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REVIEW

Effect of Curcumin on Glycaemic and Lipid Parameters in Polycystic Ovary Syndrome: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Abstract

Polycystic ovary syndrome (PCOS) is a heterogeneous condition that affects women of reproductive age. It is associated with menstrual disturbances, hyperandrogenism, and polycystic ovaries. In addition to this, it results in altered anthropometric parameters, insulin resistance, and subsequently untoward cardio-metabolic sequelae. Therapeutic approaches that target weight loss and improve insulin sensitivity are used to address the metabolic complications in PCOS. Curcumin is a phytochemical which exhibits anti-inflammatory and anti-oxidant properties, and therefore, its use in PCOS has been a subject of substantial interest and research. The aim of this study was to synthesize the existing evidence on the effects of curcumin on glycaemic and lipid parameters in PCOS. We searched PubMed, Embase, Web of Science, Scopus, and ClinicalTrials databases from inception to June 07, 2021. Only randomized controlled trials (RCT) presenting sufficient data on glycemic and lipid parameters in patients with PCOS at baseline and the end of the follow-up period in each group were included. Meta-analysis of five RCTs showed a significant reduction on fasting glucose (WMD: − 3.68 mg/dL, 95% CI: − 5.11, − 2.25, $p < 0.00001$, $I^2 = 18\%$), insulin levels (WMD: − 1.72 µUI/mL, 95% CI: − 2.53, -0.92, $p < 0001$, $I^2 = 41\%$), and HOMA-IR index (WMD: − 0.94, 95% CI: − 1.73, − 0.16, $p = 0.02$, $I^2 = 90\%$) after curcumin therapy. None of the lipid indices were significantly altered by curcumin. Curcumin administration in PCOS resulted in significant improvement in glycaemic parameters; however, no significant changes were seen in lipid parameters with its use.

Keywords Polycystic ovary syndrome (PCOS) · Curcumin · Metabolic parameters · Impact on glycemia · Impact on lipids

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Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of reproductive age with a prevalence of up to 13% [1] that may rise further subject to the diagnostic criteria used [2]. Although the etiology of PCOS is not clear, endogenous hormonal disparity and genetic, environmental factors are likely to raise androgen and insulin levels resulting in PCOS [3–5]. Clinical and biochemical features of hyperandrogenism, menstrual disturbances, and polycystic appearance of the ovaries are the characteristic features of PCOS [6]. Further, it leads to adverse metabolic sequelae, including impaired glucose tolerance, gestational diabetes, type 2 diabetes (T2D), dyslipidemias, and obesity, all of which confer a cardiovascular risk [7–9]. In clinical practice, the Rotterdam criteria [10, 11] is widely used to diagnose PCOS. A majority of the women with PCOS are overweight [12], and a weight loss of up to 5% can reinstate ovulation and increase insulin sensitivity [13]. Therefore, pharmacological and non-pharmacological strategies facilitating weight loss form a vital component for the management of PCOS [14]. Furthermore, specific abnormalities, including menstrual irregularities, manifestations of hyperandrogenism, and infertility, can be addressed with targeted therapies in a patient-centered approach [15].

Curcumin, also known as diferuloylmethane, is a biologically active polyphenol derived from turmeric [16]. By targeting a variety of signaling molecules and acting at the cellular level, it has been shown to be beneficial in metabolic syndrome and inflammatory conditions [17–23]. curcumin has been shown to exhibit anti-diabetic effects [24], reduce serum cholesterol [25] and oxidative stress [26]. These beneficial effects of curcumin administration have drawn considerable interest for its use in alleviating untoward metabolic complications in patients with PCOS.

Although some studies suggest a favorable outcome of curcumin supplementation in PCOS over the years, there are significant gaps in the available evidence, and the therapeutic effects of curcumin in PCOS remain inconclusive. This systematic review and meta-analysis of RCTs aim to evaluate and analyze the available evidence for the effectiveness of curcumin in improving glycaemic and lipid parameters in PCOS, which will help guide clinical practice.

