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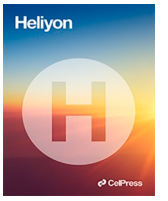

Research article

Efficacy and safety of cangfu daotan decoction as an adjuvant treatment of Diane-35 for polycystic ovary syndrome: A systematic review and meta-analysis

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ABSTRACT

Objective: Cangfu Daotan decoction is a classic traditional Chinese medicine formula that has been found to be beneficial for treating polycystic ovarian syndrome (PCOS) in animal models. This systematic review aimed to assess the efficacy and safety of Cangfu Daotan decoction as an adjuvant treatment to Diane-35 for PCOS in humans.

Methods: Seven electronic databases were searched up to June 22, 2024, to identify randomized controlled trials (RCTs) that evaluated Cangfu Daotan decoction combined with Diane-35 versus Diane-35 alone for the treatment of PCOS. The effects of individual RCTs were combined via meta-analysis and were measured as relative risks (RRs) or weighted mean differences (WMDs).

Results: Twenty-five RCTs with a moderate to high risk of bias were included, involving 1845 patients with PCOS. Meta-analyses indicated that compared with Diane-35 alone, the combination of Diane-35 and Cangfu Daotan decoction significantly improved the response rate (RR 1.19, 95 % confidence interval [CI] 1.14 to 1.24), pregnancy rate (RR 1.57, 95 % CI 1.18 to 2.09), ovulation rate (RR 1.22, 95 % CI 1.11 to 1.35), and ovarian volume (WMD -1.43 cm^3, 95 % CI -2.46 to −0.39). Cangfu Daotan decoction also significantly reduced the luteinizing hormone (LH) level, LH:FSH ratio, testosterone level, prolactin level, body mass index (BMI) and hirsutism and acne scores but had no significant effect on the follicle-stimulating hormone (FSH) level. All adverse events were mild and not related to Cangfu Daotan decoction treatment.

Conclusions: The findings suggest that Cangfu Daotan decoction, as an adjuvant therapy to Diane-35 for the treatment of PCOS, can reduce multiple sex hormone levels and BMI, relieve hyperandrogenism signs, and ultimately improve pregnancy outcomes, with good safety. The effect of Cangfu Daotan decoction on FSH remains uncertain. Due to limitations of risk of bias and heterogeneity, the quality of evidence was rated as moderate to very low.

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Abbreviations

AE	adverse event
BMI	body mass index
CI	confidence interval
FSH	follicle-stimulating hormone
GRADE	Grading of Recommendation, Assessment, Development and Evaluation
LH	luteinizing hormone
WMD	weighted mean difference
PCOS	polycystic ovarian syndrome
RCT	randomized controlled trial
RIS	required information size
RoB 2	Cochrane Risk of Bias Tool 2
RR	relative risk
TCM	traditional Chinese medicine
TSA	trial sequential analysis

1. Introduction

Polycystic ovarian syndrome (PCOS) is the most common reproductive endocrine disorder in women, with an incidence of up to 6%–10 % in women of childbearing age [1]. The pathophysiology of this condition includes abnormal hormone secretion, increased ovarian volume, and polycystic ovaries; symptoms can include menstrual irregularities, infertility, acne, hirsutism, and obesity [2]. Modern medicine typically manages PCOS symptomatically, with the primary approach being the adjustment of hormone levels. Diane-35 (cyproterone acetate and ethinylestradiol tablets) is the most common drug used; it reduces androgen levels, induces ovulation, and improves hyperandrogenic signs such as hirsutism and acne by inhibiting the release of pituitary gonadotropins [3–5]. However, long-term use of Diane-35 can result in undesirable side effects, including weight gain, mood swings, and even severe adverse events such as pulmonary embolism [6]. Due to the limitations of conventional therapy, traditional Chinese medicine (TCM) has become an important complementary and alternative treatment for PCOS in China.

From a TCM perspective, PCOS can be classified as a syndrome of menstrual disorder, infertility, and obesity, and its development is closely associated with the loss of transport due to spleen deficiency, the production of phlegm and dampness, and the stagnation of the liver and qi [7]. Cangfu Daotan decoction is a representative TCM prescription that has offered a wealth of therapeutic experience to treat these syndromes [8]. It was first recorded in *Ye Tianshi's Encyclopedia of Gynecology* and is thought to aid in the dispersal of phlegm and dampness, invigoration of the spleen, and regulation of qi [9].

The typical herbal ingredients of Cangfu Daotan decoction include Cangzhu (*Atractylodes lancea* (Thunb.) DC.), Xiangfu (*Cyperus rotundus* Linn.), Chenpi (*Citrus sinensis* (L.) Osbeck), Nanxing (*Arisaema erubescens* Schott), Zhike (*Poncirus trifoliata* (L.) Raf.), Banxia (*Pinellia ternate* (Thunb.) Breit.), Chuanxiong (*Ligusticum chuanxiong* Hort.), and Fuling (*Poria cocos* (Schw.) Wolf.). All the plant names have been checked with "World Flora Online". Basic experiments have demonstrated their role in the pathophysiology of PCOS. For example, Changzhu has a modulating effect on glycolipid metabolism [10]; Xiangfu has been found to have estrogenic activity, which promotes the development of follicles and ovulation [11]; Chenpi can lower blood glucose and prolactin [12]; Fuling has diuretic properties and can reduce blood lipids [13]; and Zhike has also been found to reduce blood lipids [14]. An experiment indicated that Cangfu Daotan decoction can improve the weight and insulin level of PCOS rats, regulate sex hormones and the levels of PCOS-related interleukin-2, interleukin-6, and tumor necrosis factor-α cytokines, and repair damaged ovaries, thus supporting its applicability in treating PCOS at the animal level [15].

At present, there is a wealth of evidence from randomized controlled trials (RCTs) concerning the use of Cangfu Daotan decoction for the treatment of PCOS; however, the conclusions of existing RCTs are conflicting, likely due to heterogeneity in patient characteristics, interventions and methodologies, or random errors associated with small sample sizes. To address this issue, we conducted a systematic review and meta-analysis of RCTs that used Cangfu Daotan decoction as an adjuvant for the treatment of PCOS, with control of inclusion and exclusion criteria to reduce heterogeneity among the included studies.

2. Materials and methods

2.1. Study profile

This study was prospectively registered on the PROSPERO platform (registration no: CRD42022372708) on June 22, 2024, and was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [16].

2.2. Inclusion and exclusion criteria

This systematic review included RCTs that assessed the efficacy or safety of Cangfu Daotan decoction for treating PCOS in

conjunction with Diane-35 as the basic therapy. Specifically, the comparison should be between Cangfu Daotan decoction + Diane-35 and placebo or no intervention + Diane-35. The diagnosis of PCOS should meet accepted diagnostic criteria, such as those recommended by the 2003 Rotterdam consensus workshop of the European Society of Human Reproduction and Embryology and the American Society of Reproductive Medicine [17]. Typically, individuals who met two of the following three criteria without the possibility of other diseases that may lead to elevated levels of androgens were included, regardless of nationality, race, or course of disease: a) irregular ovulation or anovulation; b) clinical manifestations of androgen excess and/or hyperandrogenism; and c) polycystic ovaries with $\geq$12 follicles with a diameter of 2–9 mm in unilateral or bilateral ovaries and/or an ovarian volume of $\geq$10 cm^3. The original formula of Cangfu Daotan decoction comprised 10 g each of Cangzhu, Xiangfu, Chenpi, Nanxing, Zhike, Banxia, Chuanxiong, and Fuling. The formula and dosage of Cangfu Daotan decoction can be adjusted according to the patient's condition, but the main ingredients and TCM principles of the adjusted formula should remain similar to those of the original formula.

The exclusion criteria included studies that used alternative Western medications, laparoscopic surgery, or other TCM treatments for PCOS; animal experiments; studies with missing data for all outcomes; or studies for which the full text was not available.

