model was used to analyze the results, which revealed that the intervention group outperformed the control group in lowering the diastolic blood pressure (MD = -2.8, 95%

CI: -4.53 to -1.06, p = 0.002) (Figure 5). A total of five studies (22, 23, 36, 39, 41) reported diastolic blood pressure outcomes without statistically significant homogeneity (p = 0.16, $I2$ = 40%).

A total of six studies (22–24, 36, 39, 41) reported statistically significant heterogeneity in SBP outcomes (p = 0.0004, $I2$ = 78%) and therefore used a random-effects model. According to the findings, curcumin had a negligible impact on SBP (MD = -4.82, 95% CI: -9.98 to 0.35, p = 0.07) (Figure 6).

3.4.4 Triglycerides

Eight studies (21–24, 34, 36, 41, 42) showed triglyceride outcomes with no statistically significant heterogeneity (p = 0.21, $I2$ = 27%). As such, the results of a fixed-effects model demonstrated that curcumin's influence did not significantly lower the TG (MD = 1.28, 95% CI: -3.75 to 6.30, p = 0.62) (Figure 7).
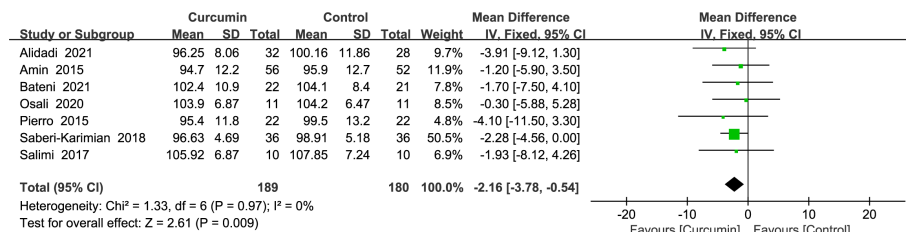
FIGURE 3

Effect of curcumin supplement on waist circumference.

3.4.5 High-density lipoprotein cholesterol

Eight trials (21–24, 34, 36, 41, 42) demonstrated significant heterogeneity in the outcomes related to HDL cholesterol (p = 0.001, $I2$ = 71%). By employing a random-effects model, the data indicated that the intervention group had a more pronounced effect in increasing HDL cholesterol levels compared with the placebo group (MD = 4.98, 95% CI: 2.58 to 7.38, p < 0.0001) (Figure 8).

3.4.6 Inflammation indicators

Two studies (24, 40) reported statistically significant heterogeneity in the results for interleukin 6 (IL-6) (p = 0.02, $I2$ = 81%). Thus, the results of a model with random effects showed that curcumin had no discernible impact on IL-6 (MD = -1.5, 95% CI: -3.97 to 0.97, p = 0.23) (Figure 9A).

The tumor necrosis factor-a (TNF-a) results from two trials (35, 40) reported high homogeneity (p = 0.004, $I2$ = 88%). After employing a model with random effects, the outcomes revealed that the intervention group surpassed the control group in lowering the TNF-a (MD = -12.97, 95% CI: -18.37 to -7.57, p < 0.00001) (Figure 9B).

Based on the results of two studies (24, 36), which did not show statistically significant heterogeneity for C-reactive protein (CRP) outcomes (p = 0.58, $I2$ = 0%), a fixed-effects model was used. The findings indicated that the intervention group exhibited a greater reduction in CRP levels compared with the control group (MD = -1.24, 95% CI: -1.71 to -0.77, p < 0.00001) (Figure 9C).

Two studies (37, 39) reported statistically significant homogeneity (p < 0.00001, $I2$ = 98%) in the results for ultrasensitive C-reactive protein (hsCRP). After employing a model with random effects, the findings revealed that the effect of curcumin did not significantly alter the hsCRP (MD = -1.10, 95% CI: -4.35 to 2.16, p = 0.51) (Figure 9D).

