



Curcumin and Polycystic Ovary Syndrome: a Systematic Review

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Abstract

Polycystic ovary syndrome (PCOS) is a gynecological endocrine disorder and the leading cause of anovulatory female infertility. This study aimed to systematically review the effects of curcumin or turmeric on PCOS-related parameters. PubMed, Scopus, Embase, and Web of Knowledge databases and Google Scholar were searched up to August 2021 using relevant keywords. All original articles evaluating the effects of turmeric/curcumin on PCOS were eligible. Out of 107 documents, eight animal studies and five randomized placebo-controlled clinical trials (RCTs) assessing the impact of curcumin on PCOS met our inclusion criteria. The reviewed animal studies indicated the beneficial effects of curcumin on the management of hormonal and metabolic disturbances in the PCOS condition. These effects also were confirmed in some, but not all, included RCTs. Therefore, despite promising animal results, the present literature is limited to conclude the beneficial effects of curcumin on the clinical management of PCOS symptoms. The impact of bioavailability-improved formulations of curcumin on PCOS should be assessed in further well-designed RCTs with longer duration and higher doses of curcumin. Besides, mechanistic investigations on the effects of curcumin on PCOS are also recommended.

Keywords Polycystic ovary syndrome · PCOS · Curcumin · Diferuloylmethane · Turmeric · Systematic review

Introduction

Polycystic ovary syndrome (PCOS) as a gynecological-endocrine disorder is the leading cause of anovulatory female infertility. It also is related to miscarriage and pregnancy-induced complications [1, 2]. According to the Rotterdam consensus, the presence of two out of three parameters of chronic oligo- or anovulation, clinical and/or biochemical signs of hyperandrogenism, and polycystic ovarian morphology defines as PCOS. PCOS is affecting 6–21% of women of reproductive age worldwide, based on the Rotterdam criteria [3, 4]. In addition, PCOS is associated with metabolic aberrations, including insulin resistance, dyslipidemia, adiposity, hypertension, type 2 diabetes mellitus, non-alcoholic fatty

liver disease, coronary heart disease, and vascular endothelial dysfunction [1, 5].

The etiology of PCOS is still unclear. However, according to a “2-hit” hypothesis, a congenital predisposition (gene variants, congenital virilization, and disturbed fetal nutrition, as “first hit”) can manifest as PCOS after exposure to an environmental risk factor (exposure to androgens, postnatal obesity, insulin-resistant hyperinsulinemia, and hyperpuberty, as the “second hit”) [6]. Moreover, oxidative stress and inflammation have undeniable roles in the pathophysiology of the disease [7, 8]. Therapeutic management of PCOS is usually limited to improve clinical manifestations, in which dietary modification, weight loss, and increased exercise are in the first-line of interventions [9]. Moreover, herbal medicine use by women with PCOS has been increased during the past years [10].

Curcuma longa L. (turmeric) is a common dietary spice and pigment with a very long history of medicinal use to treat eye infections, skin diseases, respiratory ailments, dental diseases, and digestive disorders [11]. Besides, modern science supports the effects of turmeric on such diseases [12, 13]. Curcumin (diferuloylmethane) is the main bioactive component of turmeric [14]. Recent meta-analysis studies confirm the beneficial effects of curcumin on obesity [15],

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diabetes [16], hypertension [17], hyperlipidemia [16, 18], oxidative stress, and inflammation [19]. Besides, some animal and human investigations have assessed the effects of curcumin on the management of hormonal and metabolic disturbances and complications of PCOS [20–24]. However, to the best of our knowledge, no review study has summarized the effects of turmeric/curcumin on PCOS so far. Therefore, the current systematic review aimed to comprehensively assess all published studies regarding the effects of curcumin/turmeric supplementation on the parameters of PCOS.

Materials and Methods

Research Strategy

The present systematic review was conducted according to the PRISMA (preferred reporting items for systematic reviews and meta-analysis) guideline [25] by focusing on the effects of turmeric or curcumin on PCOS. Therefore, a systematic search was performed for the relevant *in vitro*, animal, and human articles published until August 2021, on the PubMed, Embase, Scopus, and Thomson Reuters Web of Knowledge, using the MeSH terms and other related keywords (PubMed search strategy is shown in Supplementary Box 1). Moreover, the Google Scholar search and the forward and backward citation tracking were conducted, separately. The protocol of the present study has been registered in the International Prospective Register of Systematic Reviews (PROSPERO) with the identification number CRD42020214985.

Eligibility Criteria and Screening Methods

After searching in electronic databases, duplicate studies were removed using the EndNote software, version X8.0. Then, two independent investigators initially screened titles and abstracts of the studies based on the inclusion and exclusion criteria, followed by reviewing the full text of some selected articles. Discrepancies between two reviewers were resolved by discussion or the third reviewer. Study inclusion and exclusion criteria and research questions were structured using the PICOS (population, intervention, comparison, outcome, and study design) criteria. Peer-reviewed *in vitro*, animal, and human studies published in the English language that examined the effect of turmeric or curcumin (natural or synthetic forms) on PCOS compared to placebo or no treatment were included. The exclusion criteria were literature reviews, newspapers, magazines, conference abstracts, book chapters, notes, short surveys, letters, editorials, case report studies, clinical trial registration, and thesis. Moreover, investigations on the combination of turmeric/curcumin

with other agents or medications and other diseases were ineligible.