2.3. Outcomes

The primary outcome was the response to treatment, defined by a clinically significant improvement in clinical symptoms, sex hormone levels, follicle count, and ovarian volume. There were four categories of secondary outcomes: 1) pregnancy-related outcomes: pregnancy rate assessed by natural conception after treatment; ovulation rate assessed by biphasic basal body temperature or B-mode ultrasound monitoring; ovarian volume assessed by B-mode ultrasound monitoring (smaller ovarian volume being beneficial for patients with PCOS); 2) sex hormone outcomes: LH, FSH, LH:FSH ratio, testosterone, and prolactin, with better outcomes indicated by lower levels of LH, LH:FSH ratio, and prolactin, and higher levels of FSH; 3) body mass index (BMI); and 4) hyperandrogenism signs: hirsutism score evaluated by the Ferriman–Gallwey scale and acne score evaluated by the Global Acne Grading System scale, both with lower scores indicating improvement of symptoms.

2.4. Literature search

We searched seven databases (PubMed, Embase, Cochrane Library, Chinese Biomedical Literature Database, China National Knowledge Infrastructure, WanFang Data, and CQVIP) from their establishment to June 22, 2024, with no language restriction. The search terms used included "polycystic ovarian syndrome", "PCOS", "Diane-35", and "cyproterone acetate-ethinyl estradiol" (see detailed search strategies in Table S1 in the Supplementary files). All the search results were imported into EndNote X9.3.3 for management, and the reference lists of the included studies were also manually searched for any missed studies.

2.5. Screening and data extraction

Two reviewers independently screened the bibliography records according to the inclusion and exclusion criteria and extracted relevant data. Disagreements were resolved through discussion or by consulting a third reviewer. After deduplication via Endnote, ineligible studies were first ruled out by reading the titles and abstracts. The full texts of potentially eligible RCTs were subsequently read, and those meeting all eligible criteria were included. Relevant data from the included RCTs were extracted via a pilot-tested table, comprising the first author, year of publication, sample size, age, course of disease, interventions, course of treatment, baseline sex hormone levels, and outcome data.

2.6. Risk of bias assessment

The risk of bias in the included RCTs was assessed via the Cochrane Risk of Bias Tool 2 (RoB 2). This evaluation covered five domains of bias: 1) bias in the randomization process; 2) bias due to deviations from established interventions; 3) bias due to missing outcome data; 4) bias in outcome measurements; and 5) bias due to selective reporting. Each domain of risk of bias was rated as low, high, or with some concerns, and the overall risk of bias for each RCT was categorized as high, moderate, or low. Two reviewers, independently and in duplicate, assessed the risk of bias of the included RCTs and cross-checked their results. Discrepancies were resolved through discussion or, when necessary, by a third reviewer.

2.7. Statistical analysis

Meta-analyses were performed via the random-effects model for all outcomes with Review Manager version 5.4 (the Cochrane Collaboration, 2020). For dichotomous outcomes, the Mantel–Haenszel method was applied, with the effect measure of relative risks (RRs) and 95 % confidence intervals (CIs). For continuous outcomes, the inverse variance method was used, with the weighted mean difference (WMD) and 95 % CI between groups as effect sizes. Trial sequential analysis (TSA) was conducted via TSA software version 0.9 [18] to assess the reliability of hypothesis testing for between-group differences, with the probability of type 1 error set at 0.05, the power at 0.80, and the traditional threshold Z at 1.96. The required information size (RIS) was estimated based on the mean event rate in the control group and a 20 % relative risk reduction in the experimental group for dichotomous outcomes and automatically estimated by WMDs and common variance among included RCTs for continuous outcomes.

We assessed the statistical heterogeneity between studies via Cochran's Q test and the I^2 statistic. A p value of $<$0.10 in the Q test or

an I^2 value of >50 % indicated statistically significant heterogeneity. For outcomes with significant heterogeneity, we conducted subgroup analyses to investigate potential sources of heterogeneity based on three prespecified factors: course of disease (<4 years vs. ≥ 4 years), sample size (≤50 vs. > 50), and course of treatment (≤3 menstrual cycles vs. > 3 menstrual cycles). We also conducted a post hoc subgroup analysis to explore differences in mean age (<28 years vs. ≥ 28 years). To evaluate the robustness of the meta-analysis results, we conducted sensitivity analyses with a fixed effect model (only for outcomes without significant heterogeneity) or by excluding studies with an overall high risk of bias. For outcomes involving ten or more RCTs, publication bias was evaluated using funnel plots and Egger's test.

2.8. Quality of evidence appraisal

The quality of evidence derived from the meta-analysis results was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. Five factors influencing the quality of evidence were appraised: risk of bias, inconsistency, indirectness, imprecision, and publication bias. The quality of evidence for each outcome was subsequently classified as very

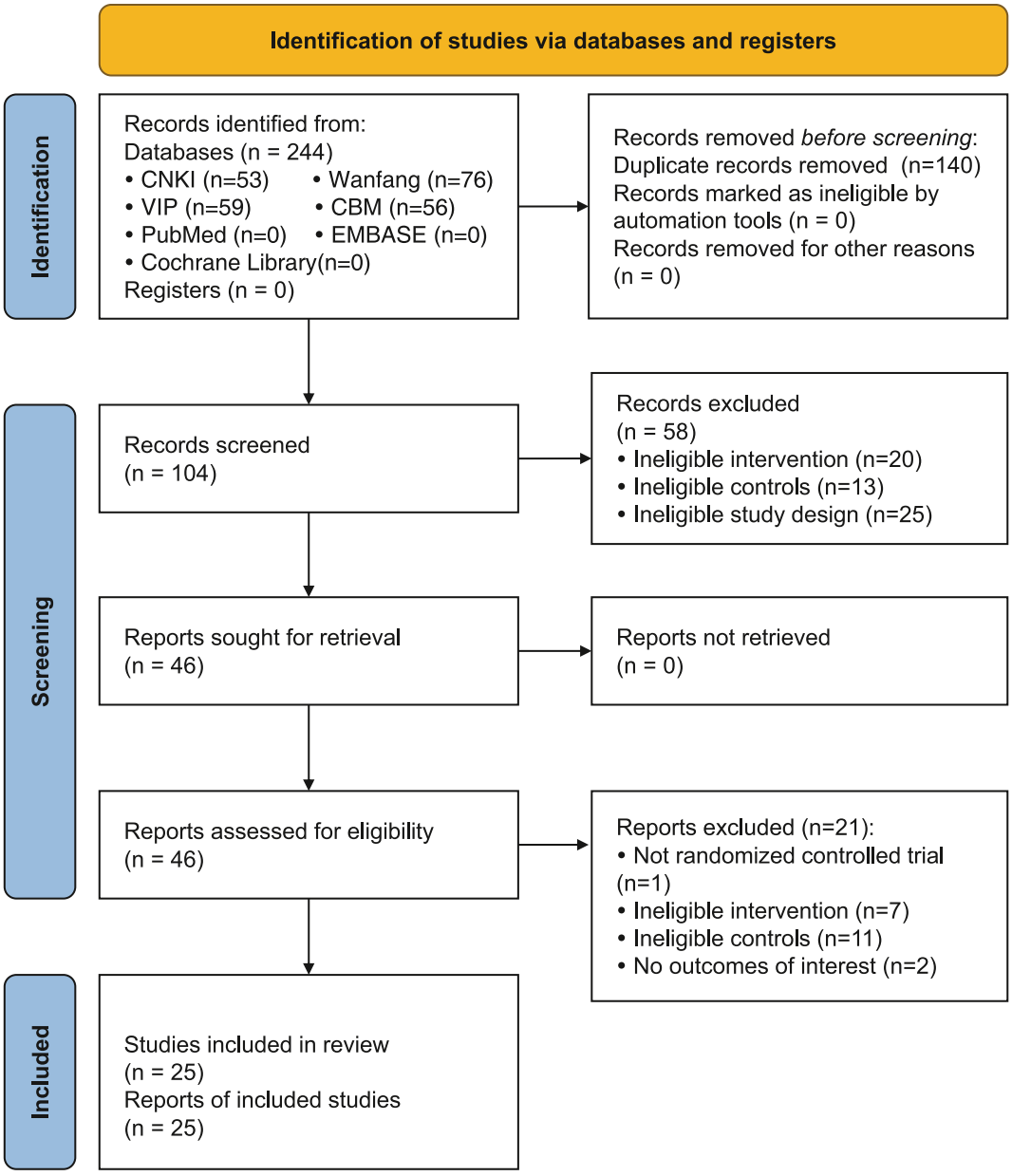

Fig. 1. Flowchart of the study screening process.

