Effect of Curcumin towards Metabolic Disturbance Parameters in Patient with PCOS: A Systematic Review and Meta-Analysis of Clinical and Preclinical Randomized Controlled Trials

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Abstract
Objective: Polycystic Ovarian Syndrome (PCOS) is a gynecologic and endocrine disorder with metabolic disturbances and infertility as the most common long-term consequences. Curcumin comes up as one of the alternative herbal remedies in PCOS treatment options. This study aimed to investigate the therapeutic effect of curcumin on metabolic disturbance parameters in PCOS patients and PCOS-modeled rats.
Method: A systematic search of eligible studies was done using PubMed, Google Scholar, EBSCO-Host, and ProQuest according to the PRISMA 2009 guideline. We further assessed for risk of bias using SYRCLE's risk of bias tool for preclinical studies and The Cochrane risk of bias assessment tool for the clinical studies. We used Review Manager (version 5.4) with random effect model to obtain a pooled mean difference with 95% CIs.
Results: Five preclinical studies and three clinical studies were selected and pooled. The significant decrease in the level of Fasting Plasma Glucose (FPG), Fasting Insulin (FI), lipid profile, and Homeostatic Model of Insulin Resistance (HOMA-IR) value, and a significant increase in Quantitative Insulin-Sensitivity Check Index (QUICKI) value found in preclinical studies. The result for clinical studies showed a significantly decreased HOMA-IR values (SMD=-0.36, p=0.001), FPG level (SMD=-3.32, p=0.0001), Serum Insulin level (SMD=-1.47, p=0.002), and increased QUICKI value (SMD=0.01, p=0.006).
Conclusion: Curcumin offers a substantial effect on metabolic disturbance parameters in PCOS patients and could be an alternative promising treatment for PCOS patients in the future.

Key words: curcumin; fasting blood glucose; polycystic ovary syndrome.

Pengaruh Kurkuma terhadap Parameter Gangguan Metabolik pada Pasien SOPK: Tinjauan Sistematis dan Meta-Analisis Uji Acak Preklinis dan Klinis Terkontrol

Abstrak
Tujuan: Sindrom Ovarian Polikistik (PCOS) merupakan suatu kelainan ginekologi dan endokrin dengan gangguan metabolisme dan infertilitas sebagai konsekuensi jangka panjang yang paling umum ditemukan. Kurkumin muncul sebagai salah satu pengobatan herbal alternatif dalam pilihan terapi PCOS. Penelitian ini bertujuan untuk menyelidiki efek terapeutik kurkumin terhadap parameter gangguan metabolik pada pasien PCOS dan model tikus yang mengalami PCOS.
Metode: Penelitian ini dilakukan dengan mencari studi penelitian yang memenuhi syarat menggunakan PubMed, Google Scholar, EBSCO-Host, dan ProQuest mengikuti PRISMA 2009. Penilaian risiko bias studi menggunakan SYRCLE's Risk of Bias Tool untuk penelitian preklinis dan The Cochrane Risk of Bias Assessment Tool untuk penelitian klinis. Sintesis kuantitatifmenggunakan Review Manager (versi 5.4) dengan random effect model untuk mendapatkan pooled mean difference dengan interval kepercayaan 95%.
Hasil: Sebanyak lima studi penelitian preklinis dan tiga studi penelitian klinis memenuhi kriteria. Terdapat penurunan signifikan kadar gula darah puasa, insulin puasa, profil lipid, dan nilai HOMA-IR, serta peningkatan nilai QUICKI pada studi preklinis. Pada studi klinis menunjukkan penurunan nilai HOMA-IR (SMD=-0,36, p=0,001), gula darah puasa (SMD=-3,32, p=0,0001), insulin serum (SMD=-1,47, p=0,002), dan peningkatan nilai QUICKI (SMD=0,01, p=0,006).
Kesimpulan: Curcumin dapat memberikan efek terapeutik terhadap parameter gangguan metabolik pasien PCOS dan menjadi salah satu tatalaksana alternatif pasien PCOS di masa depan.

Kata kunci: kurkuma; gula darah puasa; sindrom ovarium polikistik.

Introduction

The term polycystic ovarian syndrome (PCOS) refers to a mixed of endocrine and gynecologic disorder commonly occurring in reproductive age women. Criteria of Rotterdam used as the gold standard for PCOS diagnosis.[1] Fifteen to twenty percent of reproductive age women of all races and ethnicities were affected by PCOS based on the Rotterdam criteria. Metabolic disturbances, as well as infertility, are reported as the most common long-term consequences in PCOS patients. This condition comes up due to a complex underlying pathway involving many metabolic factors and hyperandrogenism, leading to cardiometabolic diseases and mortality.[2] In other words, there is a shift of PCOS paradigm from reproductive to metabolic disease in women as the patient ages.