Methods

Search Strategy

This study was conducted following the PRISMA guidelines [27]. Scopus, PubMed, Embase, Web of Science, and ClinicalTrials databases were searched using the following search terms in titles and abstracts (also in combination with MESH terms): (curcumin OR cur-cuminoid OR curcuminoids OR *Curcuma* OR "*Curcuma longa*") AND

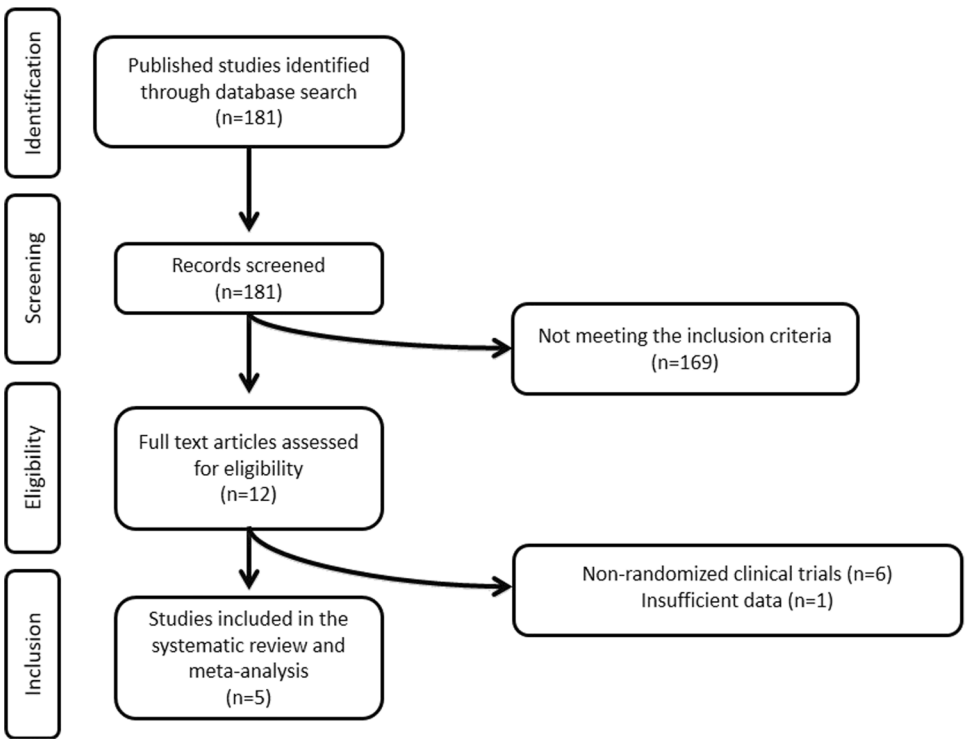

Fig. 1 Flow chart of studies included for meta-analysis

Table 1 Demographic characteristics of the included studies

Author	Study design	Target Population	Treatment duration	*n*	Study groups	Fasting glucose (mg/dl)	Fasting insulin (µUI/ml)	HOMA-IR	Total cholesterol (mg/dL)	LDL cholesterol (mg/dL)	HDL cholesterol (mg/dL)	Triglycerides (mg/dL)
Sohaei et al. (2019)[a]	Randomized, double-blind, placebo-controlled	Polycystic ovary syndrome	6 weeks	27 24	Curcumin 1 g/day Placebo	102.2 ± 9.7 99.8 ± 10.9	15.4 ± 8.0 14.1 ± 5.0	3.95 ± 2.30 3.52 ± 1.40	185.8 ± 35.9 175.7 ± 39.4	92.9 ± 24.8 92.1 ± 29.4	49.0 ± 6.6 51.6 ± 11.5	157.2 ± 75.4 170.0 ± 84.8
Asan et al. (2020)[b]	Randomized, single-blind, placebo-controlled	Polycystic ovary syndrome	8 weeks	15 15	Curcumin 93.34 mg/day Placebo	94.1 ± 6.1 90.6 ± 5.1	12.2 ± 8.9 8.0 ± 5.9	2.7 ± 1.9 1.8 ± 1.4	200.9 ± 27.2 215.2 ± 29.9	124.7 ± 22.3 132.8 ± 22.5	53.9 ± 18.2 55.8 ± 17.6	111.8 ± 54.3 132.5 ± 56.3
Jamilian et al. (2020)	Randomized, double-blind, placebo-controlled	Polycystic ovary syndrome	12 weeks	24 26	Curcumin 500 mg/day Placebo	94.9 ± 6.1 92.9 ± 4.2	11.3 ± 3.6 10.5 ± 2.5	2.7 ± 0.9 2.4 ± 0.6	192.0 ± 36.6 179.5 ± 29.9	119.6 ± 35.8 104.9 ± 32.1	39.6 ± 9.8 43.5 ± 7.7	163.6 ± 44.8 155.6 ± 33.5
Heshmati et al. (2021)	Randomized, double-blind, placebo-controlled	Polycystic ovary syndrome	12 weeks	34 33	Curcumin 1.5 g/day Placebo	105.2 ± 13.1 101.8 ± 9.3	13.5 ± 7.4 12.5 ± 10.1	3.50 ± 1.92 2.99 ± 2.57	ND ND	ND ND	ND ND	ND ND
Sohrevardi et al. (2021)	Randomized, open-label, active-controlled	Polycystic ovary syndrome	12 weeks	48 50	Curcumin 80 mg/day + metformin 1.5 g/day Metformin 1.5 g/day	110.3 ± 5.6 107.8 ± 7.0	18.0 ± 2.8 18.1 ± 2.7	4.36 ± 0.72 4.16 ± 1.42	200.3 ± 31.4 215.1 ± 37.2	114.0 ± 24.6 119.2 ± 23.5	33.1 ± 6.1 37.2 ± 5.2	129.5 ± 5.7 143.0 ± 8.3