Table 1
Characteristics of the included studies.

Study	Sample size (E/C)	Age (E/C)	Course of PCOS (E/C, year)	Intervention in Experimental group[a]	Intervention in control group	Treatment course	Baseline sex hormone level (mean, E/C)		
							FSH (mIU/ml)	LH (mIU/ml)	T (nmol/L)
Chen 2019 [21]	48/48	29.5/29.7	4.6/4.4	CFDTD 1 dose/bid + Diane-35 1 tablet/d	Diane-35 1 tablet/d	3 cycles	6.1/6.2	2.7/2.6	2.6/2.5
Chen L 2020 [19]	40/40	27.1/27.0	1.9/1.9	CFDTD 1 dose/bid + Diane-35 1 tablet/d	Diane-35 1 tablet/d	3 cycles	6.4/6.4	10.4/10.3	3.4/3.4
Chen Y 2020 [20]	30/30	29.4/28.3	2.0/2.9	CFDTD 250 ml/bid + Diane-35 1 tablet/d	Diane-35 1 tablet/d	3 cycles	NR	NR	NR
Deng 2021 [22]	60/60	29.5/26.5	NR	CFDTD 1 dose/bid + Diane-35 1 tablet/d	Diane-35 1 tablet/d	3 cycles	NR	NR	NR
Di 2019 [23]	22/22	25.2/25.2	2.0/2.0	CFDTD 200 ml/bid + Diane-35 1 tablet/d	Diane-35 1 tablet/d	3 cycles	4.2/4.4	11.1/11.5	1.6/1.6
Fu 2017 [24]	19/19	14~32	4.5/4.5	CFDTD 1 dose/bid + Diane-35 1 tablet/d	Diane-35 1 tablet/d	3 cycles	4.5/5.2	7.1/6.8	2.5/2.4
Gao 2019 [25]	40/40	30.5/31.2	5/4.9	CFDTD 1 dose/bid + Diane-35 1 tablet/d	Diane-35 1 tablet/d	3 cycles	NR	NR	NR
Jie 2020 [26]	30/30	30.8/30.6	2.8/2.8	CFDTD 1 dose/bid + Diane-35 1 tablet/d	Diane-35 1 tablet/d	3 cycles	NR	NR	NR
Li 2017 [27]	38/37	26.7	4.9/4.9	CFDTD 1 dose/bid + Diane-35 1 tablet/d	Diane-35 1 tablet/d	3 cycles	8.6/8.7	14.9/15.0	2.6/2.7
Lin 2020 [28]	40/40	31.2/31.0	2.3/2.4	CFDTD 200 ml/bid + Diane-35 1 tablet/d	Diane-35 1 tablet/d	4 Weeks	NR	NR	NR
Liu 2018 [29]	40/40	26.2/26.4	3.3/3.5	CFDTD 150 ml/bid + Diane-35 1 tablet/d	Diane-35 1 tablet/d	3 cycles	6.2/6.2	16.5/16.5	2.5/2.5
Liu 2019 [32]	30/30	28.6/28.6	1~6/1~5	CFDTD 100 ml/bid + Diane-35 1 tablet/d	Diane-35 1 tablet/d	3 cycles	5.5/5.4	11.9/12.1	3.2/3.1
Liu 2022 [30]	60/60	26.1/25.6	4.1/4.4	CFDTD 150 ml/bid + Diane-35 1 tablet/d	Diane-35 1 tablet/d	3 cycles	4.1/3.9	12.3/12.3	2.4/2.4
Liu 2023 [31]	43/43	29.8/29.5	2.8/2.8	CFDTD 150 ml/bid + Diane-35 1 tablet/d	Diane-35 1 tablet/d	3 cycles	8.5/8.7	12.4/12.4	1.8/1.9
Lu 2011 [33]	32/24	24.7/24.0	NR	CFDTD 1 dose/bid + Diane-35 1 tablet/d	Diane-35 1 tablet/d	3 cycles	4.8/4.9	9.5/7.9	3.8/3.8
Sun 2018 [34]	45/45	19~38	NR	CFDTD 1 dose/bid + Diane-35 1 tablet/d	Diane-35 1 tablet/d	3 cycles	NR	14.9/14.5	5.8/5.6
Tang 2020 [36]	23/23	26.9/27.6	4.8/4.3	CFDTD 1 dose/bid + Diane-35 1 tablet/d	Diane-35 1 tablet/d	3 cycles	NR	NR	NR
Tang 2021 [35]	37/37	26.4/26.7	4.8/4.5	CFDTD 250 ml/bid + Diane-35 1 tablet/d	Diane-35 1 tablet/d	3 cycles	NR	NR	NR
Xin 2017 [37]	51/51	26.3/26.1	3.4/3.2	CFDTD 1 dose/bid + Diane-35 1 tablet/d	Diane-35 1 tablet/d	3 cycles	6.2/6.2	16.6/16.5	2.5/2.5
Xing 2008 [38]	30/30	26.1/25.3	2.8/2.9	CFDTD 100 ml/bid + Diane-35 1 tablet/d	Diane-35 1 tablet/d	3 cycles	NR	7.1/6.8	2.5/2.4
Xu 2020 [39]	29/29	25.2/25.4	NR	CFDTD 1 dose/bid + Diane-35 1 tablet/d	Diane-35 1 tablet/d	3 cycles	5.3/6.3	13.7/16.5	2.9/2.9
Yang 2015 [40]	30/30	27.8/28.4	3.1/3.5	CFDTD 150 ml/bid + Diane-35 1 tablet/d	Diane-35 1 tablet/d	6 cycles	NR	NR	NR
Yu 2015 [41]	20/20	27.6/27.9	NR	CFDTD 200 ml/bid + Diane-35 1 tablet/d	Diane-35 1 tablet/d	9 cycles	NR	NR	NR
Zhang 2016 [42]	50/50	28.9/29.1	2.0/2.0	CFDTD 1 dose/bid + Diane-35 1 tablet/d	Diane-35 1 tablet/d	3 cycles	6.4/6.4	10.4/10.4	3.5/3.4
Zhou 2023 [43]	40/40	31.4/31.5	2.8/2.8	CFDTD 1 dose/bid + Diane-35 1 tablet/d	Diane-35 1 tablet/d	3 cycles	5.8/5.7	12.3/12.4	3.3/3.3

CFDTD= Cangfu Daotan decoction, FSH= Follicle stimulating hormone, LH=Luteinizing hormone, T = Testosterone.
[a] In China, Diane-35 is the only product available, which contains 2 mg of cyproterone acetate and 0.035 mg of ethinylestradiol per tablet.

low, low, moderate, or high.

3. Results

3.1. Results of literature search

A total of 244 records were retrieved from seven databases. After screening the titles and abstracts, 46 potentially eligible articles remained. Following a full-text review, 21 articles were excluded (see list and reasons in Table S2 in the Supplementary files), and 25 RCTs [19–43] were included in the systematic review. The screening process is shown in Fig. 1.