Many conventional PCOS treatments only alleviate the symptoms. Several side effects of existing PCOS medication are being reported, and the risk of venous thromboembolism up to three-to-six folds higher among obesity, hypertensive, and hypercholesterolemia PCOS-treated patients.[3] Therefore, alternative herbal remedies are taken into account as a novel therapeutic agent to address this concern. Curcumin, also called diferuloylmethane, is the primary natural polyphenol that acts as an active ingredient, extracted from the *Curcuma longa*'s rhizome (turmeric). *Curcuma longa* has potential effects as antioxidant, antiproliferative, anti-inflammatory and antimicrobial due to its utilization as traditional herb in some of Asian countries. Some evidence reported that curcumin acts as an antioxidant due to its effect on enhancing Superoxide Dismutase (SOD).[4] Curcumin also act as an anti-inflammatory agent, by lowering concentrations of tumor necrosis factor α (TNF-α) as a major inflammatory mediator. Other evidences suggest a hypoglycemic effect of curcumin as oral administration could reduce the levels of glycosylated hemoglobin (HbA1C) and serum glucose, as well as improve insulin sensitivity by augmenting pancreatic *β*-cell function, glucose homeostasis and insulin secretion.[5]

Curcumin can be packed into several preparations, either in solid form (tablets, capsules), or semi-solid (ointments), and has been approved by Food and Drug Administration (FDA) due to its high tolerability, efficacy and reported scanty side effects.[6] There is still lack of published systematic review and meta-analysis yet related to curcumin supplementation's potential as a treatment and/or an adjuvant for PCOS this far. Hence, this study aimed to explore the therapeutic effect of curcumin and summarize both the preclinical and clinical studies to get the best of our knowledge.

Method

This study was designed and conducted with the guideline based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

Eligibility Criteria

Inclusion criteria were (i) original interventional study that was written and/or published in English, (ii) reproductive-aged women (15 – 49 years-old) diagnosed with PCOS using Rotterdam criteria, (iii) study compared 500 mg curcumin supplementation as main treatment with placebo or control as standard treatment, (iv) the evaluated outcomes were various metabolic parameters, i.e. body mass index (BMI), body weight, Fasting Plasma Glucose (FPG), Fasting Serum Insulin (FSI) values, quantitative insulin-sensitivity check index (QUICKI), homeostasis model assessment-insulin resistance (HOMA-IR) and additional biochemical parameters, i.e. lipid

profile indices, sex hormones, antioxidant properties and anti-inflammatory markers. The studies were excluded if (i) the enrolled participants were having current or previous neoplastic disorders, thyroid disorder, Type 2 Diabetes Mellitus (T2DM), elevated levels of prolactin, cardiovascular diseases, malabsorptive disorders, digestive problems, congenital adrenal hyperplasia, any types of overt infection within the last six months; were pregnant and lactating women; were taking hormonal, anti-diabetic, anti-obesity, nutritional, and antioxidant drugs, any other medications that could interfere oxidative stress status, insulin sensitivity, inflammatory, or any kinds of oral contraceptives prior to study and (ii) the measurement of metabolic parameters were not performed.

Literature Search

A literature search was conducted systematically using four electronic databases, i.e., PubMed, Google Scholar, ProQuest, and EBSCO Host. The last search was performed on January 2nd, 2021.

Search Strategy and Study Selection

We searched for eligible studies using major medical subjects heading "curcumin" and "polycystic ovarian syndrome" with several metabolic parameters in addition to our keywords. Studies were sorted by the year ranging from 2000 to 2020 and using English as the main language. All steps were done systematically according to the PRISMA 2009 guideline. These following terms were selected according to Medical Subject Headings (MeSh): curcumin; polycystic ovarian syndrome; body weight; body mass index; fasting blood glucose; Homeostatic model assessment insulin resistance (HOMA-IR); quantitative insulin sensitivity check index (QUICKI); lipid profile. After the results were obtained, we further downloaded all the literature using Mendeley Desktop 1.19.4 version as the reference manager.

Data collection and extraction

Four reviewers independently performed the data extraction. Disagreement was resolved by consensus and further discussion to find the solution. For baseline demographic characteristics, data was categorized into two main groups, the preclinical and clinical studies. Information regarding comparison of curcumin and placebo in each study and control group were presented in detailed doses, patient-use instruction, and preparation for each material.

Results of data extraction were presented in bivariate tables that consist of metabolic parameters and several additional biochemical parameters. All outcomes were reported in continuous data and presented as mean ± standard deviation (SD) in terms of normally distributed data. The p-value was included for each item of metabolic parameters measured, to show the significance of results and will be further discussed in the narrative synthesis.

