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The Efficacy of Guizhi Fuling Capsule or Kuntai Capsule Combined With Diane-35 and Metformin in Polycystic Ovary Syndrome: A Systematic Review and Meta-Analysis

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Abstract: Background: Polycystic ovary syndrome (PCOS) is one of the most common reproductive endocrine metabolic diseases. Combined use of metformin and diane-35 has better curative effect in regulating serum hormone level (LH, FSH, T and E2) than using metformin alone. Traditional Chinese medicine (TCM) can also be used to treat PCOS. According to some studies, the combined use of metformin and diane-35 and TCM have achieved better curative effect than combining metformin and diane-35 in the treatment of patients with PCOS. **Methods:** Computerized searches of the science, Medline, VIP, Wan Fang and China HowNet (CNKI) databases were conducted to identify eligible randomized controlled trials (RCTs) from the data obtained up to March 1, 2022. The Cochrane Collaboration risk of bias tool was used to assess the risk of bias in individual RCTs, and R software(version 4.0.3) was used for data statistical analysis. **Results:** Nine RCTs involving 1035 patients were included. Comparing to D+M, significant reduce of LH(mean difference [MD]: −1.93, 95% confidence interval [CI]: -3.44, -0.42;Unit:U/L P ＜ 0.01; I2=89%)、T(MD: -1.44, 95%CI -2.59, -0.30;Unit:nmol/L P ＜ 0.01; I2=98%) and significant increase of E2(MD: 31.43, 95%CI 24.54, 38.33;Unit:pmol/L P ＜ 0.01; I2=96%) were shown in TCM+D+M. Comparing to D+M, TCM+D+M group has higher ovulation rate(RR 1.14 95%CI 1.07,1.22; P=0.42; I2=0%) and higher pregnancy rate(RR 1.29 95%CI 1.15,1.44; P=0.37; I2=7%). There is no significant difference between the two therapies in FSH changes (MD: −1.00, 95%CI -2.27, 0.28;Unit:U/L P ＜ 0.01; I2=95%).Subgroup analysis showed that compared with the Guizhi Fuling capsule group, the Kuntai capsule group had more FSH reduction and E2 increase more. In other outcome indicators, the two subgroup did not show significant differences.**Conclusion:** Kuntai Capsule + Diane-35 + Metformin is better than Guizhi Fuling Capsule in reducing FSH, and it is also better in increasing E2. There was no significant difference between the two in LH and T hormones. There was no significant difference between Kuntai Capsules + Diane-35 + Metformin and Guizhi Fuling Capsules + Diane-35 + Metformin. As for the effect in lessen insulin resistance, Kuntai Capsule+Diane-35+Metformin was significantly better than Guizhi Fuling Capsules+Diane-35+Metformin.

Keywords: PCOS; Infertility; Guizhi Fuling Capsule; Kuntai Capsule; Diane-35; Metformin

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1.Introduction

Polycystic ovary syndrome (PCOS) is one of the most common reproductive endocrine metabolic diseases, with a range of clinical manifestations such as oligo-anovulation, hyperandrogenism, metabolic abnormalities (insulin resistance and impaired fasting glucose levels), infertility and obesity[1-6], affecting up to 20% of women of all ages and 5% to 10% of women of reproductive age[5].Although PCOS don't cause sudden deaths, it will greatly reduce the quality of life of women with the disease, for it can hardly be cured but to improve symptoms.

According to some studies, insulin resistance(IR) occurs in 70% of the patients with PCOS[7-9]. International guidelines for the treatment of polycystic ovary system recommend metformin as the medicine for PCOS patients with IR. Some studies have shown that combined use of metformin and diane-35 has better curative effect in serum hormone level including Luteinizing hormone(LH), Follicle Stimulating Hormone (FSH), Testosterone (T), Estradiol(E2) than using metformin or diane-35 alone[10-12].

In recent years, many studies have concentrated on the treatment of PCOS with traditional Chinese medicine(TCM),for instance, Kuntai capsule and Guizhi Fuling capsule have been confirmed effective for reducing the serum FSH and TSH level and ameliorating insulin resistance situation with little toxic side effects[13-14].Moreover, the RCT studies of Ming Luo[15],Haiyan wang et,al[16] and Xiu Li state that the combine use of Chinese and western medicine shows a better improvement of the PCOS patients in serum hormone level(LH,FSH,T or androgen) or conditions of ovulation and pregnancy than using the western medicine alone.

However, there are few systemic reviews and meta-analysis on the effect of combine use of TCM and western medicine on the treatment of PCOS. Qian-wen Ma et,al[17]conducted a meta-analysis to conclude co-treatment with TCM and letrozole was more effective than letrozole monotherapy in the treatment of PCOS, but they didn't concentrate on certain kinds of TCM, so the conclusion can be difficult to put into clinical application, for as is well known, the prescription of some TCM can be variable and individual specific[18].

Chinese patent medicine such as Kuntai capsule[19]and Guizhi Fuling capsule[14]have fixed formulations and recommended dosage, that is to say, the extensive clinical application and promotion of them can have realistic significance. However, up to date, no study has compared the effects of combining use of Kuntai capsule or Guizhi Fuling capsule and western medicine with using western medicine alone.

2.Objectives

The primary aim of this study was therefore to undertake a comprehensive systematic review and meta-analysis comparing the effect of Guizhi Fuling capsule/ Kuntai capsule + metformin + Diane-35 with metformin + Diane-35 in PCOS on a range of indexes including serum FSH, LT, E2, T levels and reproductive parameters including ovulation rate and pregnancy rate. We also conduct subgroup analyses to provide evidences for the choice of Guizhi Fuling capsule and Kuntai capsule as the TCM in the combine medication.

3.Materials and Methods

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement to conduct our systematic review. The full review protocol was registered with PROSPERO under registration number CRD 42021281360.

3.1 Study eligibility criteria

The PICO (population, intervention, comparison, outcome) framework was used to establish a priori selection criteria and included all RCTs comparing (i) Guizhi Fuling capsule + metformin + Diane-35 versus metformin + Diane-35, (ii) Kuntai capsule + metformin + Diane-35 versus metformin + Diane-35 for women of any age with PCOS.

Exclusion criteria:(i) the participants of the study were presence of other etiologies for hyperandrogenism or infertility, such as hypothyroidism, congenital adrenal hyperplasia and Cushing's syndrome, or concurrent medication use (e.g. OCPs, orlistat, clomiphene citrate, etc.) even if the same between groups;(ii)the study did not include the outcome measures we will

be studying; (iii)abstract data from conference and scarce literature; (iv) the quality evaluation of the study shows very poor quality.

Primary outcomes included metabolic parameters including serum hormone levels: Luteinizing hormone(LH), Follicle Stimulating Hormone (FSH), Testosterone (T), Estradiol(E2); and Secondary outcomes included reproductive parameters including ovulation rate and pregnancy rate.

3.2 Literature search methodology

English literature was searched in PubMed, web of science and Medline, and the literature in Chinese was searched in VIP, Wan Fang and China HowNet (CNKI) databases. There were no limits on year of publication. Language limit is Chinese and English.

The retrieval condition is as follows: “Chinese medicine”, “Chinese herbal medicine” “traditional Chinese and western medicine”, “Fuling Guizhi capsule/pill”, “Guizhi Fuling capsule/pill”, “Kuntai capsule/pill”, “metformin”, “Diane-35”, “Ethinylestradiol cyproterone”, and “Polysystic ovary syndrome”, “PCOS” were searched in title, key words or abstract.

3.3 Study selection

In compliance with the inclusion criteria, we primarily screened the titles and abstracts, then retrieved the full texts of all potentially eligible studies. Two review authors independently examined and selected the eligible articles according to the inclusion criteria for the current review. Disagreement with respect to study eligibility was resolved via discussion with the third reviewer author.

3.4 Data extraction

Two review authors independently extracted the data from each eligible study. Any disagreements were resolved by discussion with a third review author. Data retrieved the basic characteristics of included study including sample size, mean age, interventions and duration time, as well as outcome measures. Authors were contacted for additional or missing information as required.

3.5 Risk of bias

The risk of bias of the included studies was assessed independently by two authors using the Cochrane Collaboration’s tool for assessing risk of bias with respect to the following aspects: random sequence generation, allocation concealment, blinding of participants or personnel, blinding of outcome assessment, reporting bias, loss to follow up, other sources of bias. Any discrepancies were resolved via discussion with the third review author to reach a consensus.