Data Extraction

Data extraction sheets were developed according to the study types and in line with recommendations from PRISMA [25]. After pilot-testing on one article of each study type, refinement of sheets was performed. Then, two investigators independently extracted data from all selected studies. The data extraction sheets are summarized in Tables 1 and 2.

Risk of Bias Assessment

The risk of bias assessment of the included animal studies and randomized placebo-controlled clinical trials (RCTs) was performed by two independent authors, according to the Office of Health Assessment and Translation (OHAT) [26] and Cochrane [27] handbooks, respectively. Discrepancies between the two reviewers were resolved by discussion or the third reviewer. The response options for each risk of bias question of the OHAT tool are “– –” (definitely high risk of bias), “–” (probably high risk of bias), “+” (probably low risk of bias), or “+ +” (definitely low risk of bias). After answering questions for each included animal study, using the OHAT recommendations, we gave numerical values from –2 to +2 to each question and tiered studies according to the calculated averages (three tiers of the low, moderate, and high risk of bias) [28]. Besides, the Cochrane collaboration’s tool has six bias domains with three response options of “low,” “unclear,” and “high” risk of bias [29]. Based on the discussion among the reviewers, selection bias, performance bias, and detection bias were selected as the key domains for judgment of the overall risk of bias. Each of the included studies was considered to have “low risk of bias” when it had the low risk of bias for all the three key domains, “unclear risk of bias” if it had the unclear risk of bias for ≥ 1 key domain, and “high risk of bias” when it had a high risk of bias for ≥ 1 key domain [29–31].

Results

Study Selection

The process of study selection has been depicted in Fig. 1. A total of 92 citations were identified from the electronic databases (PubMed, Embase, Scopus, and Web of Knowledge), and 15 studies were obtained from Google Scholar search. After removing duplicates ($n = 70$), title and abstract screening were conducted for the other 37 articles among them, and 22 articles were selected for full-text screening based on the inclusion and exclusion criteria. Following

Table 1 Characteristics of the included animal studies

First author, year (Ref)	Country	Animals	n/curcumin group	PCOS induction method	Curcumin treatment groups after PCOS induction	Curcumin treatment duration	Comparator	Curcumin's effects
Alibraheemi et al. 2021 [39]	Iraq	Adult Wistar rats, 150–220 g	10	Oral administration of letrozole (1 mg/kg), once daily for 21 days	i.p. injection of curcumin at the dose of: 1. 100 mg/kg 2. 200 mg/kg	14 days	Vehicle	Decrease in LH; increase in FSH; Improvement of ovarian tissue and follicles
Abuelezz et al 2020 [32]	Egypt	Virgin, adult Wistar rats, 7 weeks old, 160–200 g	10	Oral administration of letrozole (1 mg/kg), once daily for 23 days	Oral administration of: 1. NC-50 group; 50 mg/kg solution of NC 2. NC-100 group; 100 mg/kg solution of NC 3. NC-200 group; 200 mg/kg solution of NC	15 days	1. vehicle 2. clomiphene citrate (1 mg/kg)	Dose-dependently reduction of testosterone disturbance, FBG and insulin levels, insulin resistance, MDA, and TNF- α levels; Dose-dependently increment of estradiol, progesterone, GSH, and SOD levels; Dose-dependently improvement of serum lipid profile, islets area and count of β -cells, pancreatic tissue integrity, thickness of granulosa cells, and appearance of oocytes; Elevation of the PI3K/Akt/mTOR levels by all doses; Better improvement of lipid profile, oxidative stress markers, TNF- α , and Akt levels compared to clomiphene citrate by NC-100 and NC-200

Table 1 (continued)

First author, year (Ref)	Country	Animals	n/curcumin group	PCOS induction method	Curcumin treatment groups after PCOS induction	Curcumin treatment duration	Comparator	Curcumin's effects
Fatemi Abhari et al 2020 [20]	Iran	BALB/c prepubertal mice, 25 days old, ~30 g	10	Injection of DHEA (60 mg/kg), once daily for 20 days	Injection of 54 mg/kg curcumin-loaded SPIONs	20 days	Vehicle	Reduction of ovarian volume, total number of ovarian follicles, gene expression of Bax, protein expression of caspase3 in ovary tissue, and apoptotic cells death in granulosa cells and in interstitial tissue; Increment of ovarian Bcl2 expression
Raoofi et al 2018 [35]	Iran	Wistar rats, 170 ± 20 gr	10	Single S.c. injection of 2 mg/kg of E2V, after 60 days of injection PCOS was induced	i.p. injection of 600 mg/kg curcumin	14 days	No treatment	Decrease in LH, estradiol, and testosterone; Increase in FSH and progesterone levels, and number of all follicular clusters; Reduction of ovarian cysts; Improvement of serum lipid profile; No effect on body and ovarian weight
Shahmoradi et al. 2018 [36]	Iran	SD rats, 180 ± 5 g	15	S.c. injection of DHEA (60 mg/kg), once daily for 21 days	Oral administration of: 1. 100 mg/kg curcumin 2. 200 mg/kg curcumin	30 days	NR	Attenuation of body weight, FBG, insulin level, HOMA-IR, and cystic follicles, especially by the high dose; Increment of uterine gene expression of GLUT4 and ERα and corpus luteum
Mohammadi et al 2017 [33]	Iran	Adult Wistar rats, 170 ± 20 g	18	Single S.c. injection of 2 mg/kg E2V, after 60 days of injection PCOS was induced	1. injection of 100 mg/kg curcumin 2. injection of 300 mg/kg curcumin	14 days	NR	Both doses: Reduction of HOMA-IR, insulin, and IL-6 levels; Improvement of the hepatic histopathological changes High dose: Increment of QUICKI value; reduction of CRP levels