3.4.7 Oxidative stress marker

Three studies (24, 37, 39) reported statistically significant heterogeneity (p < 0.00001, $I2$ = 92%) in the results for malondialdehyde (MDA). Using a random-effects model, the results showed that the intervention group was superior to the control group in reducing MDA (MD = -2.35, 95% CI: -4.47 to -0.24, p = 0.03) (Figure 10).

3.5 Adverse events

A total of three studies (36, 40, 42) reported mild gastrointestinal and digestive adverse effects, mainly including diarrhea, nausea, and constipation, which could be attributed to the high daily dose of curcumin.

3.6 Publication bias

Publication bias was assessed for WC as an outcome indicator using a funnel plot. The Begg's test yielded a p-value of 0.548, and the Egger's test yielded a p-value of 0.946. The results suggest that there was no substantial publication bias among the included studies. The funnel plot is shown in Figure 11.

3.7 Sensitivity analysis

Significant heterogeneity was observed in studies reporting FBS, SBP, and HDL-C. As such, sensitivity analyses were performed to identify the potential causes. The sensitivity analysis indicated that
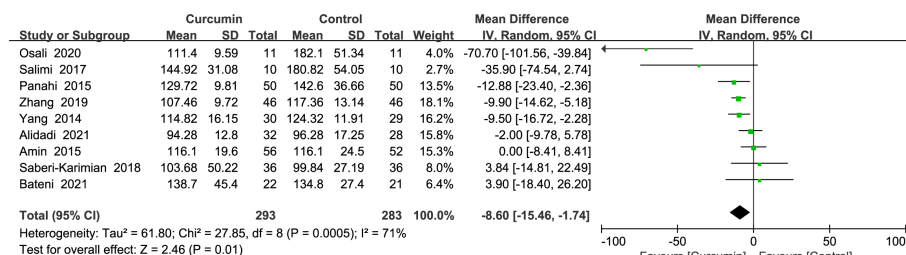

FIGURE 4

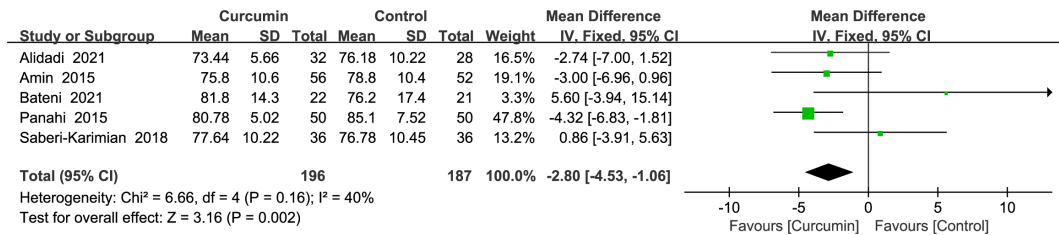Effect of curcumin supplement on fasting blood sugar.

FIGURE 5
Effect of curcumin supplement on diastolic blood pressure.

the study by Osai et al. (2020) had a notable influence on the heterogeneity of the FBS and SBP outcomes. However, after removing the study from the analysis, the heterogeneity became non-significant (Supplementary Figures S1, S2). For the heterogeneous results of HDL-C, no single study interfered with the results when any single study was excluded (Supplementary Figure S3).

3.8 Subgroup analysis

The results of the subgroup analyses by sample size or duration did not differ from those of the overall analyses of FBS, SBP, DBP, TG, and HDL-C. (Supplementary Figures S4–S8). The only exception was a significant increase in HDL-C in trials with a duration less than or equal to 6 weeks compared with trials with a duration greater than 6 weeks (Supplementary Figure S8A). The subgroup analyses by duration or sample size showed differences from the overall analysis of WC, which did not change significantly in trials with durations greater than 6 weeks (Supplementary Figure 9A) or in trials with less than 60 patients (Supplementary Figure 9B).