3.2. Characteristics of the included studies

The 25 included RCTs involved a total of 1845 patients, with 927 in the experimental group and 918 in the control group. Among the individual RCTs, the sample sizes ranged from 38 to 120, the average age ranged from 14 to 36.6 years, and the duration of disease ranged from 1 to 6 years. Twenty-two RCTs were conducted for 3 cycles, while one each was conducted for 4, 6, and 9 cycles. In all the RCTs, both the experimental and control groups were given Diane-35 (2 mg of cyproterone acetate and 0.035 mg of ethinylestradiol) once a day. The experimental group additionally received Cangfu Daotan decoction twice a day as an adjuvant intervention. The components and dosages of Cangfu Daotan decoction varied among the studies. All prescriptions included Atractylodes lancea, Cyperus rotundus, and Citrus sinensis as the main components, with nine studies fully incorporating the eight typical herbs of Cangfu Daotan decoction. Adjustments to the prescriptions were made in all studies, with four studies based on different menstrual phases, two studies based on different TCM syndromes, and the remaining studies making fixed adjustments. The detailed components and dosages of Cangfu Daotan decoction are presented in Table S3 in the Supplementary files. The characteristics of the included RCTs are presented in Table 1.

3.3. Risk of bias

Overall, 13 RCTs [19–21,27,30–33,35,38,39,42,43] were rated to have a moderate risk of bias, whereas 12 RCTs [22–26,28,29,34,36,37,40,41] had a high risk of bias. The risk of bias was attributed mainly to limitations in domain 1 (bias in the process of randomization) and domain 2 (bias arising from deviation from established interventions). The risk of bias in domain 1 was primarily due to unclear descriptions of the generation of random sequences—only two RCTs adopted the lottery method, and two allocated patients using admission numbers. The risk of bias in domain 2 was primarily due to the absence of a description regarding the use of blinding. None of the studies had issues with measurement accuracy, data completeness, or selective reporting, so domains 3 to 5 did not present a significant risk of bias. The details of the risk of bias assessments are shown in Fig. 2.

3.4. Response to treatment

Twenty-two RCTs [19–23,25–30,32,34–43] assessed the response to treatment. The definition of a response was largely consistent across RCTs, comprising improved clinical symptoms and hormone levels as well as a decrease in the number of follicles and ovarian volume (details compiled in Table S4 in the Supplementary files). The response rate was 91.0 % (758/833) in the experimental group and 73.6 % (618/840) in the control group. A meta-analysis (Fig. 3) revealed that the response rate in the experimental group was significantly higher than that in the control group (RR 1.19, 95 % CI 1.14 to 1.24, $p < 0.00001$), with low heterogeneity ($I^2 = 3$ %).

3.5. Pregnancy-related outcomes

Five [24,26,28,30,33] and seven RCTs [20,24,29,30,33,37,38] reported pregnancy (experimental group: 39.8 % vs control group: 24.9 %) and ovulation (81.1 % vs 64.8 %) rates, respectively. The meta-analysis (Fig. 4) showed that compared to patients in the

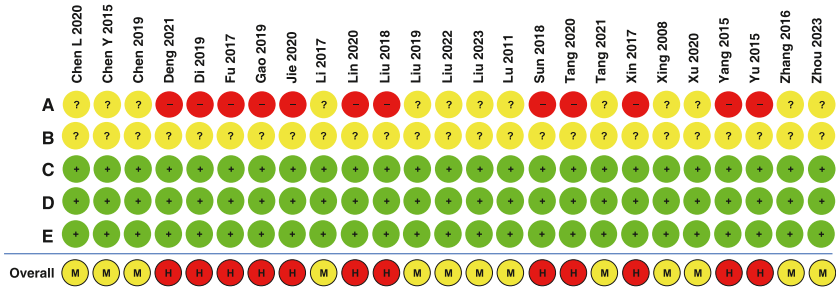

Fig. 2. Results of the risk of bias assessment. A: Randomization process; B: Deviations from intended interventions; C: Missing outcome data; D: Measurement of the outcome; E: Selection of the reported result. "+": low risk; "?": some concerns; "-": high risk; M: moderate; H: high.

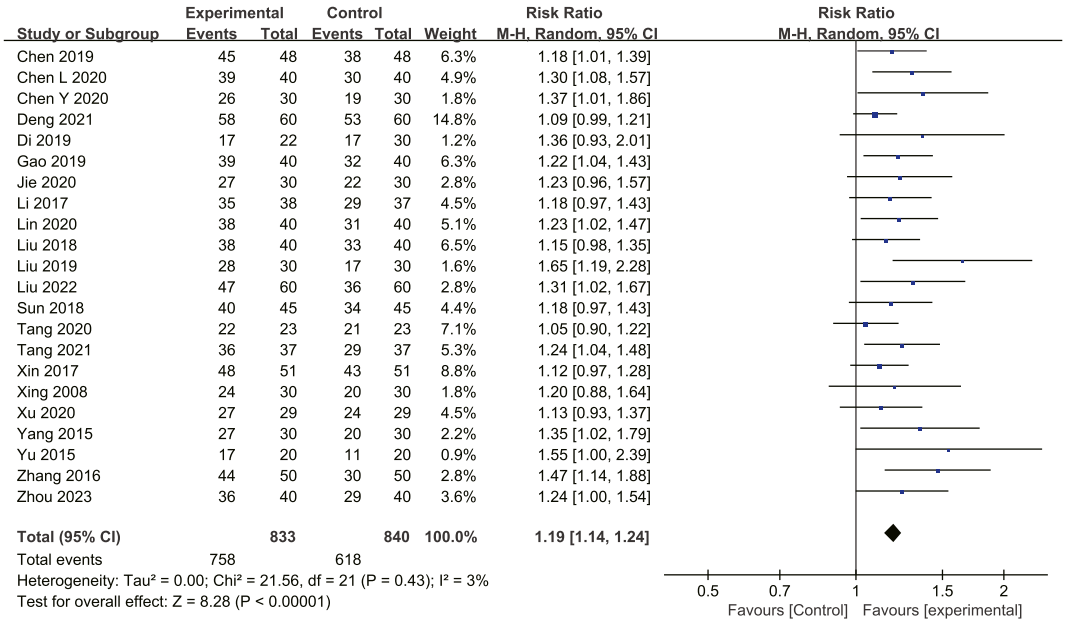

Fig. 3. Meta-analysis of the response to treatment.