Quality Assessment and Risk of Bias in Individual Studies

Systematic Review Centre for Laboratory Animal Experimentation (SYRCLE)'s risk of bias tool for animal studies has been used to assess the risk of bias in preclinical study.[7] The research articles were followed to rate each bias parameter as either high, unclear, or low risk. The Cochrane risk of bias assessment tool was also used for clinical studies. The Cochrane Handbook recommendations were followed to rate each bias parameter as either high, unclear, low risk, or no information. Three reviewers (YY, AE, and NDW) assessed the risk of bias and a fourth reviewer (MR) arbitrated the disagreements.

Statistical Analysis

The continuous outcomes from each study result were pooled using 95% confidence interval (CI) and the mean difference (MD) using the inverse-variance model, which requires mean value and standard deviation for each group. We estimate the pooled MD using random effects meta-analyses that are considered more powerful than fixed effects analyses, because the results can be generalized to different populations in terms of when new studies are performed.

We used the I^2 metric to measure heterogeneity across the studies. The I^2 values of >75%, 50 – 75%, 25 – 50%, and <25% were categorized to have extreme, high, moderate and low heterogeneity respectively. Statistical analyses were conducted using Review Manager software from the Cochrane Collaboration (version 5.4.0, 2020, Copenhagen, Denmark). Data was sorted by the alphabetical order of the author study (Figure 4). Funnel plots test was done to assess the potential publication bias (Figure 5). In terms of continuous variables, pooled standardized mean difference (SMD) obtained from change in mean score was used to analyze between group differences.

Results

A total of 461 studies were found in the literature search databases selected by the authors. After conducting a literature search, five preclinical and three clinical studies were included in our study.

Quality Assessment

Revised Cochrane risk-of-bias tool for randomized trials (Risk of Bias/RoB 2) was used to evaluate the risk of bias among eight studies included in our systematic review and meta-analysis. All studies were randomized-controlled trials, in which five of them were