Values are expressed as mean ± SD

Abbreviations: *ND* no data

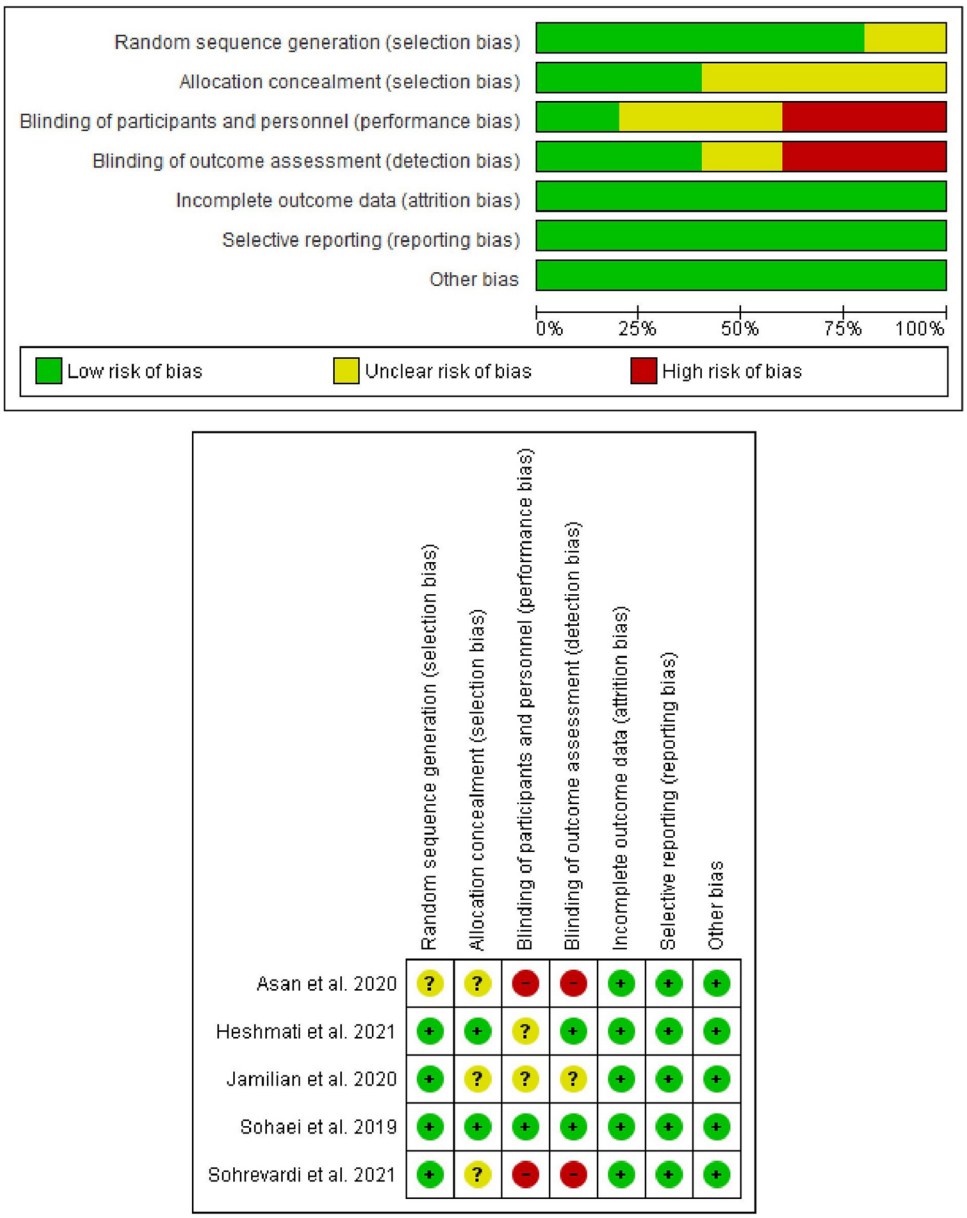

Fig. 2 Quality of bias assessment of the included studies in this meta-analysis

(glucose OR insulin OR insulin resistance OR insulin sensitivity OR HbA1c OR hemoglobin A1c OR glycated hemoglobin OR glycosylated hemoglobin OR cholesterol OR "low-density lipoprotein" OR LDL OR LDL-C OR LDL-cholesterol OR "high-density lipoprotein" OR HDL-cholesterol OR HDL-C OR triglyceride OR hyperlipidemia OR hyperlipidemic OR dyslipidemia OR dyslipidemic OR lipid OR lipoprotein). The wild-card term "*" was used to increase the sensitivity of the search strategy. The literature was searched from inception to June 07, 2021.

Study Selection

Clinical trials were included if they met the following inclusion criteria: (1) randomized controlled trials with either parallel or cross-over design, (2) evaluating the impact of curcumin on either glycemic or lipid markers, and (3) presenting sufficient data on glycemic and lipid parameters at baseline and the end of follow-up in each group or providing the net change values. Exclusion criteria were (1) non-randomized trials, (2) uncontrolled trials, (3) observational studies, and (4) lack of sufficient information of glycemic and lipid markers at baseline or follow-up (or net change). Two independent authors selected the studies and any disagreements were discussed and resolved with another author.

Data Extraction

The following data were extracted from eligible studies: (1) name of the first author, (2) publication year, (3) study