3.9 GRADE assessment

The GRADE tool was used to rate the evidence for the 11 outcome indicators (WC, FBS, DBP, SBP, TG, HDL-C, IL-6, TNF-a, CRP, hsCRP, and MDA). The evidence was categorized as "moderate", "low", or "very low" based on specific reasons for downgrading, such as a high risk of bias, inconsistency, and imprecision. The detailed ratings and reasons for downgrading can be found in Table 3.

4 Discussion

The effects of curcumin supplementation on WC, FBS, BP, TG, and HDL levels and inflammatory markers (IL-6, TNF-a, CRP, and hsCRP) in MetS patients were assessed by analyzing 13 randomized controlled trials. The minimum duration of the studies was 4 weeks, and the maximum duration was 12 weeks. The results of the present study show significant improvements in WC, FBS, DBP, HDL, and inflammatory markers (TNF-a and CRP) levels. However, there were no significant changes observed in SBP, TG levels, IL-6, and hsCRP.

In comparison with a previous systematic evaluation (19), the present results differ in terms of waist circumference, and curcumin supplementation was found to significantly reduce waist circumference. The reason for such findings could be attributed to the inclusion of new studies to increase the sample size. As has been previously demonstrated, the pathophysiological mechanism of MetS involves systemic oxidative stress brought on by central obesity (43–45), and waist circumference is a significant indicator of abdominal obesity and a proxy for visceral adipose tissue (46). Waist circumference plays a crucial role in adult metabolic syndrome early detection and the prediction of insulin resistance (47). Studies have confirmed that WC, similar to body mass index (BMI), is associated with BP, insulin resistance, and blood lipids (48). According to epidemiological research, visceral adiposity is a substantial major risk for insulin resistance, cardiovascular disease, stroke, MetS, and mortality (49). Therefore, a reduction in waist circumference can help improve the metabolic index of metabolic syndrome and reduce mortality. Through inhibiting differentiation medium-induced β-catenin downregulation and downregulating the expression of peroxisome proliferator-activated receptor γ (PPARγ) and CCAAT enhancer binding protein α(C/EBPα), the
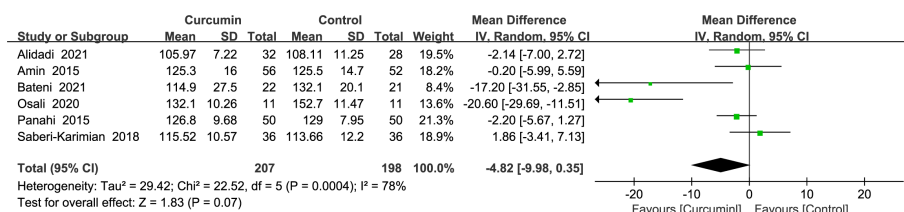

FIGURE 6
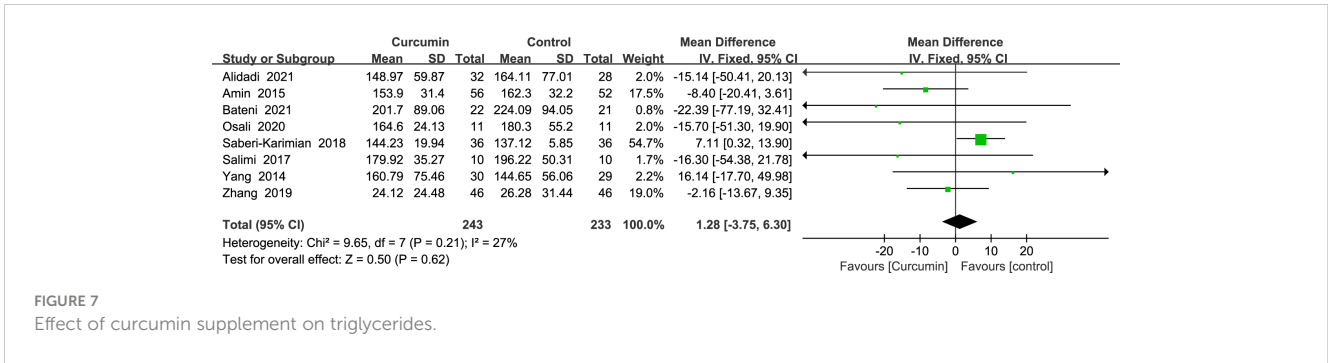Effect of curcumin supplement on systolic blood pressure.