Table 1 (continued)

First author, year (Ref)	Country	Animals	n/curcumin group	PCOS induction method	Curcumin treatment groups after PCOS induction	Curcumin treatment duration	Comparator	Curcumin's effects
Mohammadi et al 2017 [34]	Iran	Adult Wistar rats, 170 ± 20 g	12	Single injection of 2 mg/kg E2V, after 60 days of injection PCOS was induced	i.p. injection of curcumin at the dose of: 1. 100 mg/kg 2. 200 mg/kg 3. 300 mg/kg 4. 400 mg/kg	14 days	NR	Reduction of the body and ovarian weight, LH levels, TNF-α expression, follicle size, and the number of cysts; Increment of FSH and progesterone levels, and the number of corpus luteum
Reddy et al 2016 [24]	India	Virgin adult Wistar Albino rats, 160–200 g	6	Oral administration of letrozole (1 mg/kg), once daily for 21 days	Oral administration of: 1. 100 mg/kg curcumin 2. 200 mg/kg curcumin	15 days	No treatment (Control rats were killed on the 21st day)	Both doses: Inhibition of the decrease in uterine weight; reduction of the testosterone and increment of progesterone levels; Alleviation of FBG and HbA1c levels; Normalization of serum lipid profile; Increasing the activity of SOD and catalase, and reduction of TBARS; Improvement of histomorphological changes High dose: Increment of the estradiol, HDL-C, and GSH levels

Akt protein kinase B, *Bax* Bcl-2-associated X protein, *Bcl2* B-cell lymphoma 2, *CRP* C-reactive protein, *DHEA* dehydroepiandrosterone, *ERα* Estrogen receptor α, *E2V* estradiol valerate, *FBG* fasting blood glucose, *FSH* follicle-stimulating hormone, *GLUT* glucose transporter type 4, *GSH* Reduced glutathione, *HbA1c* hemoglobin A1C, *HDL-c* high-density lipoprotein cholesterol, *HOMA-IR* homeostatic model assessment for insulin resistance, *i.p.* intraperitoneal, *LH* luteinizing hormone, *IL6* interleukin-6, *MDA* malondialdehyde, *mTOR* mammalian target of rapamycin, *NC* Nanocurcumin, *NP_s* Nano-particles, *PCOS* polycystic ovary syndrome, *NR* not reported, *PI3K* phosphoinositide 3-kinase, *QUICKI* insulin sensitivity check index, *S.c.* subcutaneous, *SD* Sprague Dawley, *SOD* superoxide dismutase, *SPION_s* super-paramagnetic iron oxide (Fe₃O₄) nanoparticles, *TBARS* thiobarbituric acid reacting species, *TNF-α* tumor necrosis factor α

Table 2 Characteristics of the included randomized controlled trials

First author, Year (Ref)	Country	Total sample size (curcumin group)	Age (year), Mean \pm SD	BMI (kg/m ²) at baseline (Mean \pm SD)	Dose	Treatment duration (week)	Control	Parameters studied	Curcuma's effects
Asan, 2020 [38]	Turkey	30 (15)	27.6 \pm 3.6	29.8 \pm 6.3	93.34 mg/day	8	Placebo	Weight, BMI, WC, fat mass, FPG, insulin, HOMA-IR, CRP lipid profile, DHEAS, FSH, LH, SHBG, testosterone	Between-group analysis: reduction of weight, WC, fat mass, FPG, insulin, HOMA-IR, and CRP Within-group analysis: reduction of weight, BMI, WC, fat mass, FPG, insulin, HOMA-IR, and TC CRP, TG, and TC
Jamilian, 2020 [23]	Iran	50 (24)	28.6 \pm 4.7	27.4 \pm 3.9	500 mg/day	12	Placebo (starch)	Weight, BMI, FPG, insulin, HOMA-IR, QUICKI, lipid profile, PPAR- γ , GLUT 1, and LDLR gene expression	Between-group analysis: reduction of weight, BMI, FPG, serum insulin, HOMA-IR, TC, LDL-C, and TC/HDL-C ratio; Increasing QUICKI and HDL-C; upregulation of PPAR- γ and LDLR gene expression
Heshmati, 2020 [21]	Iran	67 (34)	30.97 \pm 5.20	28.73 \pm 4.92	1500 mg/day (thrice daily)	12	Placebo (maltodextrin)	Gene expression of PGC-1 α and SIRT1, activities of GPx and SOD	Between-group analysis: increasing serum activity of GPx and PGC-1 α gene expression Within-group analysis: Increasing PGC-1 α and SIRT1 gene expression
Heshmati, 2020 [22]	Iran	67 (34)	30.97 \pm 5.20	28.73 \pm 4.92	1500 mg/day (thrice daily)	12	Placebo (maltodextrin)	BMI, WC, FPG, insulin, HOMA-IR, QUICKI, DHEA, LH, and FSH	Between-group analysis: reduction of FPG and DHEA

Table 2 (continued)