3.6 Statistical analysis

Statistical processing was done using the statistical software package R (http://www.R-project.org/). The results were reported as mean difference (MD) with 95% CI for continuous outcomes of serum FSH, LT, E2, T levels and odds ratios (OR) with 95% confidence interval (95% CI) for dichotomous outcomes of ovulation rate and pregnancy rate. Subgroup analyses were performed based on the kind of TCM used in the integrated Chinese and Western medicine group. Publication bias was estimated by Egger’s test[20] in addition to funnel plot.

Heterogeneity between studies was examined using the I-square (I^2) index to quantify the degree of heterogeneity. If the test results present high heterogeneity ($I^2 \geq 50\%$), meta-analysis is performed using a random effect model; if the experimental results present low-moderate heterogeneity ($I^2 < 50\%$), meta-analysis is performed using a fixed effect model[21].

4.Results

4.1 Study Selection and Characteristics

In the presence of heterogeneity, the two researchers checked the data entered and explored the variation by conducting sensitivity analysis. In the initial search, 370 relevant articles were identified, of which 130 articles were from CNKI, 92 articles from VIP, 139 articles from Wan Fang,2 articles were from pubmed, 2 articles from medline, and 5 articles from web of science. After the exclusion of 197 duplicate articles using EndNote X9 software, 173 articles underwent a title and abstract review. A total of 156 studies were excluded in this process, of which 12 articles are review studies,6 articles are animal research, the intervention methods of 138 articles did not meet the inclusion criteria. For the remaining 17 articles, the full text was reviewed and 8 of them were excluded for following reasons: the dosage form is decotion but not pill or

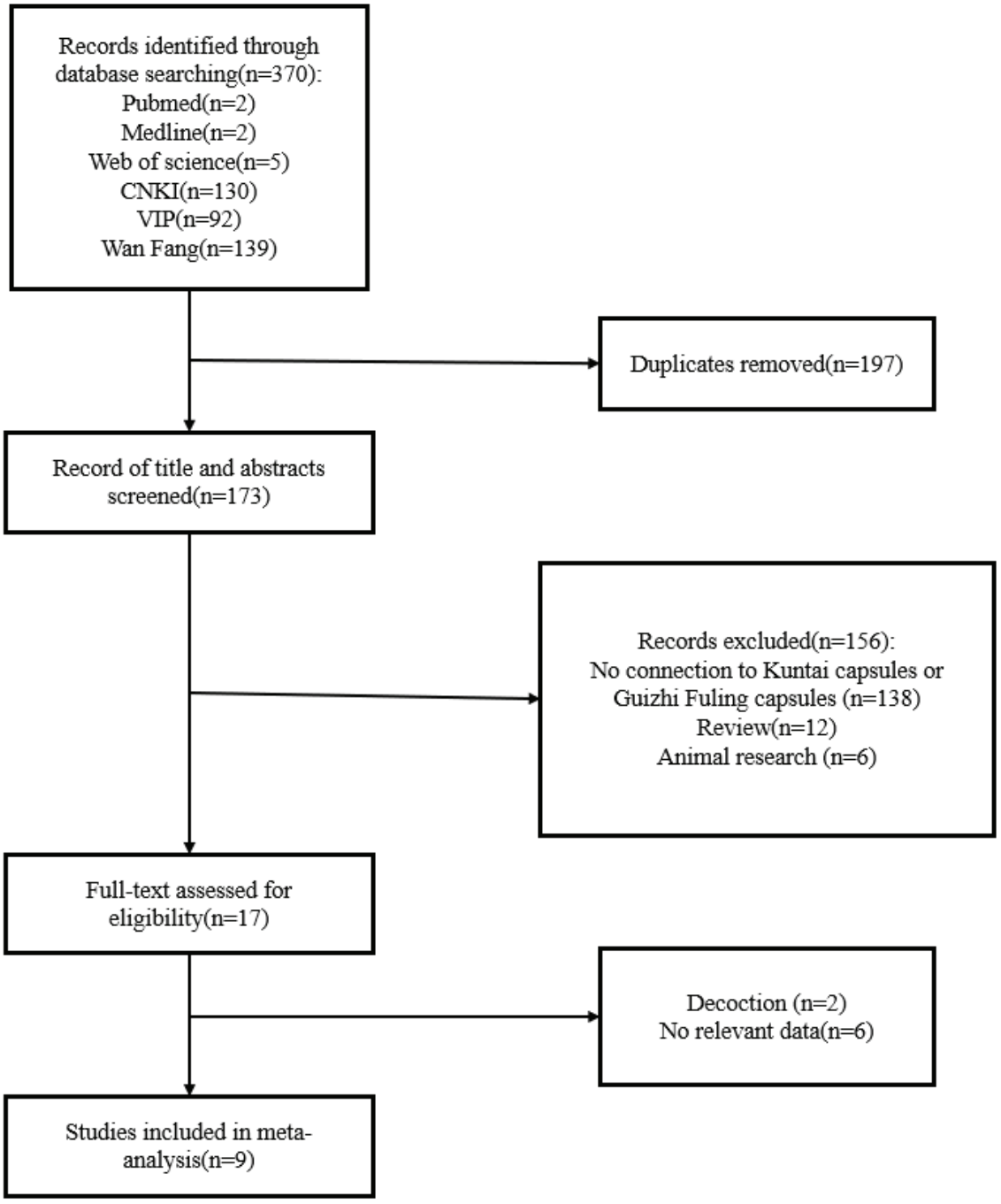
capsule(n= 2), which means that the other herbs may be added to the potion; article does not report the data required for this study (n= 6). The nine remaining studies fulfilled the eligibility criteria and were included in the meta-analysis[13,15-16,22-27]. The literature review and identification process are shown in Figure 1. The meta-analysis evaluated the efficacy of two Chinese medicine preparations combined with Diane-35 and Metformin versus Diane-35 and Metformin for a total of 1035 patients with PCOS across nine clinical studies[13,15-16,22-27]. Baseline clinical characteristics of these patients are summarized in Table 1.

Table 1 The characteristics from the eligible studies

Study	Sample size		Mean age(years)		Therapeutic method		Outcome	Duration
	Experimental	Control	Experimental	Control	Experimental	Control		
Xiu Li, 2020	40	40	31.17±6.65	30.29±5.31	Diane-35+Metformin+Cassia twig tuckahoe capsule	Diane-35+Metformin	serum sex hormone levels(LH, FSH, E2, T); adverse reaction(transaminase,myocardial enzyme, creatinine, bone density); recrudesce	63 days
Liyun ZHANG, 2016	55	55	30. 8±6.9	29. 8±6.6	Diane-35+Metformin+Cassia twig tuckahoe pill	Diane-35+Metformin	serum sex hormone levels(LH, FSH, E2, T, Fins, FBG, TC, TG, HDL-C, LDL-C,); HOMA-IR; ISI; BMI; WHR; acne	Three menstrual cycles
Ying TIAN, 2017	54	53	29.8±4.5	29.3±4.1	Diane-35+Metformin+Cassia twig tuckahoe capsule	Diane-35+Metformin	serum sex hormone levels(LH, FSH, E2, T), HOMA-IR; HOMA-β, BMI; WHR; polytrichia; Ovarian volume; acne	Three menstrual cycles
Ming LUO, 2019	53	53	26.87±1.69	27.04±1.59	Diane-35+Metformin+Kuntai capsule	Diane-35+Metformin	serum sex hormone levels(LH, FSH, E2, T); HOMA-IR; HOMA-β	4 months
Haiyan WANG, 2020	80	80	26.50±1.73	26.19±1.54	Diane-35+Metformin+Kuntai capsule	Diane-39+Metformin	serum sex hormone levels(LH, FSH, E2, T); Ovarian volume; menstrual cycle	63 days
Qionglin LIN, 2016	49	49	26.53±1.46	26.61±1.47	Diane-35+Metformin+Kuntai capsule	Diane-35+Metformin	serum sex hormone levels(LH, FSH, E2, T); HOMA-IR; HOMA-β; Dizziness; headache; nausea; vomiting; skin irritation; breast tender	84 days
Hongmei Xv, 2020	52	52	26.96±1.49	26.80±1.45	Diane-35+Metformin+Kuntai capsule	Diane-35+Metformin	serum sex hormone levels(LH, FSH, E2, T); HOMA-IR; HOMA-β; polytrichia; acne;	Three menstrual cycles
Tongshan HU, 2017	30	30	33.15±5.21	33.19±5.10	Diane-35+Metformin+Kuntai capsule	Diane-35+Metformin	HOMA-β; serum sex hormone(FSH); ovulation rate; pregnancy rate	100 days

