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Psychobiotic modulation of the microbiome-gut-brain axis in major depressive disorder: a systematic review

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ADMINISTRATIVE INFORMATION

Support - None.

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Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 2 March 2026 and was last updated on 2 March 2026.

INTRODUCTION

Review question / Objective This systematic review aimed to synthesize recent evidence on the role of the microbiome–gut–brain (MGB) axis in major depressive disorder (MDD). It evaluated the clinical efficacy of psychobiotic interventions, the diagnostic and predictive value of gut microbiome signatures, and explored the biopsychosocial and immunometabolic mechanisms linking microbial alterations to depressive phenotypes and antidepressant treatment response.

Rationale Major depressive disorder was recognized as a debilitating condition characterized by marked interindividual variability in clinical presentation and treatment response. Classical monoaminergic theories did not fully explain this phenotypic heterogeneity, delayed therapeutic effects, or persistent residual symptoms. Emerging evidence highlighted the microbiome–gut–brain axis as a fundamental pathway integrating neural, endocrine, immune, and metabolic mechanisms. Alterations in gut microbiota composition and function were associated with systemic inflammation, dysregulated tryptophan metabolism, and impaired intestinal barrier integrity, which may contribute to depressive symptoms. Psychobiotic interventions and microbiome profiling emerged as promising therapeutic and diagnostic strategies; however, recent clinical evidence remained fragmented and heterogeneous. This systematic review aimed to provide an updated synthesis of human studies to clarify the clinical relevance of microbiome-targeted interventions and the potential of microbial biomarkers in precision psychiatry.

Condition being studied Major depressive disorder and depressive symptoms.

METHODS

Search strategy A systematic search was conducted across the PubMed, Scopus, and PubPsych databases.
Search strategies were tailored to each database:

("Depression"[MeSH Terms] OR "Depressive Disorder"[MeSH Terms] OR "depress*"[Title/Abstract] OR "depressive disorder*"[Title/Abstract]) AND ("Gastrointestinal Microbiome"[MeSH Terms] OR "gastrointestinal microb*"[Title/Abstract]) AND ("Diagnosis"[MeSH Terms] OR "diagnos*"[Title/Abstract] OR ("Therapeutics"[MeSH Terms] OR "therap*"[Title/Abstract] OR "treat*"[Title/Abstract])) for PubMed database;
TITLE-ABS-KEY ("depression" OR "depressive disorder" OR depress*) AND TITLE-ABS-KEY ("gastrointestinal microbiome" OR "gut microbiota" OR "intestinal microbiota" OR "gut bacteria" OR "gastrointestinal microb*") AND TITLE-ABS-KEY ("diagnosis" OR diagnos* OR "therapeutics" OR therap* OR treat*) for Scopus database;
("depression" OR "depressive disorder" OR "depress*") AND ("gastrointestinal microbiome" OR "gut microbiota" OR "intestinal microbiota" OR "gut bacteria" OR "gastrointestinal microb*" OR "gut microb*") AND ("diagnosis" OR "diagnos*" OR "therapeutics" OR "therap*" OR "treatment" OR "treat*") for PubPsych database.

Participant or population Adults (>=18 years) with major depressive disorder, depressive symptoms, subclinical depression, specific clinical populations, including pregnancy, elderly individuals, and patients with metabolic, gastrointestinal, neurological, or oncological comorbidities. Paediatric populations, animal models, and in vitro studies were excluded.

Intervention Psychobiotic and microbiome-targeted strategies, including: prebiotics, probiotics, synbiotics, herbal formulas, supplements and dietary interventions, and fecal microbiota transplantation. Studies examining gut microbiome composition as a diagnostic or predictive biomarker (without intervention) were also eligible.

Comparator Placebo, standard antidepressant treatment alone, active comparators (other dietary/microbiome interventions), or no intervention. Observational studies without a formal comparator were included for the biomarker and population-specific domains.

Study designs to be included Clinical trials, observational studies, and interventional studies in humans. Editorials, letters, study protocols, narrative reviews, animal studies, and in vitro studies were excluded.

Eligibility criteria – Studies published between January 2022 and March 2025;
– Studies investigating psychobiotic interventions, including prebiotics, probiotics, synbiotics, herbal formulas, supplements, and dietary interventions, or fecal microbiota transplantation (FMT);
– Assessment of depressive symptomatology using validated scales such as Beck Depression Inventory (BDI), Patient Health Questionnaire-9 (PHQ-9), Montgomery-Asberg Depression Rating Scale (MADRS), Hospital Anxiety and Depression Scale (HADS);
– Clinical populations diagnosed with depression, subclinical symptoms, or at-risk groups (e.g., individuals under chronic stress);
– Original research articles providing empirical data (clinical trials, observational studies, randomized controlled trials);
– Full-text availability in English or Portuguese.