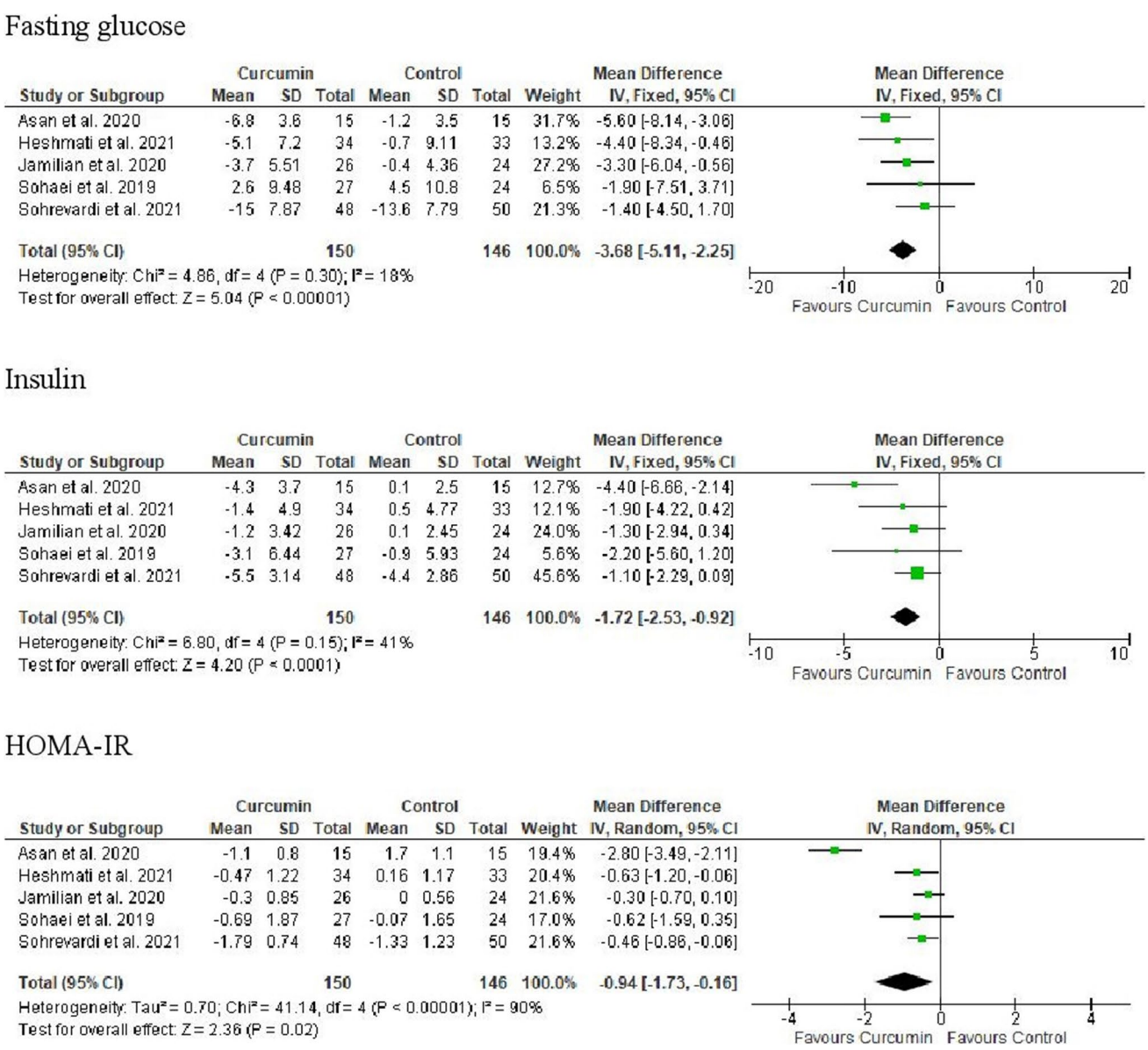

Fig. 3 Forest plot displaying the mean difference and 95% confidence intervals for the effects of curcumin on fasting glucose, insulin levels, and HOMA-IR index

design, (4) dose of curcumin, (5) treatment duration, (6) number of participants, (7) patients characteristics, and (8) levels of glycemic and lipid parameters.

Quality Assessment

The bias evaluation of the clinical trials was performed using the Cochrane criteria [28]. The blinding of participants, sequence generation, allocation concealment, incomplete outcome data, personnel and outcome assessors, selective outcome reporting, and other sources of bias were the items used for quality assessment.

Quantitative Data Synthesis

Meta-analysis was performed using the Review Manager statistical software version 5.3. A random-effects model and the generic inverse variance weighting method were used for meta-analysis. Mean and SD values were estimated when the outcome measures were reported in median and interquartile range (or 95% confidence interval [CI]) [29]. If the standard error of the mean (SEM) was provided, SD was calculated. Effect sizes were expressed as weighted mean difference (WMD) and 95% CI. Sensitivity analysis was performed