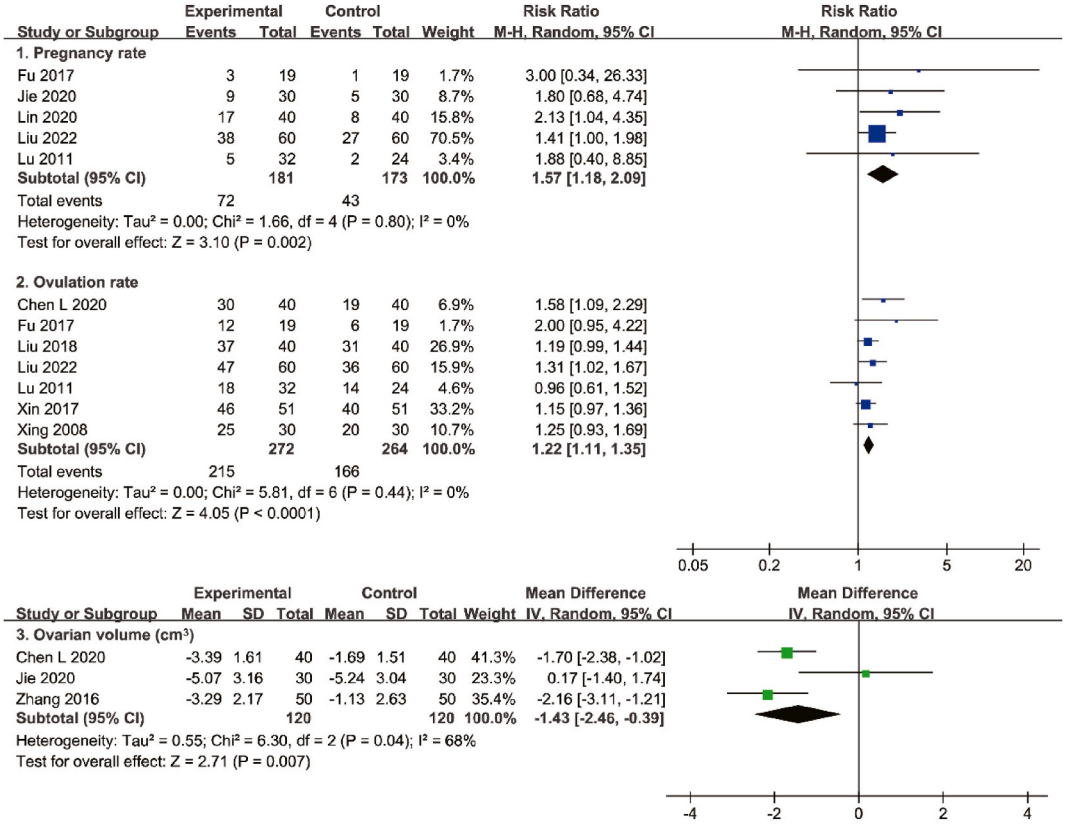

Fig. 4. Meta-analysis of pregnancy-related outcomes.

control group, patients receiving Cangfu Daotan decoction had significantly greater pregnancy rates (RR 1.57, 95 % CI 1.18 to 2.09, p = 0.002; $I^2 = 0$ %) and ovulation rates (RR 1.22, 95 % CI 1.11 to 1.35, p < 0.0001; $I^2 = 0$ %). Additionally, pooled results from three RCTs [20,26,42] indicated a significantly greater decrease in ovarian volume in patients receiving Cangfu Daotan decoction than in those who did not (WMD -1.43 cm^3, 95 % CI -2.46 to −0.39, p = 0.007; $I^2 = 68$ %).

3.6. Sex hormones

Eighteen RCTs [19,20,23,24,26–34,37–39,42,43] (n = 1365) reported sex hormone outcomes. Compared to Diane-35 alone, Cangfu Daotan decoction combined with Diane-35 significantly decreased the levels of LH (WMD -1.61 mIU/ml, 95 % CI -2.19 to −1.02; 18 RCTs), the LH/FSH ratio (−0.32, −0.48 to −0.15; 10 RCTs), testosterone (−0.55 nmol/L, −0.73 to −0.36; 18 RCTs), and prolactin (−1.62 μg/L, −2.35 to −0.90; 2 RCTs). There was no significant between-group difference in changes in FSH levels (−0.50

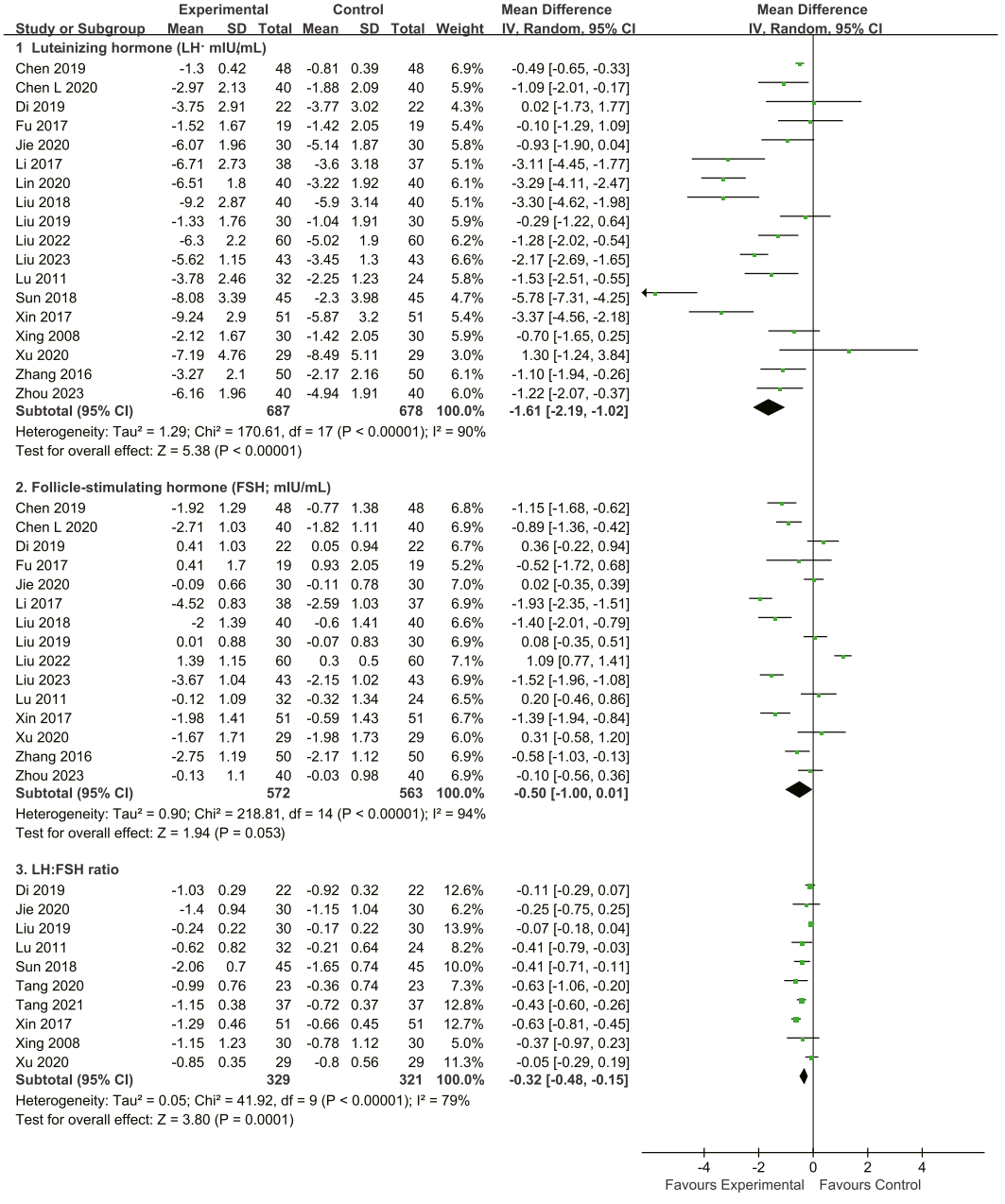

Fig. 5. Meta-analysis of LH, FSH, and the LH:FSH ratio.