FIGURE 7
Effect of curcumin supplement on triglycerides.

process may contribute to reducing lipid accumulation in 3T3-L1 adipocytes (50).

Furthermore, the impact of curcumin administration on MetS inflammatory and oxidative stress biomarkers was thoroughly examined. A previous systematic review found that curcumin supplementation improved the inflammation and oxidative stress in obesity, diabetes, and NAFLD (29). However, no studies have been conducted to independently perform a meta-analysis on the co-occurrence of metabolic syndrome, inflammation, and oxidative stress. Notably, curcumin supplementation was found to significantly improve TNF-a, but not hsCRP. The two studies included in the analysis of hsCRP were found to differ in the dose of curcumin used and the duration of the intervention, with Bateni et al. (37) using 80 mg of nanocurcumin per day for 12 weeks and Pahahi et al. (2015) using 1,000 mg of curcumin per day for 8 weeks. One study found that a 10-week intervention with 1,500 mg of curcumin daily in type 2 diabetes significantly improved the hsCRP level (51), and another study showed that a 12-week intervention with nano-curcumin in patients with NAFLD significantly improved the hsCRP level (52). Based on such findings, the present authors believe that metabolic syndrome, as a complex metabolic disorder, may require larger doses of curcumin supplementation to achieve a significant improvement in hsCRP. In the present study, there was a significant improvement in TNF-a and CRP inflammatory indexes with curcumin supplementation. The present study encompasses all available research on the association between curcumin supplementation and inflammation as well as oxidative stress in individuals with MetS. Moreover, a broader range of clinical outcome measures related to curcumin supplementation in patients with metabolic syndrome was evaluated, thereby offering additional evidence-based insights.

Curcumin is significant for the improvement of inflammatory and oxidative stress indicators. While the exact pathophysiology of metabolic syndrome remains unclear, there are widely acknowledged potential pathways that contribute to its development. Such pathways include insulin resistance and the presence of chronic low-grade inflammation, which are commonly associated with central obesity (53, 54). Chronic inflammation also interacts with oxidative stress (55). The majority of MetS patients are asymptomatic, but according to the Framingham Risk Score (56), they have a 16% to 18% chance of experiencing their first coronary event within a 10-year timeframe, which raises their risk of cardiovascular disease by fivefold and their risk of type 2 diabetes by twofold (57). Inflammation can also produce insulin resistance directly or indirectly; therefore, various inflammatory markers are considered as reliable MetS biomarkers. The administration of curcumin, which leads to improvements in inflammatory and oxidative stress markers, not only enhances the overall condition of patients with MetS but also reduces the likelihood of developing cardiovascular disease.