Study	Sample size		Mean age(years)		Therapeutic method		Outcome	Duration
	Experimental	Control	Experimental	Control	Experimental	Control		
Yan LIU, 2017	105	105	29.45±9.41	29.23±9.09	Diane-35+Metformin+Kuntai capsule	Diane-35+Metformin	serum sex hormone levels(LH, FSH, E2, T)	4 months

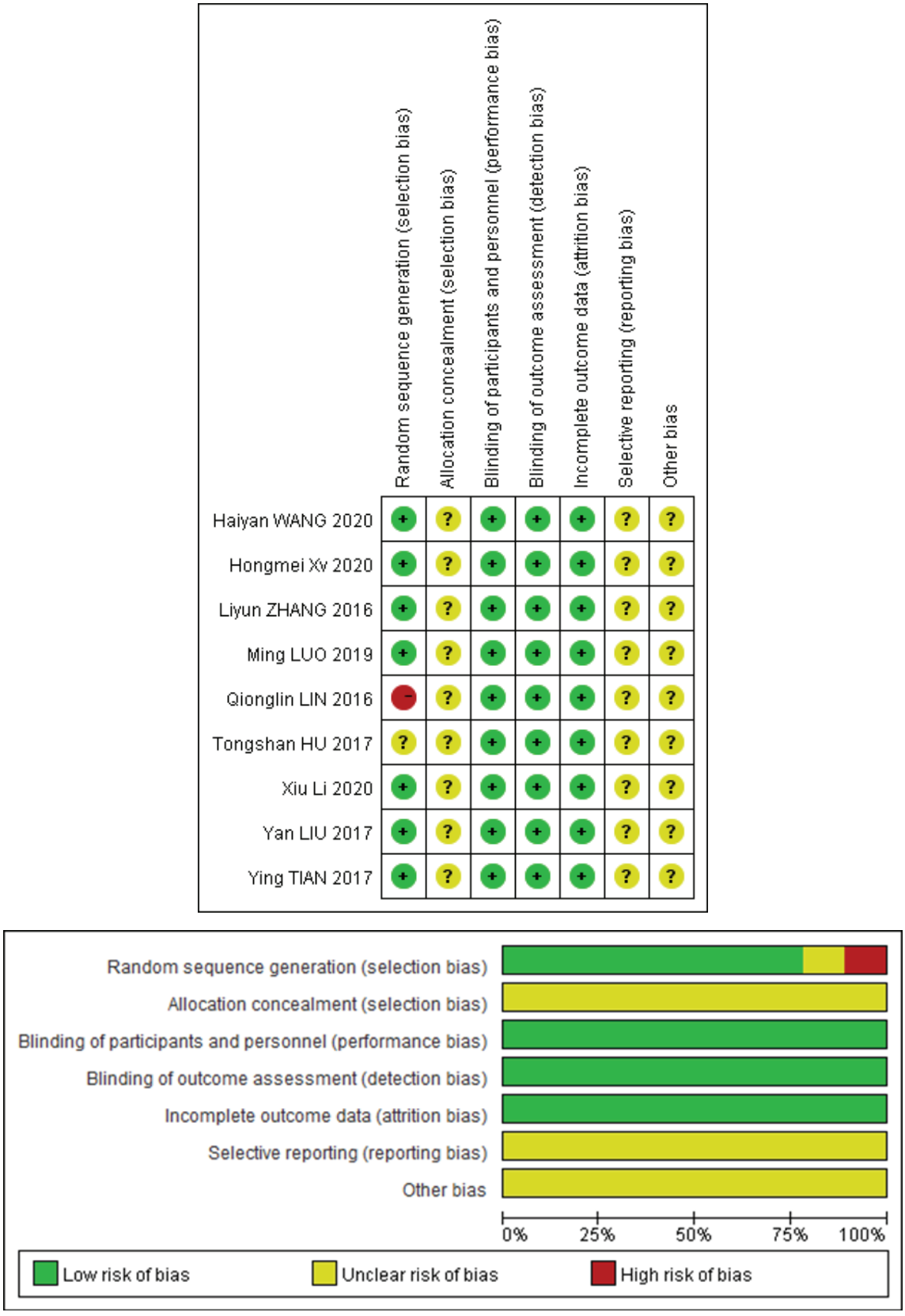
Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of the search process.



4.2 Quality Assessment

Trial quality was assessed using Cochrane risk of bias tool. In the nine studies, only one study were assessed as high risk of bias and no study were assessed as low risk of bias (Figure 2).

Figure 2. Assessment of risk of bias of included RCTs

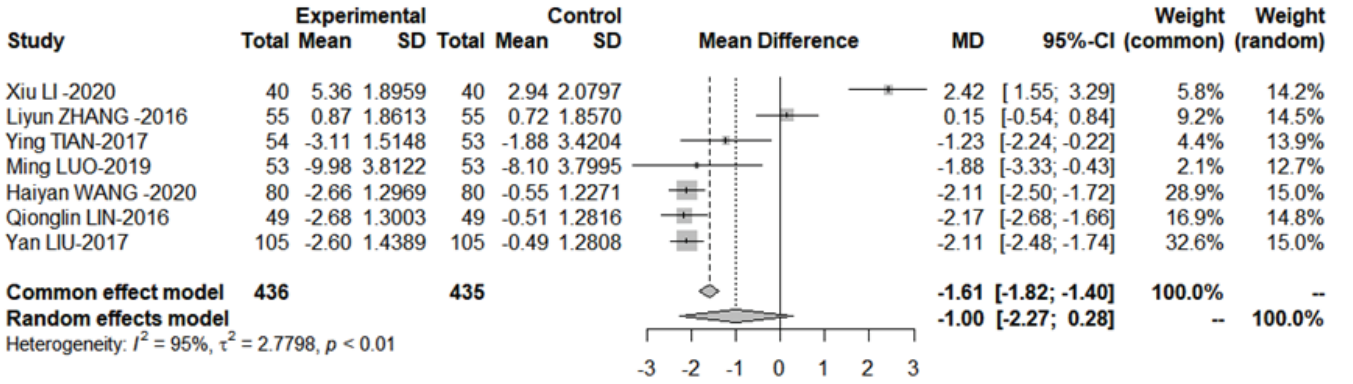


4.3 Anthropometric parameters

4.3.1 Follicle Stimulating Hormone(FSH)

Seven studies reported the change in FSH involving 871 patients. There is no significant difference between the two therapies in FSH changes (MD:−1.00, 95%CI -2.27, 0.28;Unit:U/L; $P < 0.01$; I^2=95%)(Figure 3) .

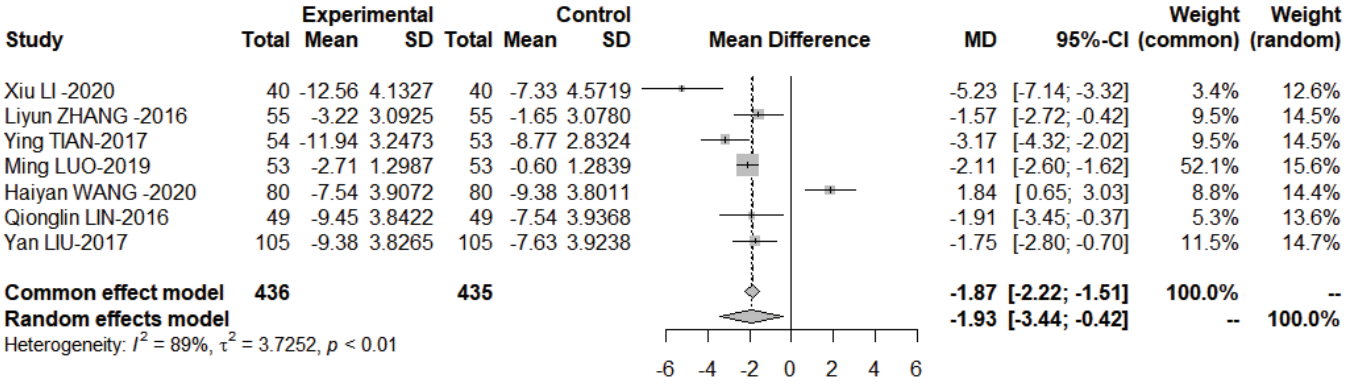
Figure 3 Meta-analysis of TCM +D+M versus D+M for FSH(U/L). CI, confidence interval.



4.3.2 Luteinizing hormone(LH)

Seven studies reported the change in LH involving 871 patients. Comparing to D+M, TCM +D+M significantly reduced LH(MD: −1.93, 95%CI -3.44, -0.42;Unit:U/L;P ＜ 0.01; I^2=89%)(Figure 4) .