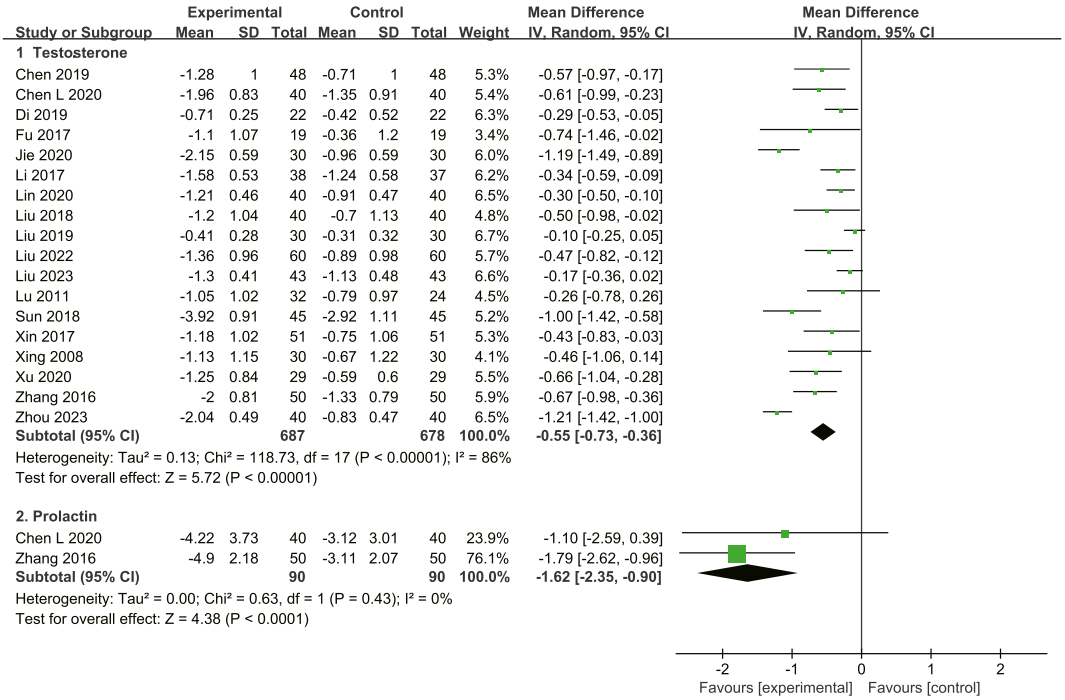

Fig. 6. Meta-analysis of testosterone and prolactin.

mIU/ml, −1.00 to 0.01, p = 0.053; 15 RCTs). Significant heterogeneity was observed for all sex hormone outcomes (I^2 ranged from 79 % to 94 %), except for prolactin (I^2 = 0 %) (Figs. 5–6).

3.7. BMI and hyperandrogenism signs

Seven RCTs [23,24,26,33,36,37,39] and three RCTs [20,40,42] assessed BMI and hyperandrogenism scores, respectively. As depicted in Fig. 7, the pooled results showed a significantly greater decrease in BMI (−1.91 kg/m^2, 95 % CI -2.94 to −0.88), acne score

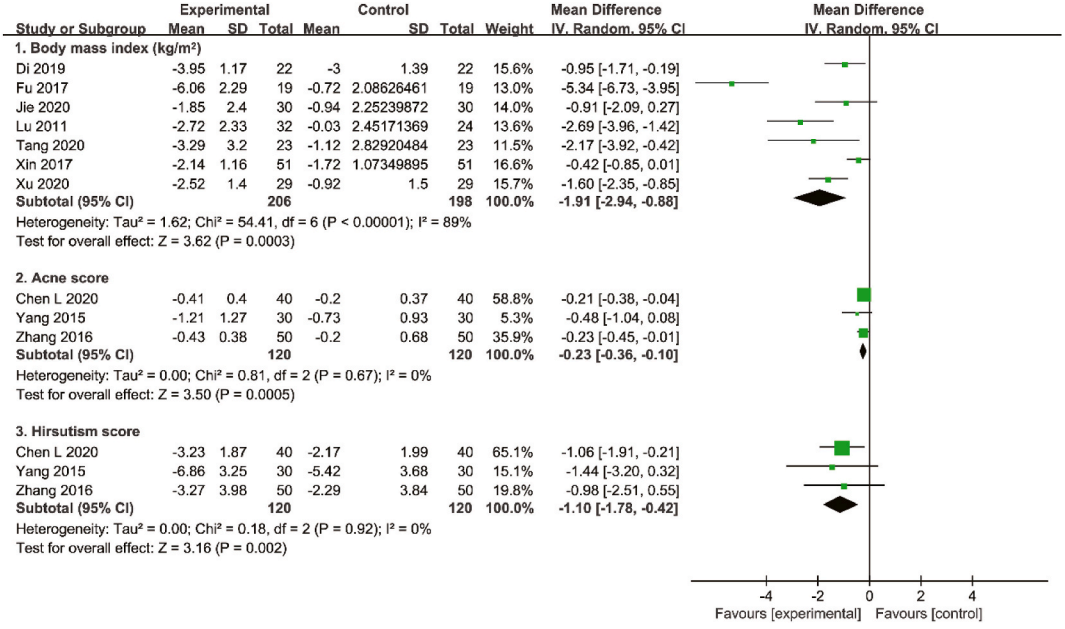

Fig. 7. Meta-analysis of body mass index and hyperandrogenism signs.

(−0.23, 95 % CI -0.36 to −0.10), and hirsutism score (−1.10, 95 % CI -1.78 to −0.42) in the experimental group than in the control group. The heterogeneity was high for the BMI analysis ($I^2 = 89$ %), while it was low for the analyses of both hyperandrogenism signs ($I^2 = 0$ %).

3.8. Subgroup analysis and sensitivity analysis

According to the subgroup analyses (Table S5 in the Supplementary file), significant differences were detected in the decrease in BMI between patients with disease durations <4 years and those with disease durations ≥4 years (WMD -0.58 kg/m^2 vs −3.80 kg/m^2; interaction p = 0.04), the decrease in LH between studies with sample sizes ≤50 and those with sample sizes >50 (−0.47 mIU/ml vs −1.99 mIU/ml; p < 0.00001), and the decrease in LH/FSH between patients aged <28 years and those aged ≥28 years (−0.36 vs −0.08; p = 0.01). The analysis of other subgroups did not reveal any significant differences. No directional change was detected in any sensitivity analyses, except that the between-group difference in the analysis excluding studies with a high risk of bias changed to be not significant for prolactin (Table S6 in the Supplementary file).

3.9. Publication bias

Tests for publication bias were available for five outcomes, and the results are presented in Fig. 8. The funnel plot of the response to treatment and LH showed poor bilateral symmetry, and Egger's test also indicated significant publication bias (p < 0.001 for the

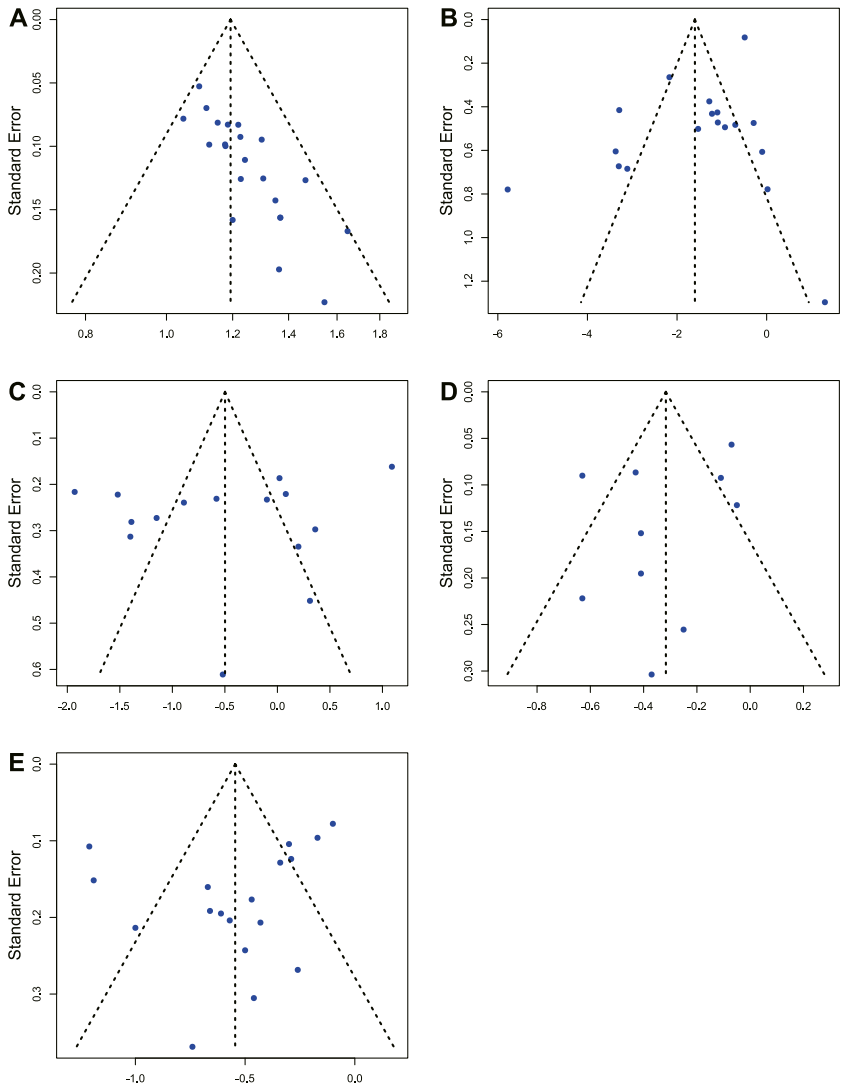

Fig. 8. Funnel plots for the detection of publication bias. Panel A: response to treatment; Panel B: luteinizing hormone; Panel C: follicle-stimulating hormone; Panel D: LH:FSH ratio; Panel E: testosterone.

response to treatment; p = 0.016 for LH). No significant publication bias was found for FSH, the LH:FSH ratio, or testosterone.