Table 2 Results of leave-one-out sensitivity analysis for glucose

Study removed	Statistics with study removed		
	Total WMD (95% CI)*	*p* value	I^2
Fasting glucose			
Asan et al. (2020)	−2.79 [−4.52, −1.05]	0.002	0%
Heshmati et al. (2021)	−3.57 [−5.11, −2.03]	<0.00001	36%
Jamilian et al. (2020)	−3.82 [−5.50, −2.14]	<0.00001	37%
Sohaei et al. (2019)	−3.80 [−5.28, −2.32]	<0.00001	33%
Sohrevardi et al. (2021)	−4.30 [−5.91, −2.68]	<0.00001	0%
Insulin			
Asan et al. (2020)	−1.34 [−6.66, −2.14]	0.002	0%
Heshmati et al. (2021)	−1.70 [−2.56, −0.84]	0.0001	56%
Jamilian et al. (2020)	−1.86 [−2.78, −0.94]	<0.0001	54%
Sohaei et al. (2019)	−1.70 [−2.52, −0.87]	<0.0001	55%
Sohrevardi et al. (2021)	−2.25 [−3.34, −1.16]	<0.001	38%
HOMA-IR			
Asan et al. (2020)	−0.44 [−0.68, −0.20]	0.0004	0%
Heshmati et al. (2021)	−1.03 [−2.04, −0.02]	0.05	93%
Jamilian et al. (2020)	−1.12 [−2.17, −0.08]	0.04	91%
Sohaei et al. (2019)	−1.01 [−1.92, −0.10]	0.03	93%
Sohrevardi et al. (2021)	−1.08 [−2.18, −0.02]	0.05	92%

**WMD*, weighted mean difference; *CI*, confidence interval

using the leave-one-out method to assess the influence of each study on the overall effect size [30, 31].