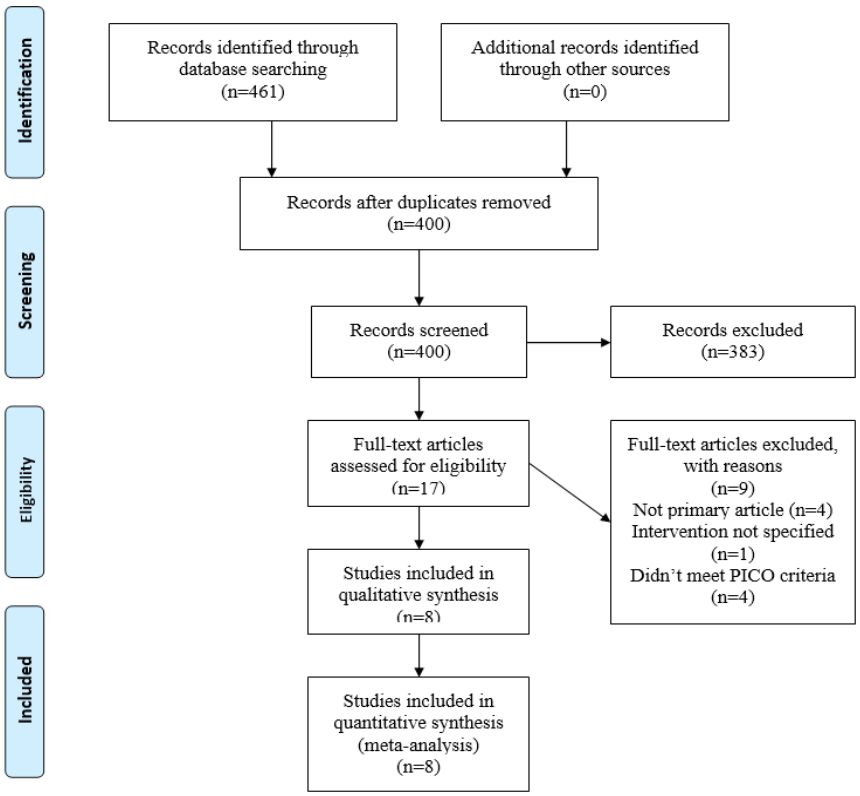

Figure 1 PRISMA 2009 Results of Literature Search and Study Selection

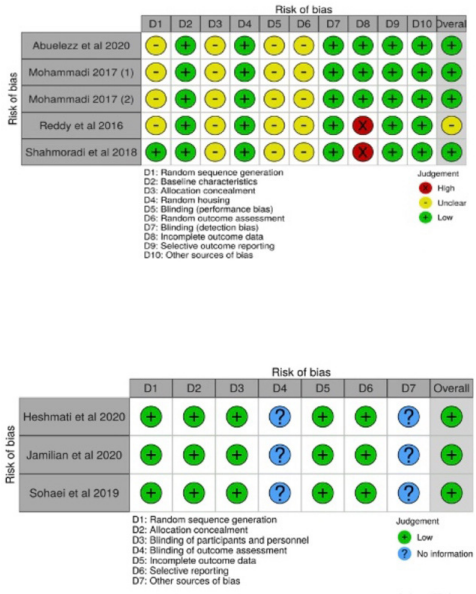

Figure 2 Risk of Bias Results of Preclinical and Clinical Studies

preclinical studies and three were clinical studies. In the preclinical study group, four studies were rated as low bias and one study has unclear results. Also, two studies reported an incomplete outcome of interest and therefore counted to have a high risk. In the clinical study group, all studies have overall low risk of bias, but none of them provide information regarding blinding of outcome and didn't clearly mention other types (source) of bias.

Study Characteristics (Univariate Analysis)

In clinical studies, 85 PCOS patients received curcumin, and 83 participants in the control group received a placebo with varying frequency and duration of intervention. The average age of the participants was around late 20 to early 30 years old. The level of FPG, FI, HOMA-IR value was decreased, and the QUICKI value was increased in the curcumin-treated PCOS patient group.

Meanwhile, in preclinical studies, animals used were female Wistar rats in four studies and Sprague-Dawley rats in one study. The forms and types of PCOS agent induction in mice were varied, such as oral Letrozole solution and subcutaneous or intramuscular estradiol valerate injection, which were given in different doses, frequencies, and durations. Curcumin is also administered in various forms, frequency and duration, and to different dosage groups. There was a significant decrease in the level of FPG, FI, lipid profile, HOMA-IR value, and a significant increase in QUICKI value in the PCOS-induction mice group administered with curcumin. Several additional biochemical outcomes affected by curcumin administration on the PCOS-induction rats are oxidative stress markers, inflammatory markers, CRP levels, sex hormones levels, liver and ovarian histomorphological, and the expression of several genes that regulate insulin.

Meta-Analysis Results

All metabolic parameters (HOMA-IR, FPG, QUICKI, Serum Insulin and BMI) have a final result of MDs (-0.36, -3.32, 0.01, -1.47 and -0.05, respectively) that favor curcumin groups. Despite having a high heterogeneity (I^2=67%), QUICKI, alongside with HOMA-IR, FPG, and Serum Insulin showed signifi-

Table 1 Characteristics of Clinical studies included in this Study

Studies	Country	Population/Participant		Materials and Methods			Outcomes		Results
		Number of Participants	Mean Age	Curcumin	Placebo	Intervention	Metabolic Parameters	Other Biochemical Parameters	
Heshmati et al.[8] (2020)	Iran	67 participants I: 34, P: 33	I: 30.97±5.20 P: 30.75±7.97	500 mg curcumin powder	Maltodextrin capsules	3 capsules daily for 12 weeks	FPG, Serum Insulin, BMI HOMA-IR, QUICKI	Sex hormone levels (FSH, LH, DHEA, Estradiol)	Significant decrease of FPG in curcumin-treated groups; Significant decrease of DHEA in curcumin-treated groups
Jamilian et al.[9] (2020)	Iran	50 participants I: 24, P: 26	I: 28.6±4.7 P: 27.2±3.4	500 mg curcumin	Starch capsules	1 capsule daily for 12 weeks	FPG Serum Insulin HOMA-IR QUICKI BMI	Lipid profile (serum TG, LDL, HDL)	Significant decrease of FPG, FI, HOMA-IR and significant increase of QUICKI in all curcumin-treated groups; Significant improvement of lipid profile in curcumin-treated groups
Sohaei et al.[10] (2019)	Iran	51 participants I: 27, P: 24	I: 29.40±5.33 P: 29.58±5	500 mg curcumin (standardized turmeric extract 95% in form of pellets)	Placebo	Daily dose of 1 g (500 mg twice daily) for 6 weeks	FPG Serum Insulin HOMA-IR QUICKI BMI	Lipid profile (serum TG, LDL, HDL) Serum hs-CRP level	Significant decrease of FPG, HOMA-IR, and significant increase in QUICKI in curcumin-treated groups

I: Intervention, P: Placebo, FPG: Fasting Plasma Glucose, HOMA-IR: Homeostasis Model Assessment-Insulin Resistance, QUICKI: Quantitative Insulin-Sensitivity Check Index, BMI: Body Mass Index, FSH: Follicle Stimulating Hormone, LH: Luteinizing Hormone, DHEA: Dehydroepiandrosterone, TG: Triglycerides, LDL: Low-density Lipoproteins, HDL: High-density Lipoproteins, hs-CRP: High-sensitivity C-reactive Protein.