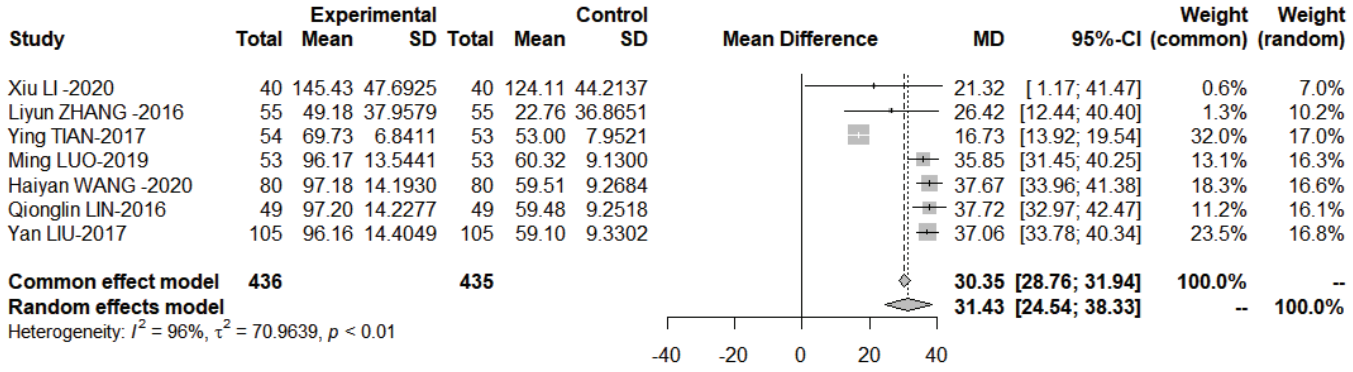
Figure 4 Meta-analysis of TCM+D+M versus D+M for LH(U/L). CI, confidence interval.



4.3.3 Estradiol(E2)

Seven studies reported the change in LH involving 871 patients. Comparing to D+M, TCM+D+M significantly increased E2(MD: 31.43, 95%CI 24.54, 38.33;Unit:pmol/L;P ＜ 0.01; I^2=96%)(Figure 5) .

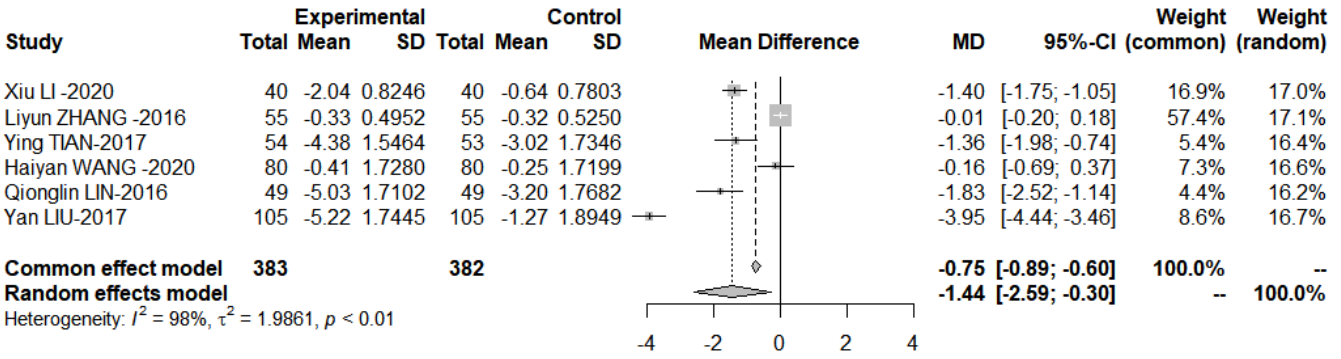
Figure 5 Meta-analysis of TCM +D+M versus D+M for E2(U/L). CI, confidence interval.



4.3.4 Testosterone(T)

Six studies reported the change in T involving 765 patients. Comparing to D+M, TCM +D+M significantly reduced T(MD: -1.44, 95%CI -2.59, -0.30;Unit:nmol/L ;P ＜ 0.01; I^2=98%)(Figure 6) .

Figure 6 Meta-analysis of TCM +D+M versus D+M for T(nmol/L). CI, confidence interval.

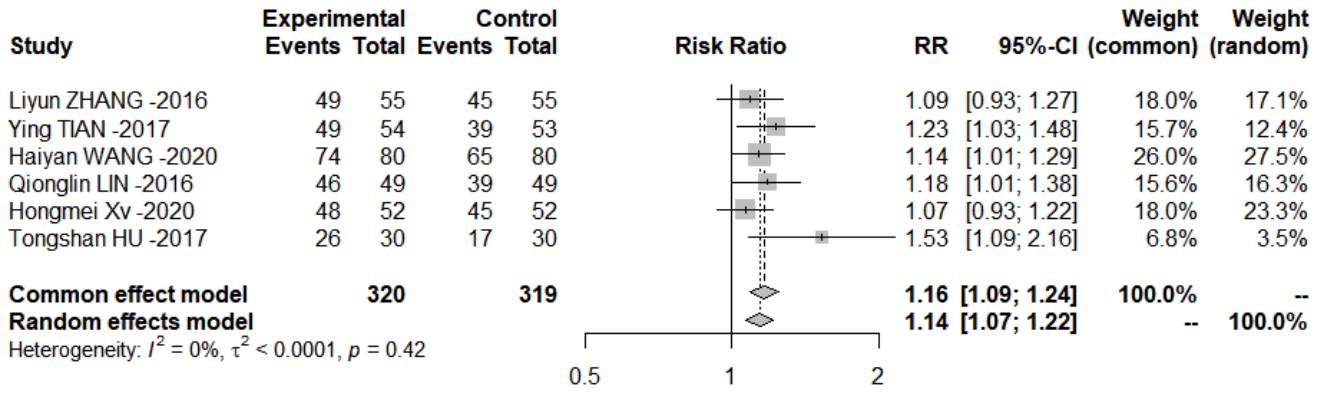


4.4 Clinical outcomes

4.4.1 Ovulation rate

Six studies were included for the meta-analysis of ovulation rate involving 639 PCOS patients. Comparing to D+M, TCM +D+M group has higher ovulation rate(RR:1.14 95%CI 1.07,1.22; P=0.42; I^2=0%)(Figure 7).

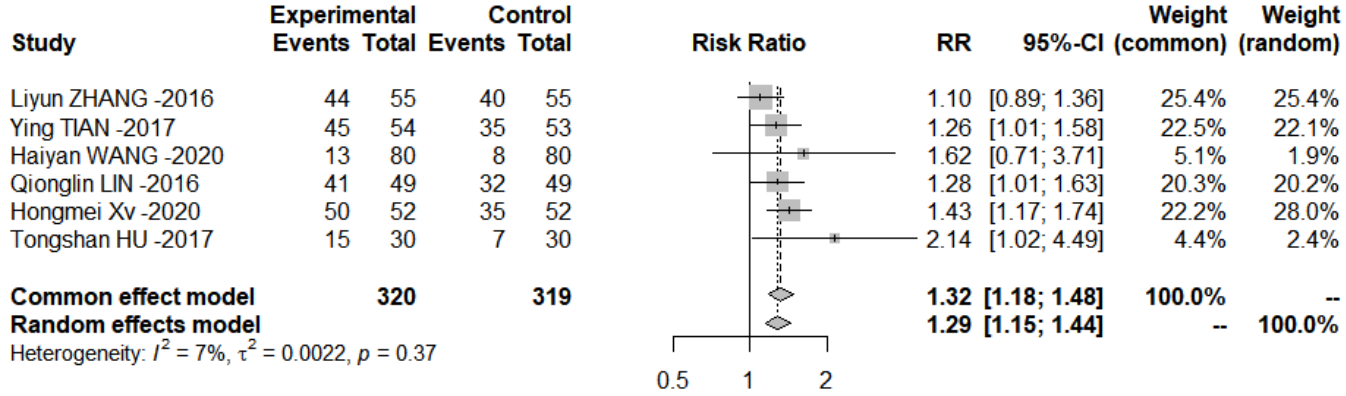
Figure 7 Meta-analysis of TCM+D+M versus D+M for ovulation rate(%). CI, confidence interval.



4.4.2 Pregnancy rate

Six studies were included for the meta-analysis of ovulation rate involving 639 PCOS patients. Comparing to D+M, TCM +D+M group has higher pregnancy rate(RR ： 1.29 95%CI 1.15,1.44;P=0.37; I^2=7%)(Figure 8).