In the obese state, adipocyte hypertrophy and overcrowding lead to the hypoxic necrosis of cells, and necrotic adipocytes attract mononuclear macrophages to cluster, and the number of macrophages in adipose tissue increases from 10%–15% to 40%–50%, leading to the infiltration of macrophages. Such infiltration induces the macrophages to polarize to M1-type pro-inflammatory phenotype and generate and emit inflammatory substances such TNF-a, IL-1, and nitric oxide synthase (NOS_2), among others, which, in turn, regulate local and systemic inflammation (58, 59). These inflammatory factors further activate the macrophages and impair insulin signaling in adipocytes, leading to systemic insulin resistance (60). According to epidemiology,
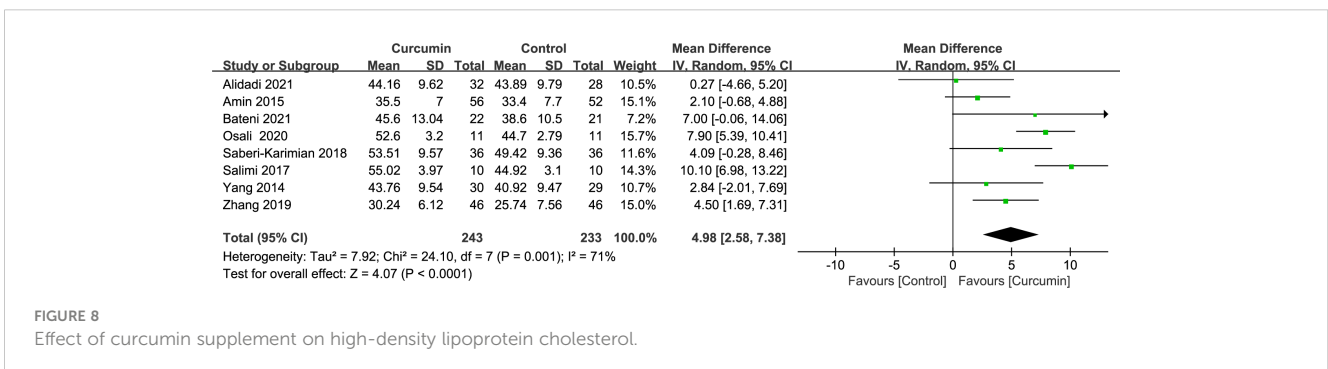

FIGURE 8
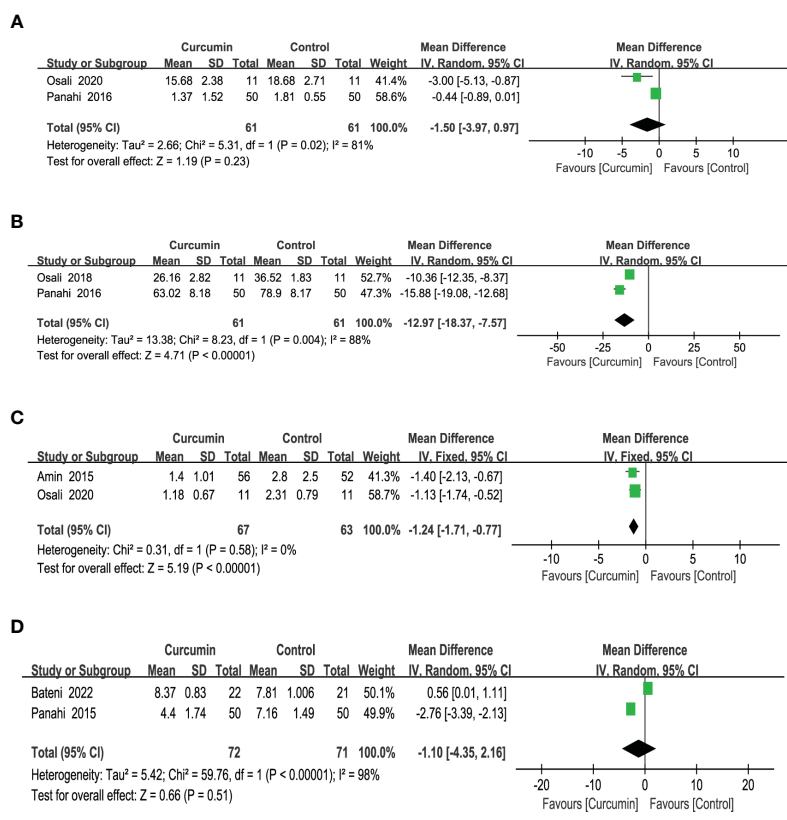Effect of curcumin supplement on high-density lipoprotein cholesterol.

