INPLASY PROTOCOL

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Conflicts of interest:
None declared.

Efficacy and safety assessment of traditional Chinese patent medicine for dyslipidemia: A meta-analysis and trial sequential analysis

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Review question / Objective: **The aim of this meta-analysis of randomized controlled trials is to evaluate the efficacy and safety of traditional Chinese patent medicine for dyslipidemia.**
Eligibility criteria: **We included studies that satisfied the following criteria: (a) Randomized controlled trials to compare traditional Chinese medicine compound with placebo, other interventions, or other drugs for dyslipidemia; (b) trials where the participants had a definite diagnosis of dyslipidemia; (c) trials with intervention period over 6 weeks; (d) trials where the only difference between the two groups was whether received Chinese herbal medicine; (e) Outcome measures were lipid parameters, including TC, TG,LDLC,HDLC, and adverse events.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 24 March 2023 and was last updated on 14 August 2023 (registration number INPLASY202330090).

INTRODUCTION

Review question / Objective: **The aim of this meta-analysis of randomized controlled trials is to evaluate the efficacy and safety of traditional Chinese patent medicine for dyslipidemia.**

Condition being studied: **Dyslipidemia is a metabolic disease caused by the imbalance of lipid metabolism in the body itself, resulting in the increase of serum total cholesterol, triglycerides, and low density lipoprotein cholesterol levels as well as the decrease of high density lipoprotein cholesterol levels. In recent years, the overall prevalence of dyslipidemia continues to increase, which brings the risk of coronary artery disease to be reckoned with. Therefore, early prevention and treatment of dyslipidemia is crucial. At present, the commonly used drugs for the**

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treatment of dyslipidemia include statins, fibrates, bile acid blockers, nicotinic acid and cholesterol absorption inhibitors, but many drugs have obvious side effects, such as increased risk of type 2 diabetes, statin myopathy, liver injury and sleep disorders. Along with the long-term treatment with statins in combination with other hypolipidemic drugs or alone, its safety and the medication compliance of patient had attracted a particular attention in clinic. So more and more comprehensive strategy is required in clinical practice.
Traditional Chinese medicine (TCM) has been applied to the treatment of dyslipidemia in China and has shown significant efficacy with no increase in side effects. More and more studies have focused on the efficacy of traditional Chinese medicine (TCM) compound prescriptions for dyslipidemia, and it needs to be systematically evaluated whether they can be used as a supplement and alternative therapy.

METHODS

Search strategy: A literature search was conducted using Web of Science, PubMed, Embase, Cochrane Library, SinoMed, China National Knowledge Internet (CNKI), WanFang and VIP from January 2013 to March 2023, with no language restriction. Search terms included the following: ("Dyslipidemias" , "Hyperlipidemias" , "Hypertriglyceridemia" , "Hypercholesterolemias" , "Hypercholesteremia" , "hyperlipoproteinemia" , "cholesterol" , "LDL" , or "HDL") and ("randomized controlled trial" , "controlled clinical trial" , "randomly" , "randomized" , or "randomized") and ("TCM" , "traditional Chinese medicine" , "Chinese patent medcine" , "Chinese patent drug" , or "proprietary Chinese medicine").The search strategy of PubMed is summarized in Supplementary Material S1. This search strategy will be modified according to the characteristics of different databases.

Participant or population: Adults diagnosed with dyslipidemia will be included.

Intervention: Traditional Chinese medicine compound, or traditional Chinese medicine compound combined with conventional therapy (e.g. statin and fibrate).

Comparator: No other treatment or placebo or conventional treatment (e.g. statin and fibrate).

Study designs to be included: Randomized controlled trials to compare traditional Chinese medicine compound with placebo, other interventions, or other drugs for dyslipidemia Randomized controlled trials to compare traditional Chinese medicine compound with placebo, other interventions, or other drugs for dyslipidemia.

Eligibility criteria: We included studies that satisfied the following criteria: (a) Randomized controlled trials to compare traditional CPM with placebo, other interventions, or other drugs for dyslipidemia; (b) trials where the participants had a definite diagnosis of dyslipidemia; (c) trials with sample size more than 48; (d) trials with intervention period over 6 weeks; (e) trials where the only difference between the two groups was whether received Chinese herbal medicine; (f) trials that used lipid parameters, including TC, TG,LDLC,HDLC as primary outcome measurement.

Information sources: Relevant clinical trials will be identified by searching for articles published in the following databases regardless of publication date or language: Web of Science, PubMed, Embase, Cochrane Library, SinoMed, China National Knowledge Internet (CNKI), WanFang and VIP.

Main outcome(s): 1. Serum lipid levels (including TC, TG, LDL-C and HDL-C).
2. Adverse events.