Results

Study Selection Process

A total of 181 published studies were identified after a systematic databases search, and 169 were excluded since they did not meet the criteria for inclusion. Next, 12 articles were carefully reviewed in full-text, and 6 were excluded for being non-randomized clinical trials. Finally, 6 RCTs were included (Fig. 1).

Characteristics of the Randomized Controlled Trials

Data were pooled from 5 RCTs, including 296 subjects: 148 and 148 individuals in the treatment and control groups. Included studies were published between 2019 and 2021 [32–36]. The treatment duration ranged from 5 to 12 weeks. All selected clinical trials had a parallel design. All studies included enrolled women with PCOS (Table 1).

Quality of Bias Assessment of Clinical Trials

Only one study showed insufficient information about sequence generation [32]. Additionally, three clinical trials lacked the information for allocation concealment [32, 34, 36]. According to the blinding of participants, personnel, and outcome assessment, two studies had a high risk of bias for these parameters. Finally, all included clinical trials exhibited a low risk of bias for incomplete outcome data and selective outcome reporting (Fig. 2).

Effects of Curcumin on Glycemic Parameters

Meta-analysis of 5 RCTs showed a significant reduction on fasting glucose (WMD: − 3.68 mg/dL, 95% CI: − 5.11, − 2.25, $p < 0.00001$, $I^2 = 18\%$), insulin levels (WMD: − 1.72 µUI/mL, 95% CI: − 2.53, − 0.92, $p < 0001$, $I^2 = 41\%$), and HOMA-IR index (WMD: − 0.94, 95% CI: − 1.73, − 0.16, $p = 0.02$, $I^2 = 90\%$) after curcumin therapy (Fig. 3). Additionally, the sensitivity analysis was robust for fasting glucose and insulin levels; however, the effect size for HOMA-IR index was sensitive to two studies (Table 2) [33, 36].

Effects of Curcumin on Lipid Profile

The meta-analysis of the pooled data revealed that curcumin treatment has no significant changes in circulating concentrations of TC (WMD: − 14.19 mg/dL, 95% CI: − 28.97, 0.59, $p = 0.06$, $I^2 = 66\%$), LDL-C (WMD: − 8.21 mg/dL, 95% CI: − 22.90, 6.47, $p = 0.27$, $I^2 = 79\%$), HDL-C (WMD: − 4.01 mg/dL, 95% CI: − 1.71, 9.73, $p = 0.17$, $I^2 = 86\%$), and triglycerides (WMD: − 9.79 mg/dL, 95% CI: − 32.44, 12.85, $p = 0.40$, $I^2 = 83\%$) (Fig. 4). The effects of curcumin on LDL-C and HDL-C were robust in the sensitivity analysis, while the estimated effect sizes for triglycerides and TC were sensitive to one study each (Table 3).

Discussion

To our knowledge, this is the first systematic review that summarizes and reports up-to-date evidence regarding the impact of curcumin administration on glycaemic and lipid parameters in patients with PCOS. The meta-analysis of 5 RCTs showed a significant reduction in fasting plasma glucose, insulin levels, and HOMA-IR index after curcumin therapy. Interestingly, however, no significant changes in circulating concentrations of TC, LDL-C, HDL-C, and triglycerides were seen. Four RCTs compared varying doses of curcumin vs. placebo [32–35] whereas one of them compared the effect of curcumin + metformin vs. metformin alone [36]. Besides, in one of these studies, all patients were matched by metformin treatment [35]; however, three RCTs did not clarify the use of this drug [32–34]. It will be interesting to assess the impact of curcumin on glycaemic parameters when used as an adjunct