Table 2 Characteristics of Preclinical Studies Included in this Study

Studies	Country	Subjects and Number of Subjects	Materials and Methods		Outcomes		Results
			Curcumin	PCOS Induction	Metabolic Parameters	Additional Biochemical Parameters	
Abuelezz et al.[11] (2020)	Egypt	7 weeks-old virgin, adult, 160-200 gram female Wistar rats; 60 were equally divided into (1) control group (2) PCOS group (3), (4), and (5) curcumin-treated PCOS groups with three different dosages.	Oral nanocurcumin solution (50 mg/kgBW, 100 mg/kgBW, and 200 mg/kgBW) daily for 15 days	Oral letrozole solution in 0.5% CMC (1 mg/kgBW) daily for 23 days	• Fasting blood glucose (using enzymatic colorimetric method) • FSI (by quantitative ELISA technique using the kit), • HOMA-IR (by HOMA2 Calculator Program), • Lipid profile (by enzymatic colorimetric assays)	• Sex hormone levels (Testosterone, estradiol and progesterone), • Oxidative stress markers (MDA level, GSH level, SOD enzyme activity), • TNF-α levels	• Significant decrease of FPG, FI, LDL, TG, TC, HOMA-IR, and increase of HDL in all nanocurcumin- treated groups. • Significant improvement of oxidative stress markers and TNF-α level in all nanocurcumin-treated groups
Mohammadi et al.[12] (2017)	Iran	Adult, female, 170 ± 20 gram Wistar rats with a 2-3 regular estrous cycle period within a 12-14 days period; 90 animals were equally divided into (1) control group, (2) PCOS group, (3) sham group, and (4) curcumin-treated PCOS groups.	Oral curcumin solution in 100 mmol/L DMSO (100 and 300 mg/kgBW) for 14 days	Subcutaneous injection sesame oil-solved estradiol valerate to sham (2 mg/kgBW) for 60 days	• HOMA-IR (by using the formula [fasting insulin (μU/mL)×fasting glucose (mmol/L)/22.5]), • QUICKI (by using the formula [1/[log (insulin μU/mL)+log glucose mg/ dL)])	• IL-6 level, • CRP level, • Liver histological examination (right lobe of the liver)	• Significant decrease of FI and HOMA-IR in all curcumin-treated groups, significant increase of QUICKI in 300 mg/kgBW dosage curcumin-treated group • Significant improvement of IL-6 level, CRP level, and liver tissue in 300 mg/kgBW dosage curcumin-treated group

Mohammadi et al.[13] (2017)	Iran	Female, 170 ± 20 gram Wistar rats; 72 animals were divided into (1) control group (n=12), (2) PCOS group (n=12), and (3) curcumin-treated PCOS groups (n=48)	Intraperitoneal injection curcumin solution in 100 mmol/L DMSO (2000 mg/kgBW) for 14 days	Intramuscular injection estradiol valerate (2 mg/ kgBW) for 60 days	Body weight (by weight scales)	• IL-6 and CRP • Sex hormones (17β-estradiol, LH, FSH, Testosterone, Progesterone). • Histological exam (ovarian samples), • TNF-alpha (ovarian immunohistochemistry)	• Significant decrease of body weight in all curcumin-treated groups • Significant decrease of LH with 100 and 200 mg/kgBW dosage curcumin-treated group • Significant increase of FSH and progesterone in curcumin-treated group • Significant improvement of testosterone and sex hormone level in curcumin-treated group
Reddy et al.[14] (2016)	India	Virgin, cyclic, adult, female, 160 ± 20 gram Wistar Albino rats; 30 animals were divided into (1) control group (n=6), (2) PCOS group (n=6), (3) standard group (n=6), (4) and (5) curcumin-treated groups with two different dosages (n=6)	Oral curcumin solution in 0.5% CMC (100 and 200 mg/kgBW) for 15 days	Oral letrozole solution in 0.5% CMC (1 mg/ kgBW) daily for 21 days	• FPG (by Trinder's method using a commercial diagnostic kit) • HbA1c (by cation-exchange method using a diagnostic kit), • Lipid profile (TC, TG, HDL-C) (by using enzymatic kits), LDL-C (by using Friedewald's equation))	• Sexual hormones, Immunoassay • SOD activity, Catalase, Glutathione content, TBARS content • Ovarian histomorphology	• Significant decrease of glucose level, HbA1c level, TG, TC, LDL, and increase HDL levels in all curcumin-treated groups • Significant improvement of sex hormones, antioxidant activity, lipid peroxidation, ovarian histomorphology in 200 mg/kgBW dosage curcumin-treated group