First author, Year (Ref)	Country	Total sample size (curcumin group)	Age (year), Mean ± SD	BMI (kg/m ²) at baseline (Mean ± SD)	Dose	Treatment duration (week)	Control	Parameters studied	Curcuma's effects
Sohaei, 2019 [37]	Iran	51 (27)	29.40 ± 5.33	29.67 ± 3.72	1000 mg/day (twice daily)	6	Placebo	Weight, BMI, body fat, visceral fat, lipid profile, FPG, insulin, HOMA-IR, QUICKI, and hs-CRP	Between-group analysis: not significant within-group analysis: improving serum insulin and QUICKI

BMI body mass index, DHEAS dehydroepiandrosterone sulfate, FPG fasting plasma glucose, FSH follicle-stimulating hormone, GLUT 1 glucose transporter 1, GPx glutathione peroxidase, HDL-C high-density lipoprotein cholesterol, HOMA-IR homeostatic model assessment for insulin resistance, hs-CRP high sensitivity C-reactive protein, LDL-C low-density lipoprotein cholesterol, LDLR low-density lipoprotein receptor, LH luteinizing hormone, PGC-1α peroxisome proliferator-activated receptor g coactivator-1, PPAR-γ peroxisome proliferator-activated receptor gamma, QUICKI quantitative insulin sensitivity check index, SHBG sex hormone-binding globulin, SIRT1 Sirtuin-1, SOD superoxide dismutase, TC total cholesterol, TG triglyceride, VLDL-C very-low-density lipoprotein, WC waist circumference

the selection process, 13 articles (eight animal studies and five RCTs) [20–24, 32–39], published until August 2021, were included in the systematic review. No additional articles were found through forwarding and backward citation tracking of eligible studies.

Study Characteristics

The main characteristics of the included studies are summarized in Tables 1 and 2. All studies assessed the efficacy of curcumin on PCOS features. Except for four studies [24, 32, 38, 39], others were conducted in Iran [20–23, 33–37]. Of the eight animal studies, seven examinations were on rats (Wistar [24, 32–35, 39] and Sprague Dawley [36] rats), and one was on BALB/c mice [20]. A total of 91 animals were included in this review. PCOS was induced in the animals with letrozole [24, 32, 39], dehydroepiandrosterone (DHEA) [20, 36], or estradiol valerate (E2V) [33–35] administration. Curcumin [24, 33–36, 39] or its nanoparticles [20, 32] was administered to animals by gavage [24, 32, 36] or injection [20, 33–35, 39], in concentrations varied from 54 mg/kg [20] to 600 mg/kg [35]. The curcumin treatment duration also ranged from 14 [33–35, 39] to 30 [36] days after PCOS induction.

The five included RCTs were extracted from four independent investigations, and PCOS was diagnosed according to the Rotterdam criteria in overweight or obese patients of reproductive age in all studies [21–23, 37, 38]. A total of 265 women were included in this review. The mean age and body mass index (BMI) of women ranged from 27.6 to 30.97 years and 27.4 to 29.8 kg/m², respectively. The participants of the intervention groups received 500 [23], 93.34 [38], 1000 [37], or 1500 [21, 22] mg/day of curcumin. The curcumin or placebo administration duration was 6 [37], 8 [38], or 12 [21–23] weeks. The number of participants in the intervention groups ranged from 15 [38] to 34 [21, 22] between studies. The data was analyzed according to the intention to treat analysis only in one of the included RCTs [22].

Risk of Bias Assessment

The risk of bias assessment and tier classifications of animal studies is presented in Table 3. Out of the eight selected animal studies, only three studies [20, 35, 36] used randomization for the allocation of animals in different groups. None of the animal studies reported the blindness of outcome assessors to the experimental groups, and only one of the included studies provided sample size calculations [32]. Moreover, in one investigation, the duration of the examination was not similar between the control and intervention groups [24]. Selective reporting bias was also detected in two of the included studies [34, 35]. Finally, two animal

