INTRODUCTION

Review question / Objective: What is the quality of systematic reviews/meta-analysis of red yeast rice (RYR) preparations for dyslipidemia? What is the comparative benefit 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, we plan to perform an overview of existing SRs/MAs.

Condition being studied: 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. Several studies support the beneficial effect of RYR on blood lipid profiles. Dyslipidemia is a worldwide public health challenge because of its high prevalence, leading to significant economic and social burdens. Many systematic reviews (SRs) /meta-analysis (MAs) have been performed to prove the effects of RYR on dyslipidemia during the past several years. High-quality SRs/MAs can provide clinicians, patients, and other decision-makers with a reliable scientific basis. However, existing SRs/MAs showed varied and heterogeneous results.

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 08 March 2022 and was last updated on 08 March 2022 (registration number INPLASY202230032).
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**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 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 treatment, placebo, lipid-lowering agents, including but not limited to statins. In addition, other natural herbs which have been proved effective compared to placebo or guideline recommended lipid-lowering agents will be included, too.

**Study designs to be included:** This overview will include all Cochrane SRs as well as non-Cochrane SRs of randomized control trials (RCTs) evaluating the efficacy of RYR for all types of dyslipidemia, with or without meta-analysis.

**Eligibility criteria:** This overview will include all Cochrane SRs as well as non-Cochrane SRs of randomized control trials (RCTs) evaluating the efficacy of RYR for all types of dyslipidemia, with or without meta-analysis. 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.

**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 pertinent MAs and SRs from their inception 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 cannot obtain the full text.

**Main outcome(s):** The outcome measures include SRs reported data concerning at least one outcome interest—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 glucose, glycated hemoglobin A1c (HbA1c), 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. After a systematic review of inclusion, 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 methodological quality of the included SR will be critically appraised by the Assessment of Multiple Systematic Reviews-2 tool (AMSTAR-2), Preferred Reporting Item for Systematic Reviews, Meta-Analysis (PRISMA), and ROBIS. A validated 16-item instrument of AMSTAR-2 will be used to appraise systematic reviews assessing critical flow critically and bias using ratings of “yes”, “partial yes”, or “no”. Then, an overall assessment of SR (high, medium, low, and critically low) will be performed based on evaluating critical and non-critical items. Moreover, 27 items of PRISMA will be assessed as “yes,” “partial yes,” and “no,” and the rates will be listed according to the evaluation of each item. The ROBIS involves three phases. The first phase is optional, and the second phase consists of four key areas: “study eligibility criteria”, “identification and selection of studies”, “data collection and study appraisal”, and “synthesis and findings”. The third phase is based on the evaluation of the four areas in the second stage for a comprehensive evaluation, and the SRs are evaluated as “low risk”, “high risk”, and “unclear risk”. The evaluation of the included SRs will be performed independently and then cross-checked. Any differences will be resolved through negotiation and unresolvable consultation with a third reviewer. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach will be adopted to evaluate CoE for all outcomes. Two reviewers will undertake an independent assessment of the evidence about outcomes; the downgraded/upgraded factors that impact the evidence’s quality will be elucidated to ensure that the results are reliable and transparent. The five key factors involve the risk of inconsistency, bias, imprecision, indirectness, as well as publication bias. The GRADE approach (GRADEpro GDT is as follows: GRADEpro Guideline Development Tool [Software] McMaster University and Evidence Prime, Inc. 2015. Ontario, Canada) categorizes CoE as high, moderate, low, and very low.

**Strategy of data synthesis:** The results will be reported in text and tables. Moreover, a network-meta analysis of the included SRs will be performed. 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.
**Country(ies) involved:** The overview will be carried out in China.

**Other relevant information:** None.

**Keywords:** Dyslipidemia; Red yeast rice; lipid-lowering agents; Overview; Network meta-analysis.

**Dissemination plans:** This systematic review results will be submitted for publication in peer review journal.

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