Additional outcome(s): 1.TCM clinical efficiency, TCM syndrome score;
2.Mean Apolipoprotein A, mean Apolipoprotein B, mean blood rheology;
3.Health-related quality of life;

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4.Weight, body mass index (BMI) , waist circumference (WC), waist-to-hip ratio (WHR)
The above indicators are subject to inclusion in the study.

Data management: Two reviewers will independently select the eligible studies by reading the title and abstracts. The further detailed screening will be conducted by full-text reading. Controversial opinions will beresolved by discussion with the third reviewer. If potential overlapping populations are repetitively reported, only the most recent study will beenrolled.
Data extraction will be performed after the screening process by two independent reviewers. The content of data extraction includes the general publication information (including the name of the first author and the publication year), trial design and methodology (including sample size, participants, and statistical methods), intervention profiles (including drug name, dosage, duration, and administration method), and outcome measurements (including Serum lipid levels , Adverse events, TCM clinical efficiency, TCM syndrome score , mean Apolipoprotein A, mean Apolipoprotein B, mean blood rheology , Health-related quality of life , Weight, body mass index , waist circumference and waist-to-hip ratio).

Quality assessment / Risk of bias analysis: The assessment of the study risk of bias will be independently conducted by two reviewers based on the Cochrane risk-of-bias tool for randomized trials (RoB 2), for assessing the risk of bias. Discrepancies between the two review authors will be resolved through discussion with a third review author. The assessment outcomes will be visualized using Review Manager software (version 5.4; Cochrane Collaboration, Oxford, UK). The publication bias will be assessed using a funnel plot if the result of the current meta-analysis contains more than ten articles. Quantitative methods including the Begg test and Egger test will be used to assess publication bias.The meta-analysis of comparable data will be carried out using RevMan. For dichotomous outcomes, the risk ratios (RRs) will be calculated with 95% confidence intervals (CIs). For continuous outcomes, we will calculate the weighted mean differences accompanied by 95% CIs. Heterogeneity will be examined by using the I^2 statistic, and its statistical significance will be calculated with the Cochran's Q test. The significance level of Q test will be set at 0.1. Besides, a fixed-effect model (FEM) will be used if $I^2 < 50\%$ and $P > 0.1$; while the random-effect model (REM) will be used if $50\% < I^2 < 85\%$. If I^2 is greater than 85%, predetermined sub-analyses will be performed to explore the cause(s) of heterogeneity. Sensitivity analysis will be performed to check whether the results are affected by the inclusion of certain trials, and the differences between the REM and FEM will also be observed to test the robustness of the results.
The trial sequential analysis will be conducted to explore whether cumulative data are adequately powered to evaluate the primary outcome. We will use the TSA program (TSA software version 0.9.5.10 Beta; Copenhagen Trial Unit, Copenhagen, Denmark) to acquire the estimation of required information size (RIS) with an adjusted threshold for statistical significance, under an overall 5% risk of type I error and 80% power.

Strategy of data synthesis: The meta-analysis of comparable data will be carried out using RevMan. For dichotomous outcomes, the risk ratios (RRs) will be calculated with 95% confidence intervals (CIs). For continuous outcomes, we will calculate the weighted mean differences accompanied by 95% CIs. Heterogeneity will be examined by using the I^2 statistic, and its statistical significance will be calculated with the Cochran's Q test. The significance level of Q test will be set at 0.1. Besides, a fixed-effect model (FEM) will be used if $I^2 < 50\%$ and $P > 0.1$; while the random-effect model (REM) will be used if $50\% < I^2 < 85\%$. If I^2 is greater than 85%, predetermined sub-analyses will be performed to explore the cause(s) of heterogeneity. Sensitivity analysis will be performed to check whether the results are

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Subgroup analysis: If data is available, we intend to explore the potential sources of heterogeneity using subgroup analyses, including duration of treatment, different intervention combinations, subtypes of dyslipidemia and combined different diseases.

Sensitivity analysis: Sensitivity analysis was performed to check whether the results were affected by the inclusion of certain trials, and the differences between the REM and FEM were also observed to test the robustness of the results. In detail, the sensitivity analysis was conducted by assessing the changes in the overall results by eliminating individual studies one-by-one and applying different effect models.

Language restriction: No language restriction was used.

Country(ies) involved: China.

Keywords: Dyslipidemias ; Phytotherapy; meta-analysis; traditional Chinese medicine compound ; trial sequential analysis.

Contributions of each author:
Author 1 - Yini Fang drafted the manuscript.
Email: fynchn@163.com
Author 2 - Haoran Wu provided statistical expertise.
Author 3 - Tianxing Li contributed to the development of the selection criteria, and the risk of bias assessment strategy.
Author 4 - Ruiting Jia contributed to the development of the selection criteria, and the risk of bias assessment strategy.
Author 5 - Lingru Li read, provided feedback and approved the final manuscript.

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