Information sources Three electronic databases were used to search and retrieve the articles: PubMed (including MEDLINE), Scopus, and PubPsych. Reference lists of relevant studies will also be screened to identify additional eligible publications.

Main outcome(s) Improvement in depressive symptoms assessed using validated clinical scales, including the Hamilton Depression Rating Scale (HAMD), Beck Depression Inventory (BDI), Montgomery–Åsberg Depression Rating Scale (MADRS), Hospital Anxiety and Depression Scale (HADS), and Patient Health Questionnaire (PHQ-9), or equivalent standardized instruments.

Data management Records retrieved from PubMed, Scopus, and PubPsych were exported as Research Information System (RIS) files and imported into Rayyan®, a web-based systematic review platform. Rayyan® was used to manage the screening process, including duplicate detection and blinded title and abstract screening by three independent reviewers. Discrepancies were resolved through consensus discussion. Full-text articles meeting eligibility criteria were retrieved and assessed independently.

Data from included studies were extracted into a structured Microsoft Excel spreadsheet using a standardized data extraction form. Extracted variables included study title, authors, year of publication, study design, objectives, population characteristics, intervention type, microbiome assessment methods, depression assessment tools, and main findings. A second reviewer verified the extracted data for accuracy and completeness.

All data were stored securely and backed up to ensure data integrity. Missing or unclear data were addressed by consulting the original articles, and, where necessary, by contacting study authors.

No additional data management software beyond Rayyan® and Microsoft Excel was used. During manuscript preparation, ChatGPT (OpenAI) was used as a support tool for text organisation, language refinement, and synthesis of scientific literature. All generated content was critically reviewed and approved by the authors, who assume full responsibility for the integrity and accuracy of the reported data.

Quality assessment / Risk of bias analysis Methodological quality and risk of bias were assessed independently by two reviewers. The Cochrane Risk of Bias Assessment tool was used for randomized controlled trials and the Newcastle-Ottawa Scale for observational studies. Disagreements were resolved by consensus.

Strategy of data synthesis Given the substantial methodological heterogeneity among the included studies—encompassing diverse study designs, populations, intervention protocols, microbiome assessment methods, and depression outcome measures—a quantitative synthesis (meta-analysis) was not performed. The data were synthesized narratively following a structured thematic approach.
The included studies were grouped according to four predefined analytical domains: (1) psychobiotic interventions, including prebiotics, probiotics, synbiotics, plant-based formulas, dietary interventions, and fecal microbiota transplantation; (2) gut microbiome as a diagnostic biomarker and marker of symptom severity; (3) gut microbiome as a predictor of response to antidepressant treatment; and (4) biopsychosocial-microbiome interactions in specific clinical populations. Within each domain, the studies were further organized by type of intervention or population subgroup, and the results were compared between studies that shared relevant characteristics.
The main characteristics and results of the included studies were summarized in structured comparative tables. The narrative synthesis was performed by identifying patterns of consistency and divergence among the studies, with particular attention to the direction of effects, the reproducibility of microbial signatures, and population-specific moderators in the relationship between microbiome and depression.

Subgroup analysis No formal subgroup analysis was pre-specified or conducted. However, within the narrative synthesis, findings were systematically examined across clinically relevant subgroups defined by shared characteristics, including: (1) type of psychobiotic intervention (prebiotics, probiotics, synbiotics, herbal formulas, supplements, and dietary interventions, and fecal microbiota transplantation); (2) depression severity and clinical subtype; (3) specific clinical populations; and (4) microbiome assessment methodology. These groupings were predefined in the review protocol and guided the thematic organisation of the narrative synthesis and comparative tables. Formal statistical subgroup analyses were not applicable given the absence of meta-analysis.

Sensitivity analysis Formal quantitative sensitivity analyses were not conducted due to the anticipated heterogeneity in study design, populations, interventions, and microbiome assessment methods, which precluded meta-analysis. However, the robustness of the narrative synthesis was explored qualitatively by considering methodological quality, study design, sample size, and population characteristics. Where appropriate, the influence of studies at higher risk of bias or involving specific clinical populations was examined across the analytical domains. This approach was consistent with the exploratory and integrative nature of the review and aimed to ensure the reliability and interpretability of the findings.

Language restriction English and Portuguese.

Country(ies) involved Portugal.

Keywords Major depressive disorder; Depression; Microbiome-gut-brain axis; Gastrointestinal microbiome; Psychobiotics; Prebiotics; Probiotics; Synbiotics; Fecal microbiota transplantation; Microbiome biomarkers; Treatment response.

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