INPLASY PROTOCOL

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Corresponding author:
Yonglang Cheng

chengyonglang666@163.com

Author Affiliation:
Department of General Surgery (Hepatopancreatobiliary surgery), The Affiliated Hospital of Southwest Medical University, Luzhou, Sichuan, China.

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Review Stage at time of this submission: **Data analysis - Completed but not published.**

Conflicts of interest:
None declared.

Lactobacillus reuteri alleviates lipid levels in patients with hypercholesterolemia: a meta-analysis of randomized controlled trials

Cheng, YL[1]; Zeng, P[2]; Huang, ZW[3]; Shi, H[4]; Cai, TY[5]; Li, TX[6]; Chen, YF[7]; Fu, WG[8]; Li, Q[9].

Review question / Objective: **The aim of this study was to evaluate the effect of L. reuteri on human lipid metabolism using an evidence-based medical approach. P: Metabolic disorder population I: Lactobacillus reuteri C: placebo O: LDL-C: low density lipoprotein cholesterin. TC: total cholesterol S: randomized controlled trials.**
Condition being studied: **Hypercholesterolemia.**
Eligibility criteria: **The studies included in this meta-analysis met the following criteria: (1) randomized controlled trial (RCT); (2) using L. reuteri as the only intervention, and the control group is a placebo or no treatment; (3) The study involved measures of lipid metabolism, such as triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C). (4) Available data were used to calculate the corresponding statistic. (5) Animal studies, review papers, and conference abstracts were excluded.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 28 April 2022 and was last updated on 28 April 2022 (registration number INPLASY202240160).

INTRODUCTION

Review question / Objective: **The aim of this study was to evaluate the effect of L. reuteri on human lipid metabolism using an evidence-based medical approach. P: Metabolic disorder population I: Lactobacillus reuteri C: placebo O: LDL-C: low density lipoprotein cholesterin. TC: total cholesterol S: randomized controlled trials.**

Rationale: The statistical analyses were conducted using RevMan software (version 5.3, Cochrane, Oxford, UK). Dichotomous data were presented using odds ratio with 95% CIs, and continuous data were analyzed using the MD or standard mean difference (SMD) with 95% CIs. The statistical heterogeneity between studies was evaluated with I2 statistics, and when the I2 value was greater than 50%, it was a high degree of heterogeneity; then, subgroup analyses were performed. Sensitivity analysis was conducted by eliminating each study in turn. Data were combined using a random-effects model. All tests were two-tailed, and $P < 0.05$ was considered statistically significant.

Condition being studied: Hypercholesterolemia.

METHODS

Search strategy: The literature search was conducted using Cochrane Library, the PubMed database, the Embase database, the clinicaltrails.gov, and the bibliography of the original articles was manually checked. The medical subject heading keywords used were Lactobacillus reuteri, cholesterol, triglycerides, clinical trial, random*, and combinations of the above terms.

Participant or population: Metabolic disorder population.

Intervention: Lactobacillus reuteri.

Comparator: Placebo.

Study designs to be included: Randomized controlled trials.

Eligibility criteria: The studies included in this meta-analysis met the following criteria: (1) randomized controlled trial (RCT); (2) using L. reuteri as the only intervention, and the control group is a placebo or no treatment; (3) The study involved measures of lipid metabolism, such as triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C). (4) Available data were used to calculate the corresponding statistic. (5) Animal studies, review papers, and conference abstracts were excluded.

Information sources: The literature search was conducted using Cochrane Library, the PubMed database, the Embase database, the clinicaltrails.gov, and the bibliography of the original articles was manually checked.

Main outcome(s): LDL-C: low density lipoprotein cholesterin. TC: total cholesterol. TG: Triglycerides.

Additional outcome(s): BMI: Body Mass Index. DBP: Diastolic blood pressure. SBP: Systolic blood pressure. HbA1c: Glycosylated Hemoglobin, Type A1C.

Data management: The statistical analyses were conducted using RevMan software (version 5.3, Cochrane, Oxford, UK). Dichotomous data were presented using odds ratio with 95% CIs, and continuous data were analyzed using the MD or standard mean difference (SMD) with 95% CIs. The statistical heterogeneity between studies was evaluated with I2 statistics, and when the I2 value was greater than 50%, it was a high degree of heterogeneity; then, subgroup analyses were performed. Sensitivity analysis was conducted by eliminating each study in turn. Data were combined using a random-effects model. All tests were two-tailed, and $P < 0.05$ was considered statistically significant.

Quality assessment / Risk of bias analysis: Two researchers assessed the study quality using the Cochrane Risk of Bias Tool. The tool was consistent in seven particular domains; specifically, sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other bias. The included studies were classified as low-quality, moderate quality, and high-quality according to the following criteria: (1) as long as randomized or blinded assessments were high-risk bias, the study was regarded as low-quality; (2)

when randomization and blinding were evaluated as low bias risk and other items were not at high risk of bias, the study was considered high-quality; (3) if the study did not meet the criteria for high-quality or low-quality, the study was of moderate quality.

Strategy of data synthesis: The statistical heterogeneity between studies was evaluated with I2 statistics, and when the I2 value was greater than 50%, it was a high degree of heterogeneity; then, subgroup analyses were performed. Sensitivity analysis was conducted by eliminating each study in turn. Data were combined using a random-effects model.

Subgroup analysis: The statistical heterogeneity between studies was evaluated with I2 statistics, and when the I2 value was greater than 50%, it was a high degree of heterogeneity; then, subgroup analyses were performed.

Sensitivity analysis: Sensitivity analysis was conducted by eliminating each study in turn.

Language: No language limits.

Country(ies) involved: China.

Keywords: Lactobacillus reuteri; Hypercholesterolemia; Lipid metabolism; Diabetes mellitus; Meta analysis.

Contributions of each author:
Author 1 - Yonglang Cheng.
Author 2 - Peng Zeng.
Author 3 - Zhiwei Huang.
Author 4 - Hao Shi.
Author 5 - Tianying Cai.
Author 6 - Tongxi Li.
Author 7 - Yifan Chen.
Author 8 - Wenguang Fu.
Author 9 - Qiu Li.