FIGURE 9

Effect of curcumin supplement on inflammation indicators: **(A)** IL-6, **(B)** TNF-a, **(C)** C-reactive protein, and **(D)** hsCRP.

patients with diabetes mellitus (DM), hypertension, atherosclerosis, and cardiovascular events had increased levels of IL-6 and TNF-a (45). Thus, an assumption could be made that the possible mechanism of curcumin treatment of MetS involves reducing chronic inflammation and oxidative stress by regulating macrophage polarization.

First, to our knowledge, the present research represents the first meta-analysis of curcumin's impact on inflammatory and oxidative stress markers in MetS. Second, in the present study, the sample size was expanded by including new studies on the basis of previous meta-analyses. Third, bias was decreased to a certain extent because only randomized controlled clinical trials were included. Fourth, the robustness of the findings was demonstrated through sensitivity analyses in which each study was omitted one at a time, indicating that the conclusions were reliable. Fifth, to evaluate the potential research characteristics of the association between curcumin

supplementation and metabolic syndrome, subgroup analyses of intervention duration and the sample size were conducted.

However, the present study also has several limitations. First, although the present study was not restricted to language and region, 12 of the 13 included studies were from Asian countries, including as many as 10 studies from Iran. The generalizability of the results needs to be further verified. Second, despite being the first meta-analysis conducted on the impact of curcumin on inflammatory and oxidative stress markers in individuals with MetS, the credibility of the results was somewhat compromised due to the limited number of publications included in the study. Third, there was a higher risk of bias in the research since two of the included studies had only male participants and two studies had only female participants. Fourth, the use of products that favorably enhance the bioavailability of curcumin (including piperine or alkaloids) was not excluded. Fifth, the limited amount of research
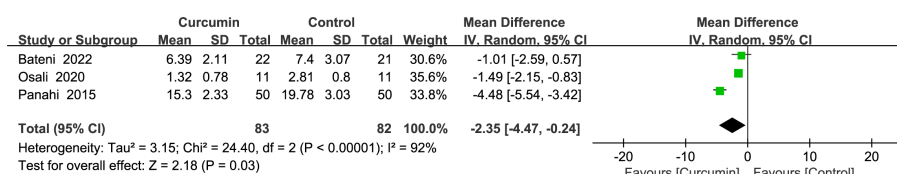

FIGURE 10

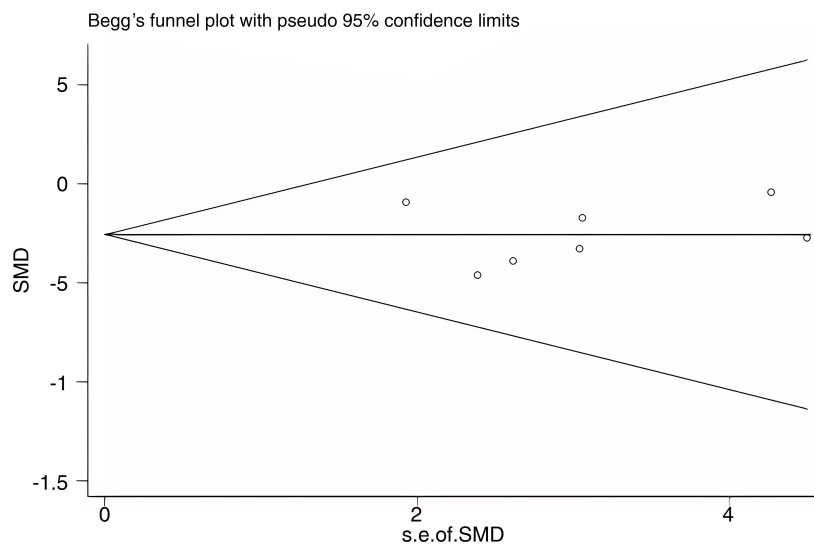Effect of curcumin supplement on malondialdehyde.

FIGURE 11
Publication bias.

TABLE 3 GRADE summary of outcomes for EG *versus* CG for patients with MetS.