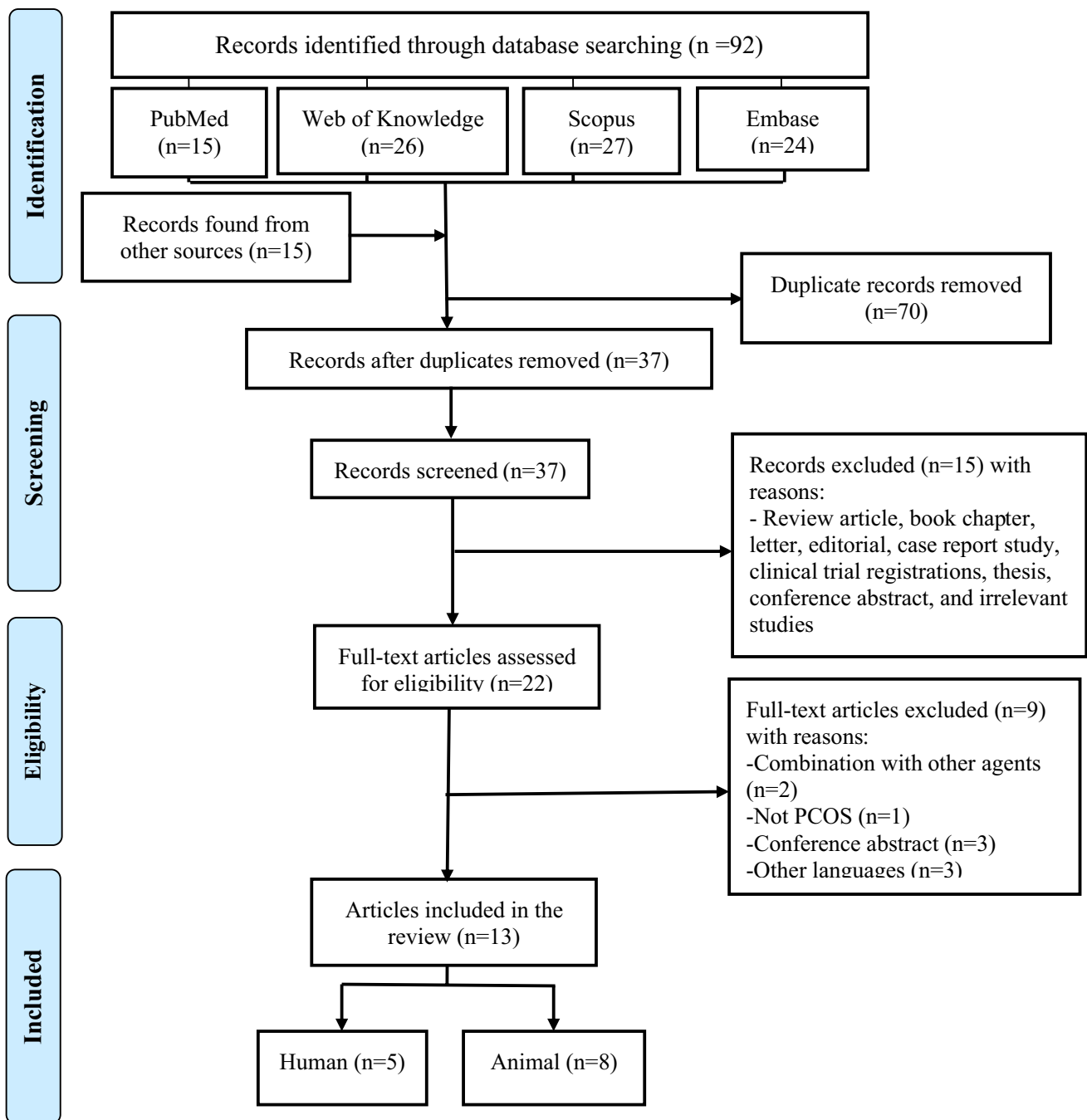


Fig. 1 PRISMA flow diagram of the literature search and study selection process

studies of the total were classified as tier 1 [20, 36] and six as tier 2 [24, 32–35, 39], according to the OHAT's tier system.

Details of the risk of bias assessment of RCTs are demonstrated in Table 4. Of five included RCTs, one trial had an overall unclear risk of bias due to selection bias [23], one had a high risk of bias because of performance bias (single-blinded) [38], and the others had a low risk of bias [21, 22, 37]. In one of the included RCTs, the data related to body weight changes during the follow-up period, as a secondary

pre-specified outcome, was not stated [22]. Moreover, in two other studies, reported data on the macronutrient and micronutrient intakes were incomplete [23, 37].

Outcomes

Morphology and Histopathology Polycystic ovarian, theca cells hyperplasia and hypertrophy, apoptosis of granulosa cells, and decreased corpus luteum are common morpho-

Table 3 The risk of bias assessment and tier classifications of animal studies (OHAT tool)

CATEGORY	QUESTIONS	Alfahnehmi, 2021 [39]	Z. Abuelezz, 2020 [32]	Fatemi Abhari, 2020 [20]	Rasoufi, 2018 [35]	Shahmoradi, 2018 [36]	Mohammadi, 2017 [33]	Mohammadi, 2017 [34]	Reddy, 2016 [24]
Selection Bias	1. Was administered dose or exposure level adequately randomized?	-	-	+	+	+	-	-	-
	2. Was allocation to study groups adequately concealed?	-	-	+	+	+	-	-	-
Performance Bias	3. Were experimental conditions identical across study groups?	+	++	++	+	+	+	+	-
	4. Were the research personnel and human subjects blinded to the study group during the study?	-	-	-	-	-	-	-	-
Attrition/Exclusion Bias	5. Were outcome data complete without attrition or exclusion from analysis?	+	+	++	+	+	++	+	++
Detection Bias	6. Can we be confident in the exposure characterization?	++	++	++	++	++	++	++	++
	7. Can we be confident in the outcome assessment?	-	-	-	-	-	-	-	-
Selective Reporting Bias	8. Were all measured outcomes reported?	++	++	++	--	+	++	--	++
Other Sources of Bias	9. Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	++	++	++	+	++	++	++	++
Overall Tier		2	2	1	2	1	2	2	2
Risk of bias response options for individual items:									
<div style="display: flex; justify-content: space-between;"> <div style="display: flex; gap: 10px;"> ++ Definitely low risk of bias -- Definitely high risk of bias </div> <div style="display: flex; gap: 10px;"> + Probably low risk of bias - Probably high risk of bias </div> </div>									

Table 4 The risk of bias assessment and tier classifications of randomized controlled trials (Cochrane collaboration’s tool)

