INPLASY PROTOCOL

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None declared.

Efficacy and safety of Chinese herbal medicine Xiao Yao San in polycystic ovary syndrome: a systematic review and meta-analysis

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Review question / Objective: **1. Are the Chinese herbal medicine, Xiao Yao San, effective in treating polycystic ovary syndrome? 2. Is it safe to use Xiao Yao San for the treatment of polycystic ovary syndrome?**
Condition being studied: **Polycystic ovary syndrome is characterised by anovulation, infertility, and hyperandrogenism, with clinical manifestations of irregular menstrual cycles, hirsutism, and acne. The condition affects an estimated 5-10% of women of reproductive age, although this varies depending on the diagnostic criteria used. One of the commonest presenting complaints of women with polycystic ovary syndrome is anovulatory infertility. They also have increased prevalence of cardiovascular risk factors similar to that seen in the metabolic syndrome.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 08 May 2021 and was last updated on 16 June 2022 (registration number INPLASY202150031).

INTRODUCTION

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METHODS

Search strategy: Seven electronic databases were searched without language limitation (from their inception to January 11, 2022). These included PubMed, EMBASE, Cochrane library, China National Knowledge Infrastructure (CNKI), China Science Technology Journal Database (VIP), Wanfang Database, and Sino-Med Database. The following search terms were used: ("xiao yao" OR "xiao-yao" OR "xiaoyao" OR "shoyo") AND ("ovary polycystic disease" OR "stein leventhal syndrome" OR "polycystic ovar$" OR "PCOS" OR "PCOD" OR "PCO" OR "stein-leventhal" OR "leventhal" OR "ovar$ degeneration" OR "ovar$ sclerocystic" OR "ovar$ polycystic") AND ("clinical trial" OR "randomized controlled trial" OR "randomization" OR "single blind procedure" OR "double blind procedure" OR "crossover procedure" OR "placebo" OR "randomi?ed controlled trial$" OR "rct" OR "random allocation" OR "randomly" OR "randomly allocated" OR "allocated randomly" OR "allocated random" OR "single blind$" OR "double blind$" OR "treble" OR "triple" AND "blind$" OR "placebo$" OR "prospective study").

Participant or population: Women patients with polycystic ovary syndrome who attain Xiao Yao San or modified Xiao Yao san alone or with western medicines, will be included. No restriction on age, or nationality.

Intervention: Trials that compared Xiao Yao San or modified Xiao Yao San as the active intervention in the treatment group versus placebo or conventional medicines will be included. Trials will be excluded if any other medications, including qigong, Tai Chi, acupuncture, cupping, moxibustion, and massage, were used as co-interventions.

Comparator: Placebo or conventional medicines for polycystic ovary syndrome.

Study designs to be included: Randomized controlled trials.

Eligibility criteria: Studies were included if they met all of the following criteria: 1) Patients met the diagnostic criteria for PCOS. 2) Studies were conducted as RCTs. 3) Effects of XYS in treating PCOS were assessed. 4) The control group received placebo or conventional medicines, including ovulation induction agents and menstrual cycle regulation agents. Patients in the trial group were treated with XYS based on conventional medicines. The conventional medicines used in the trial group should be identical to those in the control group. 5) Evaluation criteria of curative effects were sufficiently described. 6) Historically, a combination of anovulation and androgen excess was considered a hallmark in the diagnosis of PCOS, the original trials should at least include the following outcomes: ovulation/pregnancy rate and total testosterone level.

Information sources: Comprehensive search will be carried out in seven electronic databases, including MEDLINE, Embase, the Cochrane Library, Chinese Biomedical Database (CBM), China National Knowledge Infrastructure (CNKI), Wanfang Database, China Science and Technology Journal Database (VIP). No publication date or language restriction will be imposed.

Main outcome(s): The primary outcome measures included ovulation rate, pregnancy rate, and total testosterone level.

Additional outcome(s): The second outcome measures included luteinizing hormone (LH), follicle-stimulating hormone (FSH), fasting insulin (FINS), fasting plasma glucose (FPG), homeostatic model

assessment for insulin resistance (HOMA-IR) levels, and adverse effects.

Data management: Selection of studies: Two reviewers will independently screen the titles, abstracts and manuscripts retrieved from different databases engines and identify studies that potentially meet the inclusion criteria outlined above. Study selection and exclusion process will be documented and a list of potentially eligible studies in the analysis will be created. The full text of these potentially eligible studies will be downloaded and further assessed for eligibility by the two reviewers. Any disagreements will be resolved by a third reviewer as necessary. The reasons for the exclusion of any studies will be recorded on a PRISMA flow chart. Data extraction: Data extraction will be performed by two independently reviewers using a pre-designed collection form. If any discrepancies arise, an additional reviewer will be consulted. The following information will be extracted for each study: (1) Publication characteristics; (2) Participants characteristics; (3) Interventions: intervention, comparison, concomitant medications, duration of treatment and follow-up time. (4) Outcomes: primary and secondary outcomes and adverse events.

Quality assessment / Risk of bias analysis: The methodological quality of each study was assessed independently by two reviewers (R.X.L, Y.X.L) according to the Cochrane Collaboration's Risk of Bias Tool (Higgins et al., 2011). This tool consists of seven domains: random sequence generation (selection bias), allocation sequence concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias), and other sources of bias (Higgins et al., 2011). Studies were ranked as "low", "high", or "unclear" risk of bias in each of these domains. Disagreements were resolved through consultation with a third researcher (Q.Y.M).

Strategy of data synthesis: Dichotomous data were presented as relative risks (RRs) or odds ratios (ORs) with 95% confidence intervals (CIs) based on whether the XYS increases or decreases the chance of events. Standardized mean differences (SMDs) with 95% confidence intervals (CIs) were calculated for continuous outcomes (Feng et al., 2022). The chi-square test was used to evaluate the heterogeneity, and I2 was used to assess the inconsistency across studies. Values of I2 ranged from 0 to 100% (I2 = 0% - 40%, might not be important; I2 = 30% - 60%, may represent moderate heterogeneity; I2 = 50% - 90%, may represent substantial heterogeneity; and I2 = 75% - 100%, considerable heterogeneity) (Higgins et al., 2019). When I2 > 50% and P < 0.05, it was presented as significant heterogeneity, a random-effects model was used to pool estimates. When I2 ≤ 50%, a fixed-effect model was used to estimate the summary RR (OR) and SMD (Liang et al., 2022). Potential sources of heterogeneity were identified by subgroup analysis. Sensitivity analysis was conducted to evaluate the stability of our results by sequentially omitting every study from the pooled analysis. Funnel plots and Egger's test were conducted to examine the potential bias when the number of RCTs was ≥ 10. The analyses were conducted using the Cochrane RevMan software (version 5.4.0; Cochrane Collaboration, Oxford, UK) and the R software (version 4.2; R Core Team, 2022). The quality of evidence was evaluated by the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system. Summary of findings table for outcomes was performed using GRADEpro 3.6 (available at http://gdt.guidelinedevelopment.org).

Subgroup analysis: Subgroup analyses will be conducted according to interventions in trial group.

Sensitivity analysis: Sensitivity analysis will be undertaken to examine if the effects are modified by, or robust to, the type of measurement method or tool.

Language: No restriction.

Country(ies) involved: China.

Keywords: Chinese herbal medicine; Xiao Yao San; polycystic ovary syndrome; meta-analysis.

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