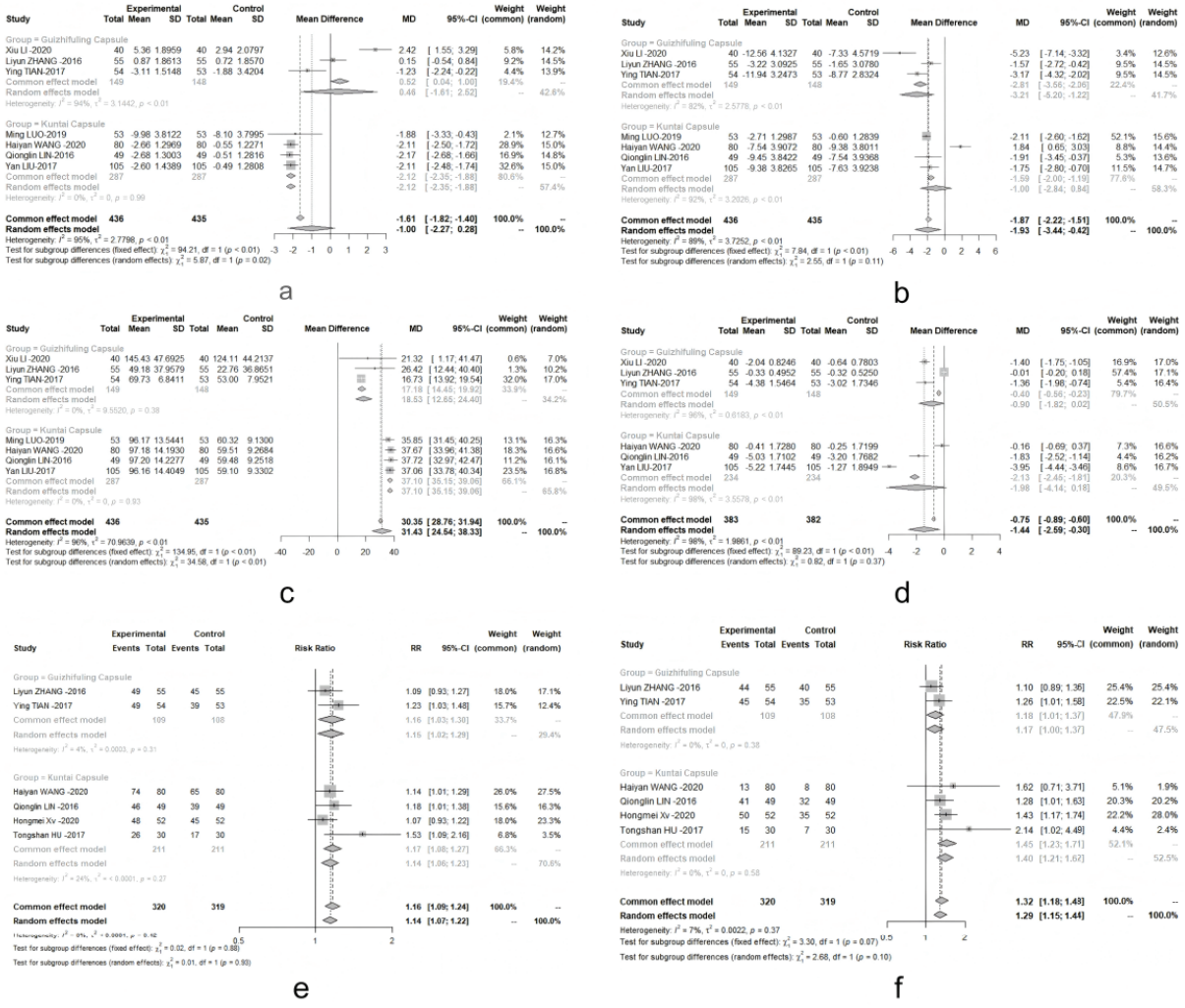
Figure 8 Meta-analysis of TCM+D+M versus D+M for pregnancy rate(%). CI, confidence interval.



4.5 Subgroup analysis

To analyze the difference in efficacy of the two kinds of traditional Chinese medicine (Guizhifuling Capsule and Kuntai Capsule), we conducted subgroup analysis of all outcome indicators(Figure 9). Compared with the Guizhi Fuling capsule group, the Kuntai capsule group had more FSH reduction and E2 increase more, suggesting that Kuntai capsule may have better efficacy than Guizhi Fuling capsule. In other outcome indicators, the two groups did not show significant differences.

Figure 9 Subgroup analysis of G+D+M versus K+D+M for LSH(a), LH(b), E2(c), T(d), ovulation rate(e), and pregnancy rate(f).CI, confidence interval



4.6 Sensitivity Analysis

Because of the high heterogeneity, we evaluated the impact of every study on the pooled results to demonstrate stability and sensitivity (Figure 10-11). The results revealed that the outcomes of FSH and LH were reliable and stable.

Figure 10 Sensitivity analysis of FSH

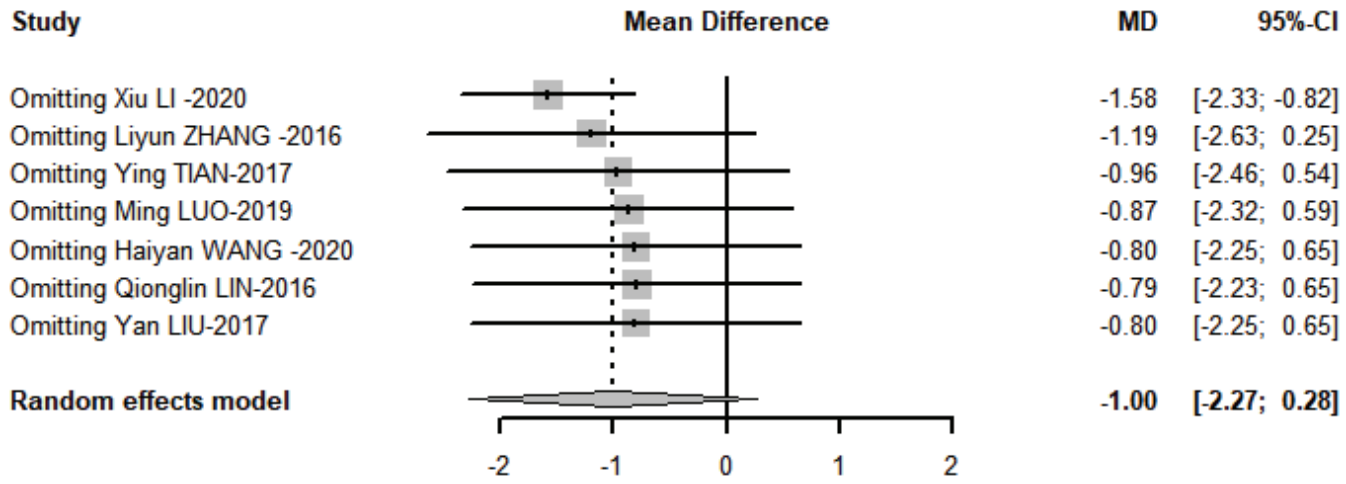
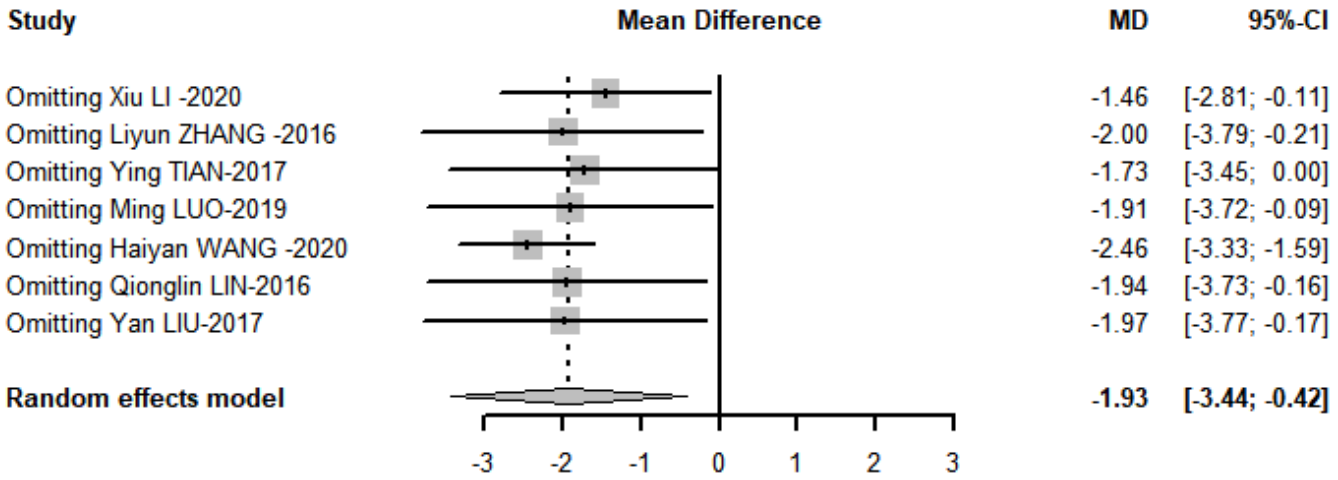


Figure 11 Sensitivity analysis of LH



4.7 Publication Bias

The publication bias of the pooled LH(Egger's test: P = 0.9776), pooled pregnancy rate (Egger's test: P = 0.2543) were examined with funnel plot and Egger's regression tests (Figure 12-15). The results did not reveal evident publication bias in LH and pregnancy rate.