Shahmoradi et al.[15] (2018)	Iran	Female, 180 ± 5 gram Sprague–Dawley rats; 60 animals were divided into (1) control group (n=15), (2) PCOS group (n=15), (3) and (4) curcumin-treated groups with two different dosages (n=15)	Oral curcumin solution in 0.5% CMC (100 and 200 mg/kgBW) for 30 days	Subcutaneously injection sesame oil solved-DHEA (6 mg/100 g) daily for 21 days	● Body weight (by weight scales), FPG (by glucose oxidase procedure) ● FSI (by a direct competitive ELISA kit) ● HOMA-IR (by using the following formula (FPG (mmol/L)×FIS (mU/L)/22.50))	● Ovarian histomorphology ● GGene expression of GLUT4 and Erα	● Significant decrease of body weight, levels of FI, FPG, and HOMA-IR in all intervention groups ● Significant improvement of ovarian histomorphology and in GLUT4 and Erα expression all curcumin-treated group

CMC: carboxmethlycellulose, DMSO: Dimethyl sulfoxide, MDA : *malondialdehyde* GSH: Glutathione Hormone, SOD: Superoxide Dismutase, TNF-α : Tumor Necrosis Factor- α
TBARS: Thiobarbituric acid reactive substances, GLUT-4: Glucose Transporter-4

cant changes due to oral curcumin administration ($p<0.05$), and only BMI result showed no significant effect due to curcumin interventions ($p=0.72$), with high heterogeneity ($I^2=68\%$). From all five metabolic outcomes, BMI has the larger CI value that crosses both the curcumin and placebo groups, with CI ranging from -0.32 to 0.22. A symmetric inverted funnel plots of HOMA-IR, FBG, and Serum Insulin indicate there is no publication bias.

Discussion

Curcumin administration has been reported to be effective in improving various metabolic disturbances in PCOS patients.[13] Therefore, turmeric or *Curcuma longa* has been considered as an essential therapeutic agent in Indian and Chinese traditional medicine and has been investigated as a potential adjuvant therapy for improving any metabolic parameters. This meta-analysis