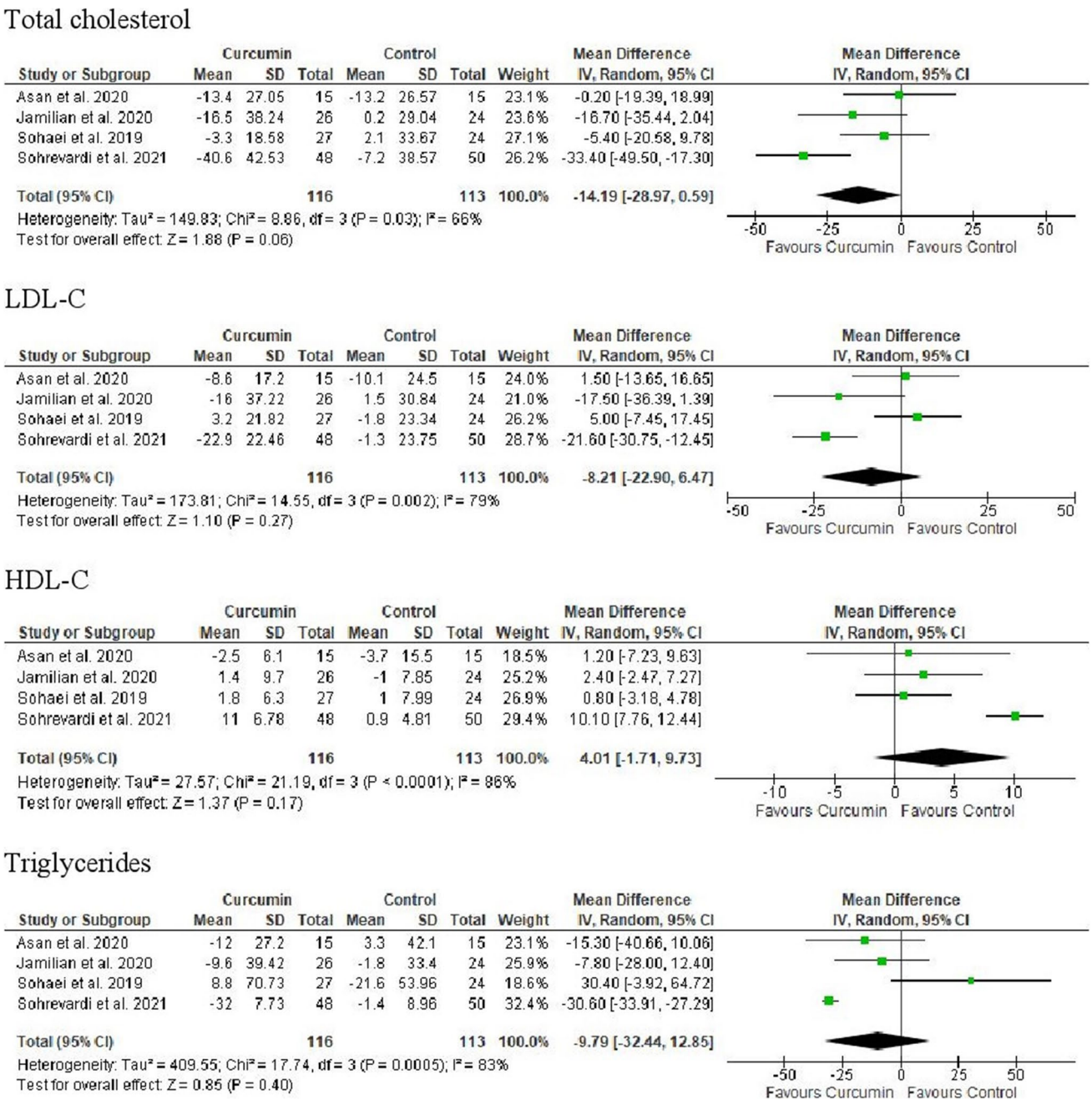

Fig. 4 Forest plot displaying the mean difference and 95% confidence intervals for the effect of curcumin on circulating lipid concentrations: total cholesterol, LDL-C, HDL-C, and triglycerides

to metformin therapy compared to its use alone in PCOS. However, this will require well-designed future studies. We report no significant effect on lipid parameters with curcumin use in PCOS, which was rather surprising as several previous studies have suggested that it improves serum lipid concentrations in humans [37, 38] and animal models [25, 39]. However, these human clinical studies were not conducted in subjects with PCOS. Particularly, patients with PCOS often exhibit dyslipidemia such as elevated levels of total cholesterol, LDL-C, and triglycerides as well as reduced concentrations of HDL-C [40]; however, it is noteworthy that some of the studies included

Table 3 Results of leave-one-out sensitivity analysis for total cholesterol, LDL-C, HDL-C, and triglycerides