Figure 12 Funnel plot of LH

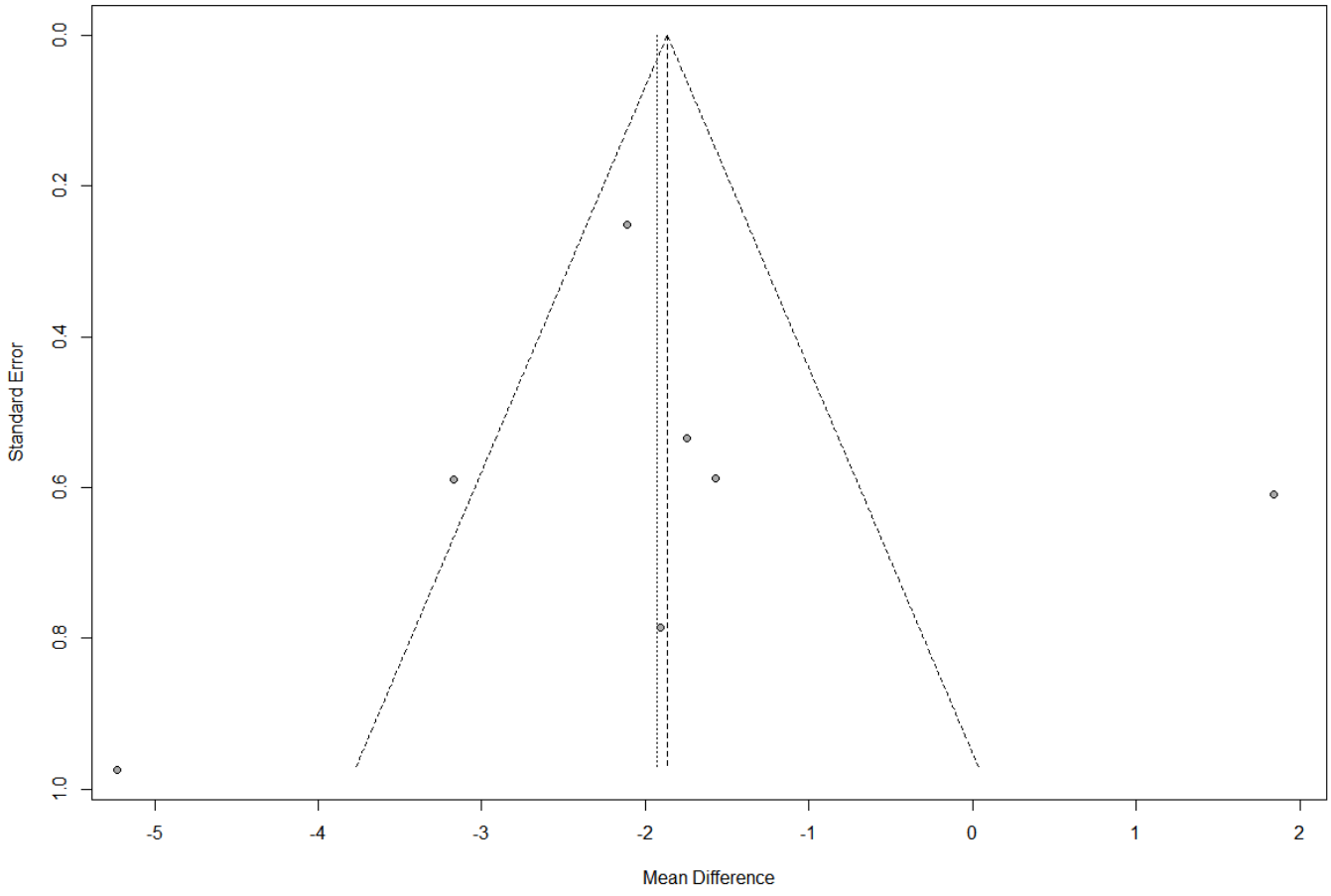


Figure 13 Egger's test of LH

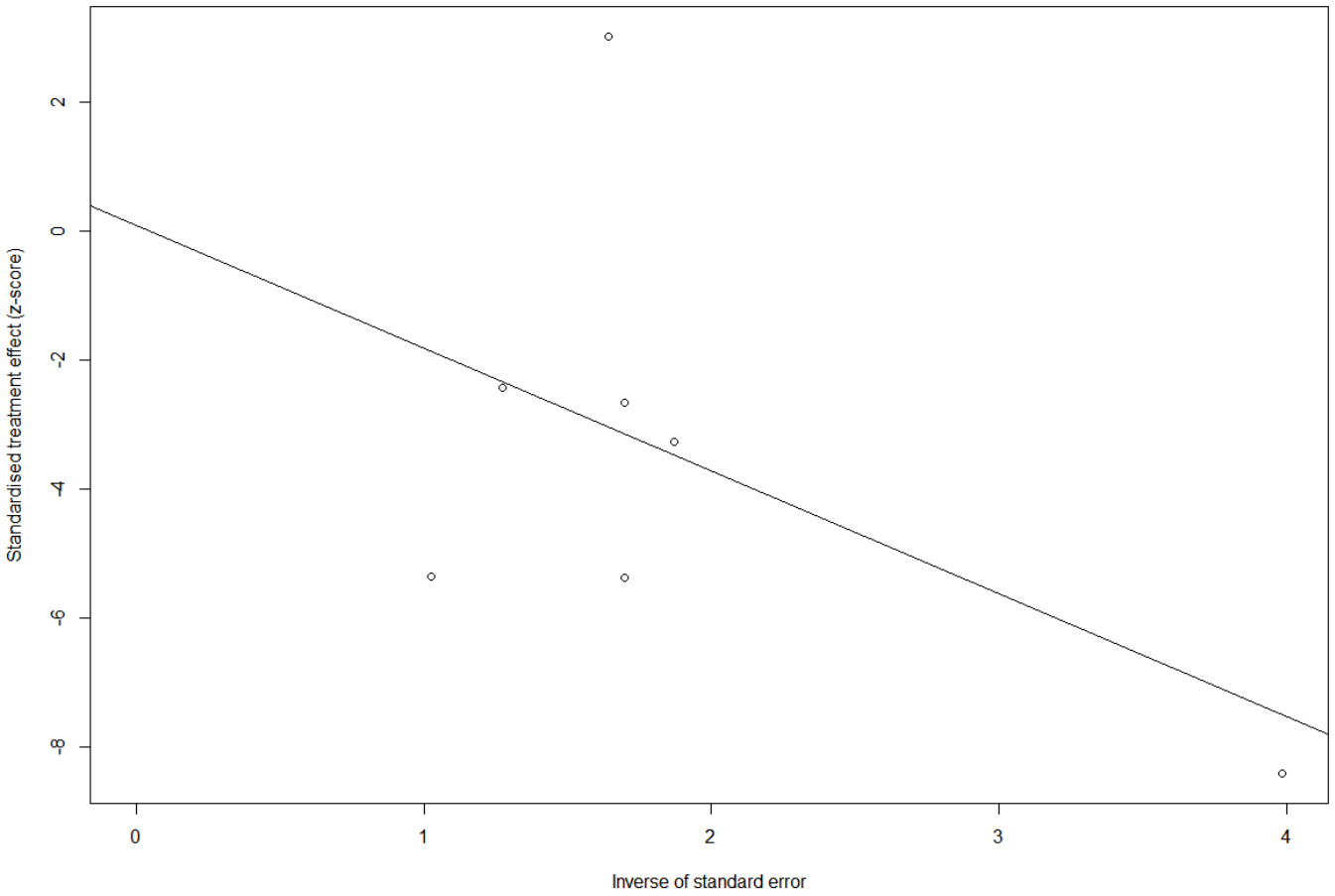


Figure 14 Funnel plot of pregancy rate

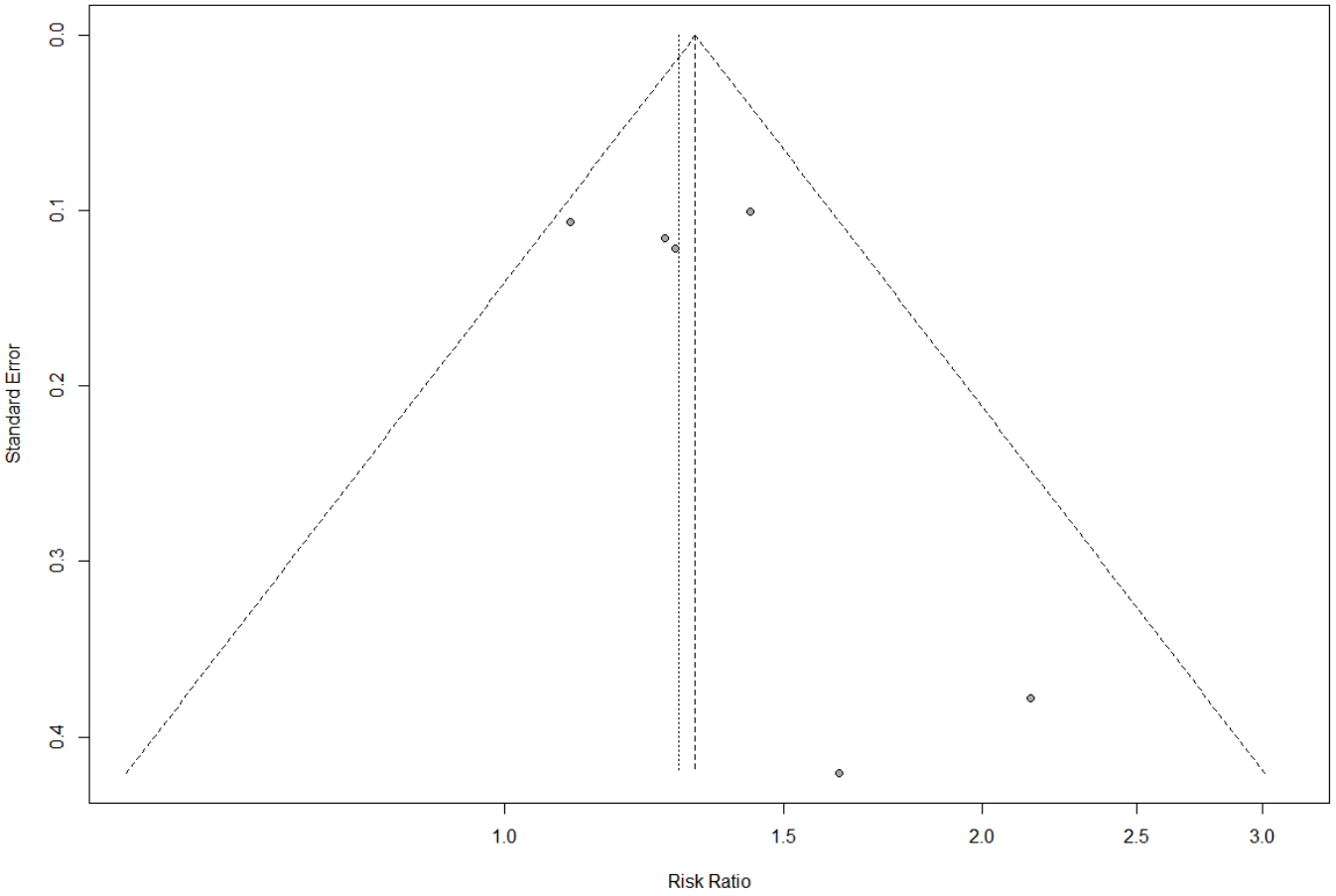
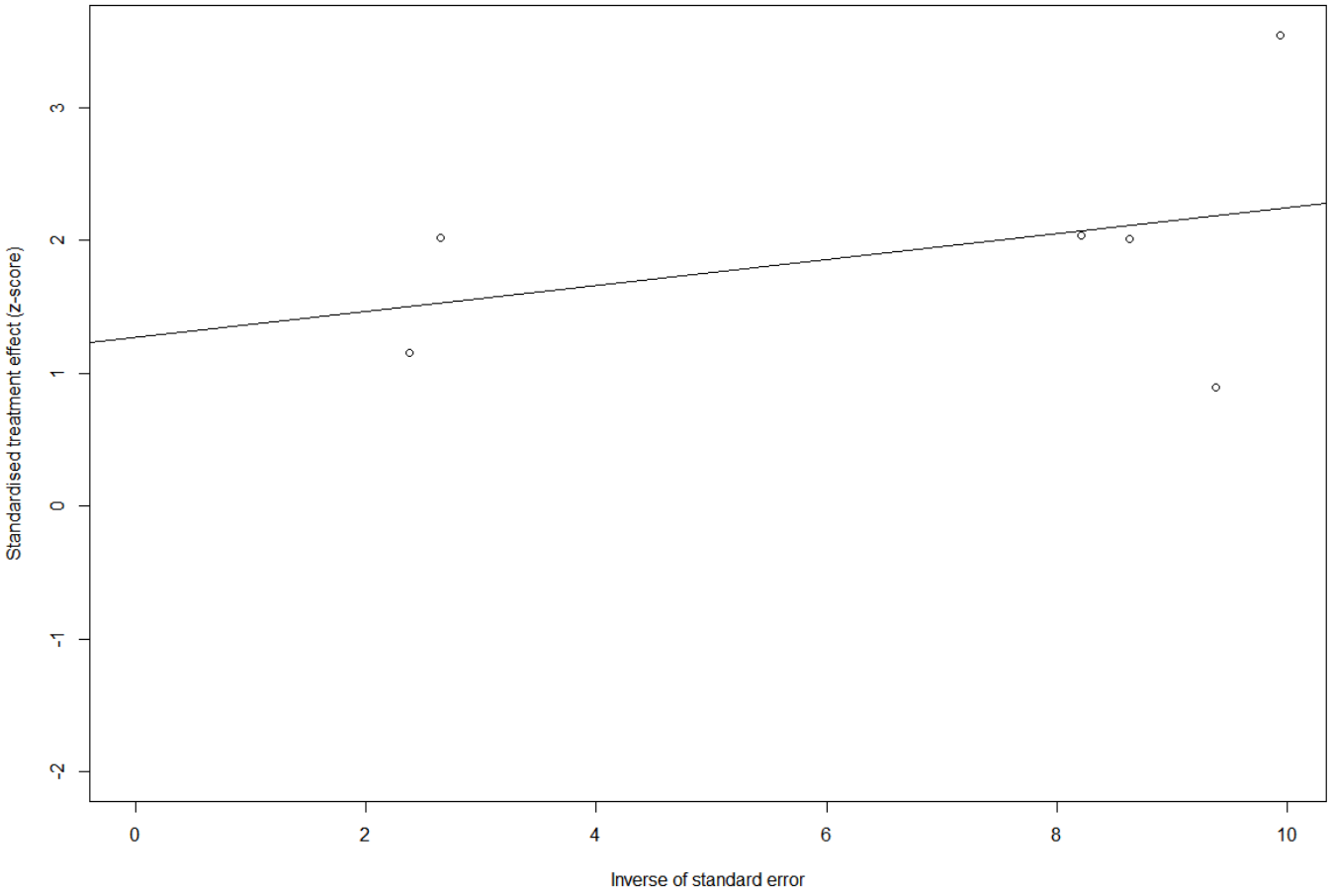


Figure 15 Egger's test of pregancy rate



5.Discussion

Polycystic ovary syndrome(PCOS) is the most common kind of endocrine disorder characterized by chronic anovulation, hyperandrogenism(HA) and insulin resistance(IR) and adversely affects the normal life of 6% to 20% of women in reproductive age globally[28-29].

Some studies found that the excessive androgen lead to the inhibition of hypothalamic feedback ,in other words , the elevated level of LH in serum cannot inhibit the further secretion of gonadotropin-releasing hormone(GnRH),which subsequently lead to the growing amount of LH[30-31]. Excessive LH and low-dose FSH continuously stimulate the ovary, which contributing to the arrest of the growing of the dominant follicle.