CATEGORY	Criteria	Asari, 2020 [38]	Jamilian 2020 [23]	Heshmati 2020 [21]	Heshmati 2020 [22]	Sohaie, 2019 [37]
Selection bias	Random sequence generation	+	+	+	+	+
	Allocation concealment	+	?	+	+	+
Performance bias	Blinding of participants and personnel	-	+	+	+	+
Detection bias	Blinding of outcome assessment	?	+	+	+	+
Attrition bias	Incomplete outcome data addressed	+	?	+	?	?
Reporting bias	Selective reporting	+	+	+	+	+
Other bias	Anything else	+	+	+	+	+
Overall risk of bias		-	?	+	+	+
<div style="display: flex; justify-content: space-between;"> <div style="display: flex; gap: 10px;"> + Low risk of bias ? Unclear risk of bias - High risk of bias </div> </div>						

logical and histopathological features of PCOS [6]. The included animal studies indicated beneficial effects of curcumin on alleviating ovarian weight [34], volume [20], cysts [34–36, 39], and theca layer [34, 35] and also increasing granulosa cells [24, 32, 35] and corpus luteum [24, 34, 36]. Moreover, oocytes were appeared in the ovaries of animals after curcumin administration, in a dose-dependent manner [24, 32]. Fatemi Abhari et al. reported a reduction in the total number of primordial, primary, secondary, and antral follicles in the animals treated with curcumin nanoparticles

[20], but the other two studies reported contradictory results [24, 34, 35] (Table 1).

Apoptosis Apoptosis was assessed only in one of the included studies. Fatemi Abhari et al. demonstrated down-regulation of the expression of Bax (B-cell lymphoma 2 (Bcl2)-associated X protein) and caspase3 apoptosis-inducing factors, and also augmentation of anti-apoptotic factor Bcl2 in the ovary tissue of animals with PCOS after treatment with curcumin-loaded super-paramagnetic iron oxide

(Fe₃O₄) nanoparticles. So, the apoptotic death of granulosa cells and interstitial tissue was diminished after curcumin therapy [20] (Table 1).

Sex Hormones An increment of the levels of luteinizing hormone (LH) and insulin can increase androgen production and lead to impairment of ovarian follicle development and PCOS. Elevation of the serum LH/follicle-stimulating hormone (FSH) ratio is also the main characteristic of PCOS women [38]. Five of the included animal studies analyzed the effects of curcumin on the serum sex hormone levels of animals with PCOS. These studies reported the attenuation of LH [34, 35, 38] and testosterone [24, 32, 35] and augmentation of FSH [34, 35, 38], estradiol [24, 32], and progesterone [24, 32, 34, 35] levels after curcumin therapy. Shahmoradi et al. also demonstrated a dose-dependently effect of curcumin on the increment of the uterine estrogen receptor α (ER α) gene expression in the animals with PCOS [36] (Table 1).

Two RCTs assessed the effects of curcumin on sex hormone levels in PCOS patients and reported no influence of this phytochemical on the LH and FSH levels [22, 38]. Asan et al. also detected no significant change in the DHEAS, sex hormone-binding globulin, and testosterone levels with 93.34 mg/day curcumin supplementation for 8 weeks [38]. Although, Heshmati et al. indicated the reduction of DHEA levels in the PCOS patients treated with 1500 mg/day curcumin for 12 weeks, after adjustment for basic value of the variable, treatment type, age, and BMI [22] (Table 2).

Glycemic Control The effects of curcumin intake on the glycemic control of animals with PCOS were examined in four included studies [24, 32, 33, 36], and the reduction of fasting plasma glucose (FPG) [24, 32, 36], fasting insulin levels (FIL) [32, 33, 36], hemoglobin A1C (HbA1c) [24], or insulin resistance [32, 33, 36] were reported. Insulin resistance was assessed by calculation of homeostatic model assessment of insulin resistance (HOMA-IR) using the equation of $[\text{FPG (mg/dL)} \times \text{FIL } (\mu\text{U/mL})] / 405$. Administration of curcumin at dose of 300 mg/kg also increased the quantitative insulin sensitivity check index (QUICKI), which was calculated by $1 / (\log(\text{FIL } \mu\text{unit/mL}) + \log(\text{FPG mg/dL}))$ formula [33]. Besides, Abuelezz et al. reported the increment of β cell functionality (HOMA- $\beta\%$) with 50, 100, and 200 mg/kg of nanocurcumin, and also an improvement of the insulin sensitivity by the high doses (100 and 200 mg/kg). They also demonstrated dose-dependently augmentation of the pancreatic tissue integrity, islets area, and count of β -cells by the administration of nanocurcumin [32]. In the other study by Shahmoradi et al., an augmentation of the gene expression of glucose transporter 4 (GLUT4) was also reported after curcumin therapy of animals with PCOS [36] (Table 1).

In four included RCT investigations, the effects of curcumin supplementation on glycemic parameters were assessed in PCOS patients [22, 23, 37, 38]. Among them, three studies indicated the reduction of FPG [22, 23, 38], and two reported a decrease in FIL and HOMA-IR levels [23, 38] following curcumin administration compared to the placebo. Three studies [22, 23, 37] also evaluated QUICKI levels in PCOS women, which only one RCT reported increased QUICKI in women receiving 500 mg/day curcumin for 12 weeks [23]. Although, the GLUT-1 gene expression levels were not affected by 500 mg/day curcumin administration for 12 weeks, according to the study by Jamilian et al. [23] (Table 2).

Lipid Profile Despite the heterogeneity in the methods of the included studies, all three investigations assessing the effects of curcumin on the lipid profile of animals with PCOS reported a significant decline in the serum triglyceride (TG), total cholesterol (TC), and low-density lipoprotein cholesterol (LDL-C) and also an increase in the high-density lipoprotein cholesterol (HDL-C) levels [24, 32, 35] (Table 1).