3.10. TSA

In the TSA (Fig. 9), the Z-curve of the response to treatment, pregnancy rate, ovulation rate, LH, LH:FSH ratio, testosterone, prolactin, BMI, and acne score crossed both the TSA and RIS thresholds, confirming the significant between-group differences in these outcomes. The Z-curves of ovarian volume, FSH, and hirsutism score crossed the TSA threshold but not the RIS threshold or did not cross the TSA threshold, indicating the need for further RCTs to support the conclusion of statistical significance.

3.11. Quality of evidence

Based on the GRADE assessments (Table S7 in the Supplementary file), the results of the pregnancy rate, ovulation rate, acne score,

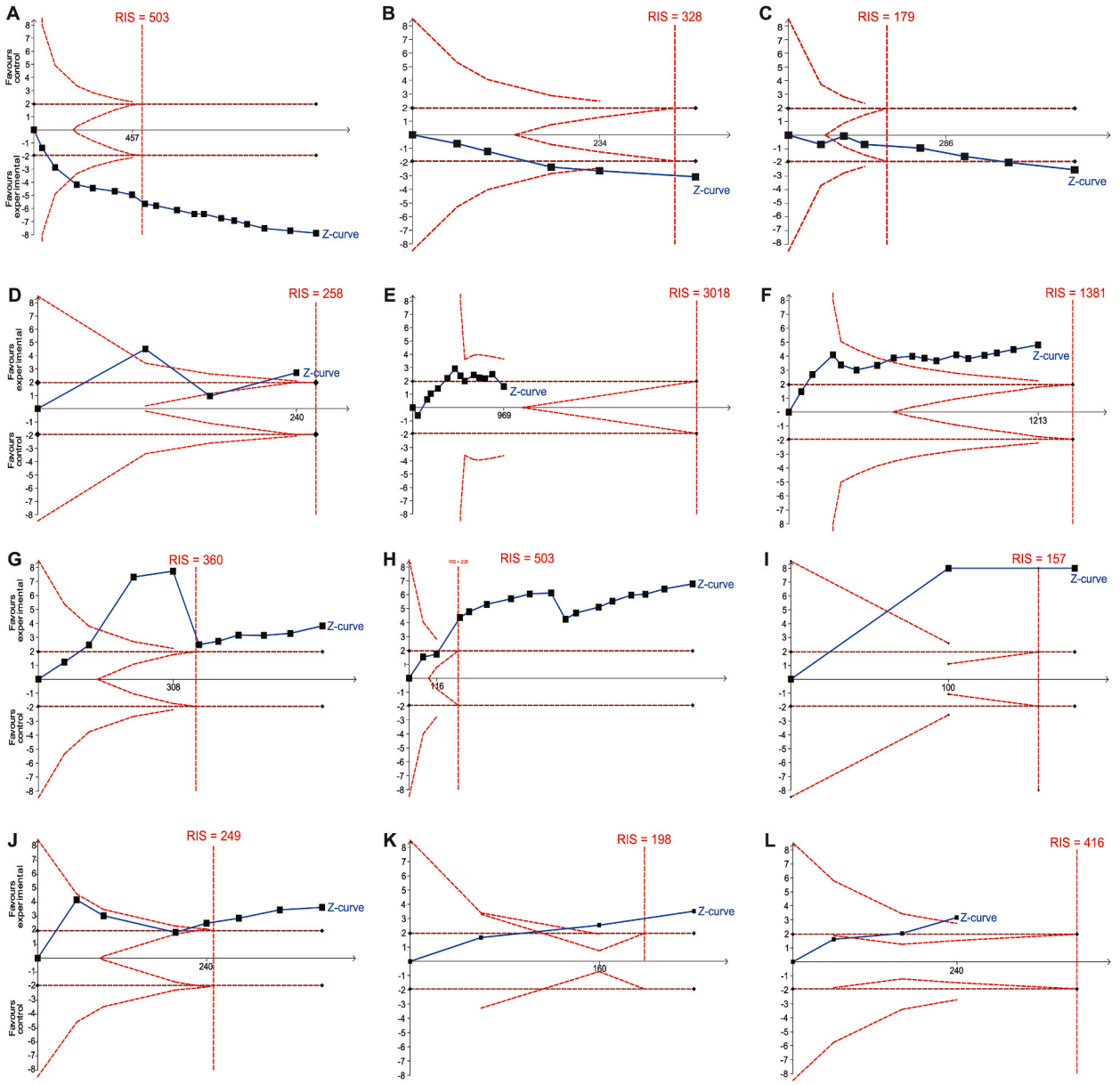

Fig. 9. Results of trial sequential analyses. Panel A: response to treatment; Panel B: pregnancy rate; Panel C: ovulation rate; Panel D: ovarian volume; Panel E: follicle-stimulating hormone; Panel F: luteinizing hormone; Panel G: LH:FSH ratio; Panel H: testosterone; Panel I: prolactin; Panel J: body mass index; Panel K: acne score; Panel L: hirsutism score.

and hirsutism score only had limitations on the risk of bias and were rated as moderate-quality evidence. The results of five outcomes were of low quality of evidence, including the response to treatment, LH:FSH ratio, testosterone, prolactin, and BMI. The quality of evidence for three outcomes (ovarian volume, LH, and FSH) was determined to be very low due to multiple limitations.

3.12. Safety

Thirteen RCTs [22,26–28,31,33–35,38–41,43] reported safety outcomes, of which five [20,25,26,31,43] reported adverse events (AEs). The overall AE rate was 8.3 % in the experimental group and 15.8 % in the control group, with a significant between-group difference ($p = 0.043$). No correlation between AEs and Cangfu Daotan decoction was reported in the experimental group (see Table S8 in the Supplementary file for details).

4. Discussion

PCOS is a common and complex reproductive endocrine disorder in women of reproductive age, with diverse clinical manifestations and underlying pathophysiology. Despite global efforts, the treatment of PCOS remains a challenge [44]. This meta-analysis of 23 RCTs showed that Cangfu Daotan decoction combined with Diane-35 resulted in a better clinical response and greater pregnancy, ovulation, and live birth rates than monotherapy with Diane-35 for the treatment of PCOS. This combination therapy also had significant efficacy for reducing ovarian volume, sex hormone levels (LH, LH:FSH ratio, testosterone, and prolactin), BMI, and the severity of acne and hirsutism but had no obvious effects on FSH levels.