However, the exact pathogenesis of PCOS still remains unclear, which result in the treatment strategy of this disease is dominated by symptomatic treatment, including weight control, life-style modification for the mild case and the regulation of menstrual cycle, anti-hyperandrogenemia (HA) therapy, management of insulin resistance(IR)and metabolic disorders for the severe one[32-34]. One of the first line medication, Oral contraceptive pills (OCPs), have long been used to reduce HA level in serum and to regulate menstrual cycles in women with PCOS [35-36].OCPs not only possess the ability to increase the production of sex hormone-binding globulin (SHBG) to reduce serum free testosterone (T) hormone, the precursor of androgen, but also can reduce LH and androgen secretion by inhibiting hypothalamic gonadotropin[37]. Diane-35, ethinyl estradiol (EE) plus cyproterone acetate (CPA), is the representative of OCPs and widely being used in China, Australia and Europe[38].

As a biguanide used for the standard first-line treatment of type-2 diabetes mellitus, Metformin is applied in clinics to handle IR of patients with PCOS, it can enhance insulin sensitivity both in the liver and in the peripheral tissue through inhibiting hepatic glucose production and promoting uptake and utilization, respectively[39-41]. A meta-analysis including 12 RCTs compared the effect of metformin +lifestyle change with placebo +lifestyle change, the result of which indicated that the former demonstrated more admirable effect in lowering BMI (MD: 20.73 kg/m2 , 95% CI: 21.14, 20.32) and decreasing

subcutaneous adipose tissue (MD :292.49 cm2 , 95% CI: 2164.14, 220.84) and increasing the number of menstrual cycles (MD :1.06, 95% CI :0.30, 1.82) than the latter after 6 months intervention[42]. Another meta-analysis focused on the Effect of metformin in overweight women also come to the similar conclusion that metformin reduces BMI, FSH, LH, low density lipoprotein (LDL), cholesterol and testosterone level in individuals with PCOS[43].

An systematic review published in 2008 compared the efficacy of Diane-35 and metformin with Diane-35 alone, the result of which indicated that Diane-35 and metformin combination showed better result than Diane-35 monotherapy in lowering BMI(WMD 1.05; 95% CI 0.09, 2.01) in patients with PCOS[38] .

Some studies hypothesized that obesity might be more responsible than the elevated androgen level for the development of anovulation in PCOS and obesity induced metabolic abnormalities are closely related to insulin resistance(IR) [44- 47]. When IR occurs in individuals, the function of insulin cannot be exerted which results in the synthesis and secretion of insulin from pancreatic cell being increased in a compensatory way[48]. Hyperinsulinemia further deteriorates androgen-dependent anovulation via two main pathways[48]. One is that insulin indirectly accelerates the androgen production through enhancing the effects of LH on ovarian theca cells[49-50]. Another is that insulin inhibits the release of sex hormone-binding globulin (SHBG) from the liver, therefore the amount of bio-active androgen (unbound with SHBG) in blood circulation will increase[51-52]. The excess androgen lead to menstrual irregularity, which in turn inhibit follicular maturation[53].Thus, obesity and IR will deteriorate hyperandrogenism in this feed-back circle, in addition to directly control the level of androgen, the active management of IR induced by obesity is of vital importance in the treatment of PCOS.

Western medicine treatment is mainly to adjust the menstrual cycle, improve ovulation, but none of them can permanently relieve the symptoms of patients, and even lead to ovarian overstimulation and low pregnancy rate[54-56]. Moreover, metformin frequently induces gastrointestinal discomfort in patients, and in some cases even causes hypoglycemia, as dangerous as hyperglycemia, when uptake overdose or in fasting circumstances[57-58].

Therefore, we intended to investigate whether the addition of Traditional Chinese Medicine(TCM) to metformin and Diane-35 would improve the clinical outcome of patients with PCOS.

TCM possess two major characteristic distinct from western medication, holistic therapy and multisystem regulation[59] .

In viewpoint of traditional Chinese medicine (TCM), the disorders of the kidneys, liver and spleen might result in the occurrence of PCOS, the deficiency in kidney in particular, since kidney is believed to govern reproductive function of humans[60-62]. When the function of the liver is impaired, the blood circulation and the menstrual cycle of an individual will be adversely affected, while the condition of spleen will influence body type, obesity might occur if it doesn't perform well[63].

Guizhi fuling capsule (GF) is one of the most frequently prescribed Chinese herbal formulas for treating uterine fibroids and widely accepted for the management of gynaecological conditions[64].The ingredients of guizhi fuling capsule consist of the following 5 herbs: Cinnamomum cassia (L.) J. Presl (Guizhi), Poria cocos (Schw.) Wolf (Fuling), Paeonia lactiflora Pall. (Chishao), Juglans regia L. (Taoren), and Paeonia suffruticosa Andr. (Mudanpi)[65].

Some studies indicated that GF might ameliorate PCOS-IR through regulating related target proteins and pathways in hormone generation and secretion[66-68]. The function of GF is not limited to alleviating IR resistance , reducing fasting blood glucose together with insulin and correcting abnormal lipid metabolism, can also shorten the menstrual cycle, restore ovulation, and improve the pregnancy rate[69-71].

Another kind of the traditional Chinese medicine, Kuntai capsule (KT), consists of prepared Dihuang (Rehmannia glutinosa (Gaertn.) DC.), Huanglian (Rhizoma Coptidis), Baishao (Radix Paeoniae Alba), Huangqin (Radix Scutellariae Baicalensis), Ejiao (Colla Corii Asini), and Fuling (Poria)[72]. The result of a meta-analysis demonstrated that Kuntai capsule has better performance in regulating serum sex hormone levels including LH, LH/FSH and T than placebo in patients with PCOS[72].

In the mechanism analysis of the modern pharmacology, the component dang gui and baishao may reduce the release of insulin and androgen through phosphatidylinositol 3-hydroxy kinase(PI3K)/protein kinase B (AKT)/glucose transporter 4 (GLUT4) signal pathway and oxidative stress[73-75].

Studies have shown that traditional Chinese medicine can inhibit the apoptosis and excessive autophagy of ovarian granulosa cells, reduce follicular atresia, improve ovarian reserve function, regulate serum endocrine hormone levels, restore the

number of ovarian granulosa cells, so as to maintain ovarian function and promote follicle development[76-77].

The pooled results indicated that the efficacy of TCM+ diane-35+ metformin was significantly superior to that of diane-35+ metformin in lowering LH level (MD: −1.93, 95%CI: -3.44, -0.42;Unit:U/L; P ＜ 0.01; I^2=89%) and T level (MD: -1.44, 95%CI:-2.59,-0.30;Unit:nmol/L; P ＜ 0.01; I^2=98%)and increasing Estradiol(E2)(MD: 31.43, 95%CI 24.5,38.3;Unit:pmol/L; P ＜ 0.01; I^2=96%),Ovulation rate(RR 1.14 95%CI: 1.1,1.2; P =0.42; I^2=0%)and Pregnancy rate(RR 1.29 95%CI 1.2,1.4; P =0.37; I^2=7%).

A similar result can be find in a systematic review, which concludes that traditional Chinese medicine (TCM) has the competence to significantly increase the pregnancy rate and the ovulation rate in participants struggling with infertility due to anovulation[78].

In attempt to find out whether there was some difference towards the type of TCM ,we conducted subgroup analysis stratified studies in according to the type of TCM.KT achieved better performance in increasing Estradiol (E2) (pooled MD: 31.4, 95%CI:24.5,38.3, Unit: pmol/L, P<0.01; I^2 = 95.6%) and lowering FSH (pooled MD: -1.00,95%CI: -2.27,0.28;Unit: pmol/L, P =0.02;I^2 =95%) in comparison with GF.

Only one study reported the incidence of drug related adverse events[23], as mentioned by which ,there were no severe adverse events in both groups and occasionally some patients developed slight increase in transaminase, myocardial enzyme and creatinine, which return to normal after two weeks. As a consequence, the pooled analysis is only conducted to the efficacy, while toxicity hasn't undergone pooled analysis.

6.Limitation

Limitation of our studies include :first ,the included studies have not reported the diagnostic criteria and important outcome indicator like the live birth rate and adverse events ,which result in the limited information was obtained in this meta-analysis ;Second ,although we conducted comprehensive search ,included studies were all carried out in China ,the result of the current meta-analysis might cannot be applied to the other part of the world[79] ;last, we suppose there might exist methodological flows since neither of them reported the calculation of sample size in the initiation and the drop-out rate in the end.

7.Conclusion

The results of our systematic review and meta-analysis validated the efficacy of TCM including GF and KT in the treatment of patients with PCOS. TCM containing therapy might be a potential option to enhance the efficacy of metformin and Diane-35. However, since the number of eligible studies is limited and most of them are relatively moderate quality, the results should be interpreted with caution. To provide stronger evidence for the application of GF or HYKT-containing TCM in the treatment of PCOS, more high quality randomized controlled trials are needed.

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Conflict of Interests

The authors declare that there is no conflict of interest regarding the publication of this paper.

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