Three of the included RCTs examined the impact of curcumin supplementation on lipid profile in PCOS women [23, 37, 38]. Reduction of TC, LDL-C, and TC/HDL-C ratio and HDL-C increment were only demonstrated in one RCT in which supplementation with 500 mg/day curcumin was applied. The attenuation of LDL receptor (LDLR) gene expression after curcumin administration was also reported in this study [23] (Table 2).

Anthropometric Parameters Three investigations have examined the effects of curcumin on body weight in the animal models of PCOS [34–36]. Among them, two studies reported a dose-dependently reduction of the PCOS-induced overweight with 100–400 mg/kg of curcumin administration [34, 36]. Although, there was no effect of 600 mg/kg curcumin injection on body weight in the other study [35] (Table 1).

All included RCTs evaluated the impact of curcumin on the anthropometric parameters in PCOS subjects [22, 23, 37, 38]. Of the four RCTs, two demonstrated the effects of curcumin at the dose of 93.34 or 500 mg/day and duration of 8 or 12 weeks, respectively, on body weight reduction [23, 38]. Although, BMI attenuation was reported only by 500-mg/day curcumin supplementation [23]. Moreover, from two articles assessing the effects of curcumin on waist circumference [22, 38] and body fat mass [37, 38], only one study reported beneficial effects [38] (Table 2).

Inflammation and Oxidative Stress The anti-inflammatory and antioxidant potential effects of curcumin on the animal models of PCOS are assessed in four investigations [24,

32–34]. In these studies, curcumin dose-dependently suppressed inflammation by attenuating the levels of inflammatory biomarkers such as interleukin-6 (IL-6), C-reactive protein (CRP), and tumor necrosis factor- α (TNF- α) [32–34]. Moreover, an increment of the levels of antioxidant enzymes (superoxide dismutase (SOD), glutathione (GSH), and catalase), and a reduction of the lipid peroxidation marker malondialdehyde (MDA) were also reported after curcumin administration [24, 32] (Table 1).

The effects of curcumin on serum glutathione peroxidase (GPx) and SOD enzyme activities in PCOS women were assessed by only Heshmati et al. In this study, 1500-mg/day curcumin supplementation for 12 weeks increased serum activity of GPx [21]. Furthermore, high-sensitivity CRP (hs-CRP) and CRP were evaluated in two studies [37, 38], and only a significant reduction in CRP levels was detected in PCOS women following 93.34-mg/day curcumin supplementation for 8 weeks [38] (Table 2).

Other Outcomes The downregulation of phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt)/mammalian target of rapamycin (mTOR) pathway in the animal model of letrozole-induced PCOS was reported by Abuelezz et al. In this study, nanocurcumin administration increased the protein expression of the main players of the PI3K/AKT/mTOR pathway [32] (Table 1). Moreover, in two of the included RCTs, curcumin also upregulated the expression levels of peroxisome proliferator-activated receptor- γ (PPAR- γ) and PPAR- γ coactivator 1- α (PGC1- α) in the peripheral blood mononuclear cells of PCOS women [21, 23] (Table 2).

Discussion

In the present study, the available evidence concerning the influence of turmeric/curcumin supplementation on PCOS was reviewed. The included animal studies revealed the favorable effects of curcumin on PCOS. Furthermore, some of the included RCTs indicated improvement of hormonal disturbances, glycemic control, lipid profile, and anthropometric features in PCOS women. However, these beneficial effects were not supported in all reviewed RCTs.

Curcumin may improve hormonal profiles in PCOS condition by reducing oxidative stress, inflammation, ovarian androgen receptor proteins, and also targeting nuclear factor-erythroid 2 related factor 2 (Nrf2)/heme oxygenase-1 (HO-1) and PI3K/Akt signaling pathways to attenuate apoptosis in granulosa cells [40–42]. Upregulation of PPAR- γ is another mechanism underlying the positive effects of curcumin on PCOS. PPAR- γ is a ligand-activated transcription factor playing crucial roles in the regulation of insulin sensitivity, energy metabolism, adipocyte differentiation, inflammation, and lipid metabolism [43]. Activation of PPAR- γ

also contributes to the control of the synthesis of steroid hormones in the granulosa cells, follicle growth, and oocyte maturation [44]. Although, there are not sufficient clinical data regarding the effectiveness of curcumin on improvement of hormonal disturbances in PCOS women.

Raising the levels of free testosterone by lowering the liver synthesis of sex hormone-binding globulin levels [45, 46] and decreasing ovulation, conception, and pregnancy [47] occurs in the hyperinsulinemic condition. On the other hand, androgens may also contribute to insulin resistance in PCOS. Some studies are supporting the amelioration of the clinical and biochemical parameters of PCOS by improvement of insulin resistance [48]. The reviewed animal investigations in the present study suggested the insulin-sensitizing effects of curcumin in the animal models of PCOS [24, 32, 36]. Evidence suggests that these effects of curcumin are partly mediated by inhibition of hepatic glycogenolysis and gluconeogenesis and also increment of hepatic and peripheral glucose uptake. Stimulation of hepatic glucokinase, PPAR- γ , PGC1- α , AMP-activated protein kinase (AMPK), incretin secretion, lipid metabolism, and GLUT4 are some proposed mechanisms of curcumin in this regard [16, 23, 32, 36, 49, 50]. PGC1- α is a transcriptional coactivator involved in mitochondrial biogenesis, brown adipose tissue differentiation, glucose metabolism, thermogenesis, fatty acid oxidation, antioxidant defense, and insulin sensitivity [21, 51]. Most of the included RCTs also supported the beneficial effects of curcumin on reducing FPG in PCOS women. Although, data regarding insulin sensitivity was inconsistent and should be further investigated.

