INPLASY PROTOCOL

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Conflicts of interest:
None declared.

Red yeast rice preparations for dyslipidemia: A protocol for a network meta-analysis

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Review question / Objective: **What is the comparative benefit ranking of red yeast rice preparations on dyslipidemia compared to other lipid-lowering drugs?Based on the current controversies in dyslipidemia guidelines and clinical practice, to explore the relative benefits of red yeast rice compared with other lipid-lowering drugs, and explore the effects ranking of various red yeast rice preparations, we plan to perform a network meta-analysis.**
Eligibility criteria: **This network meta-analysis will include randomized control trials (RCTs) evaluating the efficacy of RYR for all types of dyslipidemia. Patients with dyslipidemia will be included without restricting gender, race, or age. The intervention will include any preparations of red yeast rice. The control intervention will include no treatment, placebo, lipid-lowering agents. The outcome measures include SRs reported data concerning at least one outcome interest—major adverse cardiovascular events (MACE) and serum lipid profiles. Additional outcomes will include waist circumstances, body mass index, blood glucose, glycated hemoglobin A1c (HbA1c), blood pressure, adverse events, and cost-effectiveness.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 25 October 2022 and was last updated on 25 October 2022 (registration number INPLASY2022100102).

INTRODUCTION

Review question / Objective: **What is the comparative benefit ranking of red yeast rice preparations on dyslipidemia compared to other lipid-lowering drugs? Based on the current controversies in dyslipidemia guidelines and clinical practice, to explore the relative benefits of red yeast rice compared with other lipid-lowering drugs, and explore the effects**

ranking of various red yeast rice preparations, we plan to perform a network meta-analysis.

Condition being studied: Dyslipidemia has been a public health challenge with high prevalence, leading to significant economic and social burdens. Red yeast rice (RYR), a traditional Chinese medicine, has been used as an alternative to statin therapy in treating patients with dyslipidemia, particularly in those considered to be statin intolerant due to statin-associated myalgia (SAM). Moreover, clinical studies suggest that RYR is well-tolerated, safe, and effective for the primary prevention of cardiovascular disease (CVD). Many systematic reviews (SRs) /meta-analysis (MAs) have been performed to prove the effects of RYR on dyslipidemia during the past several years. However, existing SRs/MAs showed varied and heterogeneous results. Furthermore, as a main lipid-lowering component of RYR, Monacolin contents vary significantly in different RYR mono-preparations. Currently, in China, mono-preparations of RYR include Xuezhikang(XZK), Zhibituo(ZBT), and RYR powder. Internationally, mono-preparations of RYR include Cholestin and Hypocol. Therefore, it is necessary to take complete account of the heterogeneity of RYR mono-preparation and further analyze the efficacy and safety of different mono-preparations of RYR using network meta-analysis.Red yeast rice (RYR) has been used as an alternative to statin therapy in treating patients with dyslipidemia, particularly in those considered to be statin intolerant due to statin-associated myalgia (SAM), and clinical studies suggest that RYR is well-tolerated, safe, and effective for cardiovascular disease (CVD) primary prevention. Dyslipidemia is a worldwide public health challenge because of its high prevalence, leading to significant economic and social burdens.

METHODS

Participant or population: Patients with dyslipidemia will be included in this overview without restricting gender, race, or age.

Intervention: The intervention will include any mono-preparations of red yeast rice, whether raw herb or extracts, combined with or without conventional lipid-lowering agents.

Comparator: The control intervention will include no intervention, placebo, lipid-lowering agents, including but not limited to statins.

Study designs to be included: This network meta-analysis will include all randomized control trials (RCTs) evaluating the efficacy of RYR for all types of dyslipidemia.

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Information sources: The four international electronic databases of the Cochrane Library, PubMed, Embase, and Web of Science, and four Chinese electronic databases of China National Knowledge Infrastructure Database (CNKI), Wanfang Data, Chongqing VIP (CQVIP), and Chinese Biomedical Literature Database (SinoMed) will be searched for randomized controlled trials up to March 2022 without language restriction. The Medical Subject Heading (MeSH) terms comprising the following search terms will be utilized for searching the database: ("dyslipidemia" OR "cholesterol'' OR "triglycerides" OR "lipoproteins" OR "apolipoprotein") AND ("red yeast rice" OR "RYR" OR "xuezhikang" OR "Monascus") AND ("systematic review" OR "meta-analysis").

Meanwhile, we will review the references included in the literature to avoid the occurrence of omission. Also, we will contact the author if we can not obtain the full text.

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Main outcome(s): The outcome measures include major adverse cardiovascular events (MACE) and serum lipid profiles including but not limited to LDL-C, total cholesterol, triglyceride, and HDL-C.

Additional outcome(s): Additional outcomes will include waist circumstances, body mass index, blood metabolism indicators, blood pressure, adverse events, and cost-effectiveness.

Data management: Two reviewers will undertake an independent screening of the titles and abstracts for the studies (searched ones), undertake the selection of studies, and record their decisions based on predefined criteria. The third reviewer will resolve disagreements in study selection.

The documentation and summarization of study selection will be done on a flow chart compliant with preferred reporting items for systematic reviews and meta-analysis. The data extract includes publication year, author, search date, the number of searches databases, the number of primary studies (total sample size), type of comparator, type of RYR, quality assessment tool, outcome measures, overall bias risk, conclusion (quote from the original paper), effect estimates for primary outcomes (meta-analysis), and adverse events.

Quality assessment / Risk of bias analysis: The risk of bias of the included RCTs will be critically assessed using Cochrane's risk of bias tool.

We will assess the risk of bias from the following six domains: the risk of bias arising from the randomization process in the included studies, the risk of bias due to deviations from the intended interventions in the included studies, the risk of bias due to missing outcome data in the included studies, the risk of bias in measurement of the outcome in the included studies, the risk of bias due to selective reporting, and risk of bias due to the funders' participation in the included studies.

The RCTs will be evaluated as “low risk”, “high risk”, and “unclear risk” in every domain.

The evaluation of the included RCTs will be performed independently and then cross-checked. Any differences will be resolved through negotiation and unresolvable consultation with a third reviewer.

Strategy of data synthesis: The results will be reported in figures and tables. The net plot for the comparison of interventions for each outcome will be mapped by the R-project, and the data will be analyzed by Bayesian Markov Chain Monte Carlo (MCMC) random model.

Subgroup analysis: Subgroup analysis will be further performed based on the type of complications, type of RYR preparations, control intervention, and treatment duration, if sufficient data is available.

Sensitivity analysis: We will ensure the stability of the comprehensive results by performing sensitivity analysis if necessary.

Language restriction: None.

Country(ies) involved: China.

Keywords: yslipidemia; red yeast rice; lipid-lowering agents; systematic review; Network meta-analysis.

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