Study removed	Statistics with study removed		
	Total WMD (95% CI)*	*p* value	I^2
Total cholesterol			
Asan et al. (2020)	−18.40 [−35.27, −1.54]	0.03	68%
Jamilian et al. (2020)	−13.30 [−33.58, 6.99]	0.20	77%
Sohaei et al. (2019)	−17.33 [−36.49, 1.83]	0.08	71%
Sohrevardi et al. (2021)	−7.22 [−17.27, 2.82]	0.16	0%
LDL-C			
Asan et al. (2020)	−11.28 [−29.36, 6.80]	0.22	83%
Jamilian et al. (2020)	−5.59 [−24.01, 12.82]	0.55	86%
Sohaei et al. (2019)	−13.08 [−27.83, 1.67]	0.08	70%
Sohrevardi et al. (2021)	−2.08 [−14.42, 10.27]	0.74	49%
HDL-C			
Asan et al. (2020)	4.63 [−1.94, 11.21]	0.17	90%
Jamilian et al. (2020)	4.46 [−2.91, 11.83]	0.24	89%
Sohaei et al. (2019)	5.25 [−1.15, 11.65]	0.11	81%
Sohrevardi et al. (2021)	1.41 [−1.48, 4.31]	0.34	0%
Triglycerides			
Asan et al. (2020)	−6.82 [−36.94, 23.31]	0.66	88%
Jamilian et al. (2020)	−9.02 [−40.28, 22.24]	0.57	85%
Sohaei et al. (2019)	−20.73 [−36.91, −4.54]	0.01	67%
Sohrevardi et al.(2021)	−0.61 [−23.80, 22.57]	0.96	58%

**WMD*, weighted mean difference; *CI*, confidence interval

in our meta-analysis were characterized by lipid levels within the normal range, which could explain the lack of effect of curcumin administration. In this regard, a previous meta-analysis of lipid levels in PCOS indicated a wide variability of LDL-C values among the evaluated studies, which may be affected by several factors such as ethnicity, severity of PCOS, diet, and body weight [41]. Also, although triglyceride levels were higher in women with PCOS, only 3 out of 30 included studies showed values greater than 150 mg/dl; this finding could be related to age or steroid production which can partially prevent elevated triglycerides [41]. Additionally, it has been suggested that the short treatment period following curcumin supplementation (2 months) is insufficient to affect the lipid parameters [42]. This was a comprehensive and systematic search of relevant databases that only included RCTs with either a parallel or cross-over design, while uncontrolled, non-randomized, and observational studies were excluded to reduce the risk of bias. Some limitations of this meta-analysis include a paucity of well-designed RCTs reporting these outcomes. Well-designed clinical research is required for an in-depth analysis of the beneficial effects of curcumin in PCOS. Furthermore, in this meta-analysis, only trials reported in the English language were included, and therefore, several clinical trials in foreign languages may not have been retrieved. Assessing such trials requires sophisticated translation, which is challenging, and could also affect the methodology of this review. In addition to this, only fully published trials were eligible, and publication bias was not performed. All the included trials were of a smaller sample size, and the statistical power used to calculate sample size and detect the meaningful differences between the groups were not reported. All the trials were of short duration and reported baseline and immediate post-intervention data. Therefore, the long-term effects of curcumin on glycaemic and lipid parameters in PCOS women are not studied extensively.

Based on our findings, it is clear that there is a lack of robust clinical trials assessing the effect of curcumin on metabolic parameters in PCOS. Therefore, further clinical trials with robust and standardized designs are needed to enable informed clinical practice in this domain.

Conclusion

This systematic review and meta-analysis of 5 RCTs shows that curcumin alone or in combination with metformin, regardless of the dose and duration of administration, results in significant improvement in fasting plasma glucose, insulin, and HOMA-IR. However, a similar effect was not observed in lipid parameters as there was no significant change in serum TC, triglycerides, LDL-c, and HDL-c with curcumin use. The results of this review are encouraging as they support curcumin supplementation in PCOS by showing that its use improves glycaemic parameters and, therefore, will help manage metabolic sequelae in PCOS. However, further large-scale, well-designed clinical trials over a longer duration are required to underpin the effectiveness of curcumin in PCOS conclusively.

Data Availability Not applicable.

Code Availability Not applicable.

Declarations

Ethics Approval and Consent to Participate Not applicable.

Consent for Publication Not applicable.

Competing Interests Muhammed Majeed is the founder of Sabinsa Corporation and Sami Labs Ltd. Other authors have no conflicting interests to disclose.

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