Outcomes	No. of participants (studies)	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Certainty of the evidence (GRADE)
		Risk with CG	Risk difference with EG		
WC	369 (7)	The mean WC ranged from 95.9 to 107.85	The mean WC in the EG was 2.16 lower (3.78 to 0.54 lower)	–	⊕⊕◯◯ LOW[a,b]
FBS	576 (9)	The mean FBS ranged from 96.28 to 182.1	The mean FBS in the EG was 8.6 lower (15.46 to 1.74 lower)	–	⊕⊕◯◯ LOW[a,c]
DBP	383 (5)	The mean DBP ranged from 76.18 to 85.1	The mean DBP in the EG was 2.8 lower (4.53 to 1.06 lower)	–	⊕⊕◯◯ LOW[a,b]
SBP	405 (6)	The mean SBP ranged from 108.11 to 152.7	The mean SBP in the EG was 4.82 lower (9.98 to 0.35 lower)	–	⊕⊕◯ LOW[a,c]
TG	476 (8)	The mean TG ranged from 26.28 to 224.09	The mean TG in the EG was 1.28 higher (3.75 lower to 6.3 higher)	–	⊕⊕⊕◯ MODERATE[a]
HDL-C	476 (8)	The mean HDL-C ranged from 25.74 to 49.42	The mean HDL-C in the EG was 1.28 higher (2.58 to 7.38 higher)	–	⊕⊕◯◯ LOW[a,c]
IL-6	122 (2)	The mean IL-6 ranged from 1.81 to 18.68	The mean IL-6 in the EG was 1.50 lower (3.97 lower to 0.97 higher)	–	⊕◯◯◯VERY LOW[a,b,c]
TNF-a	122 (2)	The mean TNF-a ranged from 36.52 to 78.9	The mean TNF-a in the EG was 12.97 lower (18.37 to 7.57 lower)	–	⊕◯◯◯ LOW[a,b]
CRP	130 (2)	The mean CRP ranged from 2.31 to 2.8	The mean CRP in the EG was 1.24 lower (1.71 to 0.77 lower)	–	⊕⊕◯◯ LOW[a,b]
hsCRP	143 (2)	The mean hsCRP ranged from 1.006 to 1.49	The mean hsCRP in the EG was 1.10 lower (4.35 lower to 2.16 higher)	–	⊕◯◯◯ VERY LOW[a,b,c]
MDA	165 (3)	The mean MDA ranged from 2.81 to 19.78	The mean MDA in the EG was 2.35 lower (4.47 to 0.24 lower)	–	⊕◯◯◯ VERY LOW[a,b,c]

CG, control group; CI, confidence interval; EG, experimental group.
[a]Poor methodology including the method of randomization, allocation concealment, and blinding.
[b]Small sample sizes.
[c]$I^2 \geq 50\%$ for heterogeneity.
⊕:Meets the quality of evidence rating. ◯:Does not meet the quality of evidence rating.

available did not allow for a breakdown of the dosage of curcumin utilized in the smaller groups. Sixth, one of the studies included in the analysis used a combination of curcumin and black seed extract. Nigella sativa seed extract had a beneficial effect on MetS, which may have caused a bias in the analysis.

5 Conclusion

The present meta-analysis demonstrates that curcumin supplementation has a positive impact on MetS patients. Future randomized controlled studies should focus on addressing the limitations identified in the present analysis. Future research should aim to include larger sample sizes that encompass diverse ethnic groups, consider gender differences, and explore various forms of curcumin supplements to ensure high bioavailability. In addition, more thorough research is required to determine how curcumin affects inflammatory and oxidative stress indicators in metabolic syndrome. Further exploration is needed to better understand the mechanisms by which curcumin may be effective in treating metabolic syndrome.

Author contributions

LQ and JZ conceptualized the research question. CG and YR participated in drafting and writing the review. CG, HW, and YR participated in the formulation of retrieval strategies, data acquisition, data analysis, and quality assessment. JL and ML participated in the drawing of tables and figures. XD and WL participated in the critical revision of the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2023.1216708/full#supplementary-material

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