INPLASY

# The potential clinical benefits of probiotics, prebiotics, synbiotics, and postbiotics for depression via microbiota-gut-brain axis

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**ADMINISTRATIVE INFORMATION**

**Support -** Wenzhou Seventh People's Hospital.

**Review Stage at time of this submission -** The paper has been successfully published.

**Conflicts of interest -** None declared.

**INPLASY registration number:** INPLASY202530039

**Amendments -** This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 10 March 2025 and was last updated on 10 March 2025.

## INTRODUCTION

**Review question / Objective** To assess the potential benefits of PPSP on patients with depressive disorder.

**Condition being studied** Depression is a common and disabling mental disorder around the world. Accumulating studies have demonstrated the effects of gut microbiota-targeting interventions such as probiotics, prebiotics, synbiotics, and postbiotics (PPSP) on depression.

## METHODS

**Participant or population** Patients with depressive symptoms.

**Intervention** Probiotics or prebiotics or synbiotics or postbiotics or heat-killed probiotics or paraprobiotics or metabiotics.

**Comparator** Comparative studies on PPSP and placebo.

**Study designs to be included** Studies that used a randomized controlled trial (RCT) design.

**Eligibility criteria** The search terms were "probiotics", "prebiotics", "synbiotics", "postbiotics", "heat-killed probiotics", "paraprobiotics", "metabiotics", "depression", "microbiota", and "microbiome". The same search strategy was applied to all the databases. In addition, the references of eligible articles were screened to find further eligible studies that were not captured from the database.

**Information sources** The PubMed, Web of Science, and Elsevier Science Direct databases from January 2015 to March 2024 were screened.

**Main outcome(s)** Fourteen studies involving 906 patients with depressive symptoms were included. PPSP improved depression (standardized mean difference [SMD]: -0.39, 95% confidence interval [CI] [-0.60, -0.17], P<0.001) compared to placebo. Analysis based on the two common depressive

rating scales indicated that PPSP resulted in significant reductions in scores for the Hamilton Depression Rating Scale (HDRS) (MD: -1.72, 95% CI [-2.57, -0.88]; P<0.001) and Beck Depression Inventory (BDI) (MD: -2.69, 95% CI [-4.67, -0.71]; P<0.001). The sub-analysis confirmed the apparent antidepressant effects of probiotics in depression (SMD: -0.32, 95% CI [-0.48, -0.16], P<0.001). However, prebiotic use had no effect in depression (SMD: -0.08, 95% CI [-0.39, -0.23], P=0.62). Synbiotics had statistically significant benefits in depressive symptoms (SMD: -1.09, 95% CI [-1.45, -0.73], P<0.001).

**Quality assessment / Risk of bias analysis** Data extraction
The following data were extracted from eligible studies: (1) clinical trial characteristics including first author, publication year, country, study design, intervention and comparator group details, intervention duration, trial number; (2) patient characteristics including diagnostic criteria, sample size, age, and sex; and (3) endpoints: depressive symptoms measured with valid rating scales.
Quality assessment
Two independent reviewers evaluated the risk of bias in the included studies using Cochrane Collaboration's risk of bias tool. The judgement of overall bias involved seven domains, including the randomization process, allocation concealment, blinding of participants, outcome measurements, missing outcome data, selection of reported results and other bias. All domains were assessed as a low, unclear, or high risk of bias.

**Strategy of data synthesis** The pooled results were calculated by mean difference (MD) or standardized MD (SMD) with 95% confidence interval (CI) for each outcome. Heterogeneity was examined using the I2 statistic. A fixed-effect model was used for I2 0.1; otherwise, a random-effect model was adopted.

**Subgroup analysis** Subgroup analysis was performed to assess the heterogeneity and influencing factors for outcomes: gut microbiota-targeting interventions.

**Sensitivity analysis** Funnel plots were used to detect the potential publication bias. A sensitivity analysis was conducted to examine the robustness of the results. RevMan 5.4 software was used for this study and a statistical significant was set at P<0.05.

**Country(ies) involved** China.

**Keywords** Probiotics; Prebiotics; Synbiotics; Postbiotics; Depression; Gut microbiota.

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