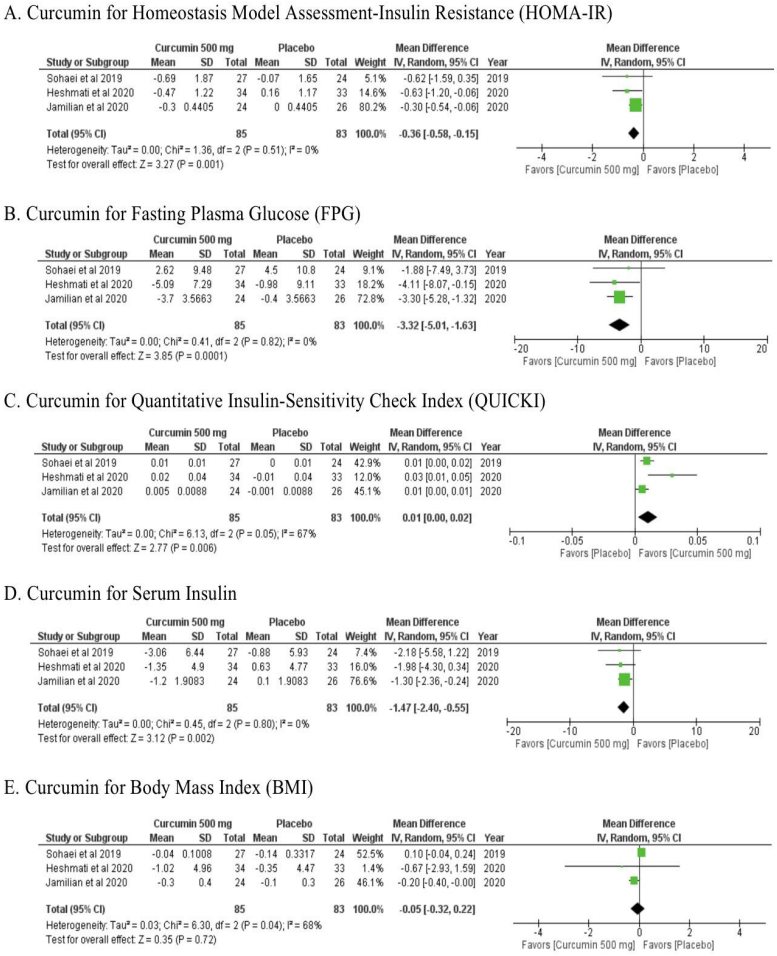

Figure 3 Results of Meta-Analysis

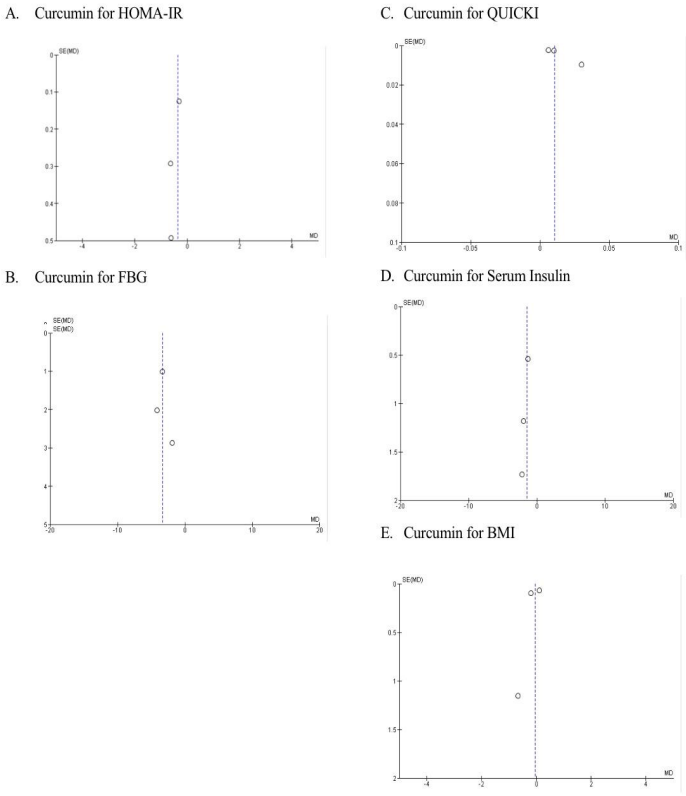

Figure 4 Funnel Plot with Standard Error (SE) of Effect of Curcumin Supplementation on Metabolic Outcomes in Pcos Patients.

provided evidence from three RCT studies consist of five parameters that were able to meta-analyze of 6 to 12 weeks curcumin supplementation, indicate that curcumin can significantly reduce the level of HOMA-IR (SMD=-0.36, Z=3.27, p=0.001), FPG (SMD=-3.32, Z=3.85, p=0.0001), FI (SMD=-1.47, Z=3.12, p=0.002), significantly increase the value of QUICKI (SMD=0.01, Z=2.77, p=0.006), but insignificantly reduce the BMI (SMD=-0.05, Z=0.35, p=0.72) in PCOS patients group (Figure 1).

The subgroup analysis shows that curcumin may have a contribution in lowering the metabolic parameters at a starting dose of 500 mg, ranging from one to three capsules daily for six to twelve weeks. The high heterogeneity for QUICKI suggests that there may be other factors that could modulate the effects of curcumin towards metabolic parameters.

According to the previous meta-analysis, curcumin could decrease FPG, HbA1c and HOMA-IR, however, did not affect HOMA-IR on the other meta-analysis and a clinical trial.[16,17] An increase of QUICKI value was also reported in patients with T2DM on a clinical trial after curcumin intake, as an addition to the previously mentioned effect. Findings regarding glycemic indices in our study are in line with Dadgar et al.[18], that has reported a significant suppressing effect of curcumin nano micelles on levels of serum glucose concentration in streptozotocin-induced diabetic rats. This report is consistent with the original research results carried out so far, as mentioned by Rivera-Mancia et al.[19], about the utility of curcumin to reduce insulin resistance by targeting the JNK/IRS pathway that has been tested in several *in vivo* and *in vitro* models. The JNK/IRS-1 pathway plays a pivotal role in insulin

resistance mechanisms by causing oxidative stress to the endoplasmic reticulum (ER) in islet **β**-cell, resulting in **β**-cell dysfunction. It is also supported by Kato et al.[20] in the study that has been reported a reduction in glucose intolerance after curcumin supplementation which happened because the release of GLP-1 would lead to insulin secretion, with the consequent glucose-lowering effect.