Dyslipidemia may promote the development of insulin resistance, oxidative stress, hyperandrogenism, and infertility. Besides, hyperandrogenism can also lead to lipid abnormalities [52]. Lipid profile improvement after curcumin therapy is reported in animals with PCOS [24, 32, 35]. In this line, a recent meta-analysis of RCTs reported that curcumin reduces blood lipid levels in patients suffering from different disorders, including metabolic syndromes, type 2 diabetes, non-alcoholic fatty liver disease, chronic kidney disease, and obesity. The lipid-lowering impact of curcumin could be mediated by its inhibitory effects on cholesterol esterification, cholesterol uptake in the intestine, cholesterol biosynthesis, and TG deposition in the liver [53]. Nevertheless, most of the currently available RCTs did not support the influence of curcumin on lipid profile in PCOS women, and more studies in this field are necessary.

There is a bi-directional relationship between obesity and PCOS. Hyperandrogenism may cause visceral adiposity in PCOS women. Meanwhile, reproductive and metabolic disturbances such as insulin resistance, hyperandrogenism, and anovulation are more common in obese women, even independent of PCOS diagnosis [54, 55]. Curcumin supplementation is supposed to ameliorate fat mass and obesity

by increasing energy expenditure, lipolysis, and AMPK and PGC1- α expression. Inhibition of the inflammatory and oxidant pathways, adipocyte differentiation, Janus kinase, and 11 β -hydroxysteroid dehydrogenase type 1 enzyme are also other proposed mechanisms for the anti-obesity effects of curcumin [15, 56]. Nonetheless, the included animal studies and RCTs revealed inconsistent results regarding the effects of curcumin on anthropometric features in PCOS that should be more investigated in future examinations.

Amelioration of inflammation and oxidative stress can improve the complications of PCOS, especially insulin resistance [8, 57]. In this study, curcumin showed its robust anti-inflammatory and antioxidant effects in the animal models of PCOS by lowering IL-6, CRP, TNF- α , and MDA and also increasing SOD, GSH, and catalase [24, 32, 34]. However, only GPX and CRP, but not SOD and hs-CRP, were affected by curcumin in the included RCTs [21, 37, 38]. Upregulation of PPAR- γ , PGC1- α , and Nrf2/HO-1 pathway and down-regulation of nuclear factor kappa B, activator protein-1, and signal transducer and activator of transcription (STAT) proteins are some suggested mechanisms for anti-inflammatory and antioxidant properties of curcumin [21, 23, 40, 58–60].

The most important limitation of this systematic review was the small number of trials that prohibited performing a meta-analysis. Second, although all reviewed RCTs were conducted on obese/overweight PCOS patients, there was considerable heterogeneity regarding curcumin dose, duration of investigations, sample sizes, and age of patients. Third, most of the included studies were conducted in Iran, and therefore, the findings are not generalizable to other populations and may cause possible bias.

Conclusion

Animal studies underlined the potential effects of curcumin on the management of hormonal and metabolic disturbances related to PCOS. Reducing oxidative stress, inflammation, and Nrf2/HO-1 and PI3K/Akt signaling pathways and stimulation of hepatic glucokinase, PPAR- γ , PGC1- α , AMPK, and incretin secretion are some proposed mechanisms related to the observed effects. Although present clinical literature is limited to conclude the beneficial effects of curcumin on the management of PCOS symptoms. Further well-designed RCTs with longer duration and higher doses of curcumin, especially bioavailability-improved formulations, are warranted to be performed on PCOS women. Besides, mechanistic examinations on the effects of curcumin on this syndrome are also suggested.

Abbreviations AMPK: AMP-activated protein kinase; Akt: Protein kinase B; BMI: Body mass index; Bax: B-cell lymphoma 2

(Bcl2)-associated X protein; CRP: C-reactive protein; CI: Confidence intervals; ER α : Estrogen receptor α ; FSH: Follicle-stimulating hormone; FPG: Fasting plasma glucose; FIL: Fasting insulin levels; GLUT: Glucose transporter; GPX: Glutathione peroxidase; GSH: Glutathione; HbA1c: Hemoglobin A1C; HOMA-IR: Homeostatic model assessment of insulin resistance; HDL-C: High-density lipoprotein cholesterol; hs-CRP: High-sensitivity CRP; HO-1: Heme oxygenase-1; IL-6: Interleukin-6; LH: Luteinizing hormone; LDL-C: Low-density lipoprotein cholesterol; LDLR: LDL receptor; MD: Mean difference; MDA: Malondialdehyde; mTOR: Mammalian target of rapamycin; Nrf2: Nuclear factor-erythroid 2-related factor 2; PCOS: Polycystic ovary syndrome; PI3K: Phosphoinositide 3-kinase; PPAR- γ : Peroxisome proliferator-activated receptor- γ ; PGC1- α : PPAR- γ coactivator 1- α ; QUICKI: Quantitative insulin sensitivity check index; RCTs: Randomized placebo-controlled clinical trials; SOD: Superoxide dismutase; STAT: Signal transducer and activator of transcription; TG: Triglyceride; TC: Total cholesterol; TNF- α : Tumor necrosis factor- α

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