The main finding of our systematic review is that Cangfu Daotan decoction can increase the response rate to anti-PCOS treatment, indicating a comprehensive improvement in sex hormone levels, clinical symptoms, and ovarian shape and function, which is associated with improved pregnancy outcomes. The exact mechanism underlying the efficacy of Cangfu Daotan decoction in treating PCOS remains unclear. Rat model experiments have suggested a few possibilities. First, Cangfu Daotan decoction may inhibit TLR-4/NF-κB signaling by downregulating HMGB1, reducing the release of inflammatory factors such as interleukin-6, tumor necrosis factor-α, and C-reactive protein and increasing the expression of OATP2B1 and OATP3A1 in ovarian and uterine tissues, which in turn decreases sex hormone levels and improves pregnancy outcomes [15]. Second, a study has shown that TCM phlegm dampness syndrome and abnormal lipid metabolism are improved after administering Cangfu Daotan decoction, providing sufficient energy for the biological function of oocytes and increasing their developmental potential [45]. This study also revealed the mechanism by which Cangfu Daotan decoction improves pregnancy outcomes from the perspectives of inflammatory factor release, OATP gene expression, and oocyte development [45]. However, whether other important mechanisms, such as the MAPK/ERK and TLR4/NF-κB p65 signaling pathways, are involved remains to be explored.

PCOS is always accompanied by reproductive endocrine disorders, characterized mainly by disturbed sex hormones, anovulation, or rare ovulation. Therefore, the key treatment goals are to adjust hormones and induce ovulation. Our results showed that Cangfu Daotan decoction, as an adjuvant therapy, significantly improved PCOS at the level of hormone secretion, including reducing LH, LH/FSH, and testosterone levels, and simultaneously alleviating hirsutism and acne signs caused by hyperandrogenism. The sex hormone adjustment effect induced by Cangfu Daotan decoction can also help address the psychological problems caused by patients' self-abasement about their appearance by improving hyperandrogenism signs. A rat study showed that Cangfu Daotan decoction can increase the expression of OATP4a1, a protein closely related to the molecular biological level of phlegm-dampness transport, in the endometria and ovaries of obese PCOS rats, thus reducing the levels of abnormally elevated sex hormones [46]. This study provides evidence to support our results at the molecular level. The CYP17 gene is involved in the development of hyperandrogenism in PCOS patients; it encodes the P450-17α enzyme and 17,20-lyase of cytochrome and is a key enzyme for androgen synthesis. It has been demonstrated that lowering the expression of the CYP17 gene in the follicular theca cells of PCOS patients in vitro can inhibit the activity of the P450-17α enzyme and 17,20-lyase, resulting in a decrease in the secretion of testosterone [47]. A rat experiment showed that Cangfu Daotan decoction can downregulate the expression of the CYP17 gene and lower the level of androgen, suggesting another mechanism underlying its effects on hyperandrogenism [48].

Our study showed that Cangfu Daotan decoction had no significant effect on FSH levels. It is generally believed that FSH levels in PCOS patients remain unchanged or decrease, while LH levels increase, ultimately resulting in an elevated LH/FSH ratio, which is an important diagnostic marker and efficacy indicator for PCOS [49]. Research has shown that when insulin resistance is improved, FSH levels in patients with PCOS may increase [50]. However, our study showed that both groups experienced a small, comparable decrease in FSH levels after treatment, which may not have clinical significance, possibly due to the background treatment of Diane-35 [51]. Due to significant heterogeneity and imprecision, the meta-analysis results for FSH were rated as very low-quality evidence, indicating the need for further research to verify the impact of Cangfu Daotan decoction on FSH.

In accordance with the guidelines for the management of overweight women with PCOS in the UK, the BMI should be reduced to less than 30 kg/m^2 prior to initiating ovarian stimulant therapy [52]. It has been reported that a 5–10 % decrease in weight in PCOS patients can lead to a 30 % reduction in central fat, which is associated with improved insulin sensitivity and ovulation function [53]. Our results indicated that Cangfu Daotan decoction induced an additional reduction in BMI in the treatment of PCOS. In a rat experiment, Cangfu Daotan decoction improved the levels of endocrine hormones, glucose and lipid metabolism, and insulin resistance in obese PCOS rats via the NF-κB signaling pathway [54] and reduced body mass by increasing the activity of the insulin signaling pathway PI3K/PKB/mTOR [55]. Molecular evidence thus supports the weight loss effect of Cangfu Daotan decoction. These findings suggest that Cangfu Daotan decoction may be a novel option for meeting weight loss requirements in obese patients with PCOS and in obese individuals in general.

A previous systematic review evaluated the effects of Cangfu Daotan decoction on PCOS. However, this review included only 14 studies and was limited in scope. This study also has serious methodological limitations. For example, the background treatment in the review was uncertain, with only "Western medicine" mentioned, and studies with an add-on comparison and studies with an active comparison medicine were combined by meta-analysis, which resulted in serious clinical heterogeneity in the results. Second, an incorrect sensitivity analysis was conducted, unreasonably excluding certain studies to reduce heterogeneity. Third, standardized mean differences were used as the effect measure for continuous outcomes, where units among primary studies can be unified, which cannot intuitively show actual effects. Fourth, only one factor was subjected to subgroup analysis, and significant subgroup differences were not correctly determined based on the interaction p value. Fifth, due to the limited number of included studies, publication bias detection was conducted for only one outcome. These limitations substantially reduce the reliability of effect estimates and affect the quality of evidence. In contrast, our systematic review specifically focused on assessing the effects of Cangfu Daotan decoction as an adjuvant therapy for the first-line drug Dian-35 in PCOS patients, substantially enhancing the degree of clinical homogeneity between the included studies and facilitating precise medication recommendations. Even though the inclusion criteria were narrowed, we still increased the number of included studies to 25. Additionally, we substantially expanded the evaluation contents, including adding important outcomes for PCOS (treatment response rate, ovarian volume, LH/FSH ratio, prolactin, hirsutism score, and acne score), conducting risk of bias assessment based on RoB 2, assessing multiplicity adjustment of statistical significance based on TSA, exploring the source of heterogeneity through prespecified and post hoc subgroup analysis, and detecting publication bias for multiple important outcomes. These rigorous methodologies allowed us to make objective and standardized assessments. Finally, we summarized all the assessment results to appraise the quality of evidence of each meta-analysis result via the GRADE approach, allowing clinical physicians and guideline developers to use the evidence more accurately and effectively.

Nevertheless, our study has several limitations. First, the risk of bias of the included RCTs was moderate to high, mainly due to the lack of reporting of the allocation concealment and blinding methods. This is the primary factor influencing the final quality of evidence. Second, there was significant heterogeneity in the meta-analysis of some outcomes, particularly sex hormones. Although we partially explained the source of heterogeneity through subgroup analyses of age, duration of disease, and sample size, there were still some suspicious effect modifiers for which we lacked sufficient data to conduct subgroup analyses, such as components and dosages of Cangfu Daotan decoction (due to too many subgroup values that could lead to type I errors) and course of treatment (due to the lack of RCTs with a treatment course of more than three menstrual cycles). Further evidence is needed to optimize treatment strategies based on these subgroup factors, such as the best components, dosages, and treatment course of Cangfu Daotan decoction. Third, the number of studies on certain outcomes was insufficient to detect publication bias.

5. Conclusions

The current RCT evidence suggests that Cangfu Daotan decoction, when used as an adjuvant therapy to Diane-35, can reduce sex hormone levels (except for FSH) and BMI, relieve symptoms of hyperandrogenism, and improve pregnancy outcomes while being safe. However, the overall quality of evidence was reduced by a risk of selection bias. Future RCTs should focus on improving the reporting of allocation concealment and blinding methods to enhance validity.

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Data availability statement

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

CRediT authorship contribution statement

Xianjie Feng: Writing – original draft, Investigation, Formal analysis, Data curation. **Shaomin Cheng:** Writing – review & editing, Supervision, Methodology. **Sheng Xu:** Writing – review & editing, Investigation, Formal analysis, Data curation. **Xin Chen:** Writing –

review & editing, Supervision, Methodology, Funding acquisition, Conceptualization. **Xu Zhou:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no conflicts of interest.

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None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e36959.

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