Some molecular explanations try to depict the causal association between curcumin and glycemic indices. Significant improvements may be held because curcumin may exert glucose lipid-lowering effects by promoting gene expression of PPAR-ɣ that has pleiotropic effects in refinement of insulin sensitivity, glucose homeostasis and modulating gene expression which plays critical roles in lipid and glucose metabolisms that leads to improvement of insulin secretion and lipid homeostasis.[9] Curcumin could also restore the impaired glucose stimulated insulin secretion (GSIS) in a dose-dependent manner, enhancing B-cells insulin secretion. Another possible mechanism is curcumin could stimulate glucose uptake through increasing phosphorylation of AMP-activated protein kinase (AMPK), along with inhibiting hepatic glucose production, thus resulting in decreased hepatic glycogenolysis and gluconeogenesis.[21]

Despite curcumin's ability to refine body weight by decreasing fat mass and increasing energy expenditure, BMI parameters showed insignificant results in this meta-analysis. Reduction of pro-inflammatory cytokines, such as monocyte chemoattractant protein-1 (MCP-1), plasminogen activator inhibitor type-1 (PAI-1) and TNF-α, as well as increasing energy expenditure and stimulating weight loss are estimated to be the refining property of curcumin to decrease body weight and BMI. The possible reason could probably explain the insignificant changes in BMI measure between groups that PCOS patients are suggested to have lifestyle modification, including intensify physical activity and preserve energy-balanced diet that might interfere the reduction in mean BMI, despite they were asked to keep their normal lifestyle constant.[22]

Several preclinical studies have reported significant changes in the metabolic parameters and other additional biochemical parameters in PCOS-modeled rats, which were given various curcumin doses. It is concluded that curcumin has a positive effect on all metabolic parameters. The decrease of FPG, FI, HOMA-IR levels, and the increase of QUICKI in PCOS-modeled rats administered with curcumin can be caused by escalated expression of GLUT4 and ERα genes. This phenomenon could improve insulin resistance and glycemic indices closer to its typical values.[15]

Another beneficial effect of curcumin administration is a significant reduction of serum lipid profiles due to decreased cholesterol biosynthesis via HMG-CoA reductase's downregulation and increased cholesterol clearance by stimulating bile secretion. Therefore curcumin can be considered to have a hypolipidemic effect, that might be related to the anti-inflammatory effect by reducing lipid-induced dysregulation of inflammatory signals in resident or recruited tissue inflammatory cells.[23] Several sex hormones, including estrogen and progesterone were increased due to the phytoestrogen effects of curcumin, thus resulted in increased ovulation, which marked by appearance of the oocytes on ovarian histological examination.[11] Although these findings were not discussed because it is not in accordance with the aim of the study, it is interesting to be studied further.

Furthermore, decreased levels of oxidative stress markers, e.g. Malondialdehyde (MDA), is due to curcumin as an antioxidant that could ward off different forms of free radicals and potentially to modulate the total antioxidant potential.[24]

Curcumin also significantly improved the ovarian histomorphology marked by different stages of follicle's development and transparent granulosa cell layers indicating the role of curcumin as anti-tissue/organ fibrosis agent.[37,39] Despite its glucose-lowering effect, anti-inflammatory and antioxidant benefit, one major obstacle with curcumin's oral administration is its poor bioavailability, where the low absorption as well as rapid metabolism and elimination are presumed to be the reason. However, oral administration of curcumin has been reported to be safe, with human studies indicate that large oral doses of curcumin up to 8,000 mg/day can be tolerated without reported toxicity and does not appear to cause any significant side effects except minor gastrointestinal problems.[25]

Conclusion

The findings of our meta-analysis suggested curcumin offers a substantial effect on metabolic parameters in patients suffering from PCOS. Those receiving doses of curcumin at 500 mg/day showed a significant decrease in HOMA-IR, FPG, Serum Insulin, and significant increase in QUICKI, but no significant change in BMI parameter was observed. Curcumin and its preparation also provide tolerable safety administration with no adverse effect being reported, therefore encapsulated curcumin could be an alternative promising treatment for PCOS patients in the future.

Limitation And Strength of the Study

This review had several limitations; one included study for meta-analysis did not mention the range of BMI from its participants, heterogeneity of one study is relatively high, the bioavailability of each curcumin used in the included studies has not been revealed and we do not perform subgroup analysis by dosage and duration of curcumin supplementation due to lack numbers of studies. Despite the limitation, preclinical and clinical studies support positive effect curcumin on metabolic parameters and additional biochemical parameters on PCOS patients. Furthermore, as far as our knowledge, this study is the first meta-analysis that has assessed the effect of curcumin supplementation on metabolic and biochemical parameters in PCOS subjects this far.

Future Directions

Considering that curcumin plays a significant role as hypoglycemic, hypolipidemic, antioxidant agent in treating and preventing metabolic disorders in PCOS, curcumin might be considered as an additional treatment for PCOS. We suggest several future reviews using larger clinical trials with different doses and duration of curcumin to support the existing findings. Several agents might be considered to be added to curcumin supplementation to increase its bioavailability. Moreover, some other curcuma active compounds need to be extracted in order not to confound the main effect of curcumin on the metabolic parameters in patients with PCOS.

Conflict of Interest

All authors declared that they have no conflicts of interest and have no specific funding nor grant for this publication.

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Author Contribution

All authors shared equal contributions in this article.

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