PRINCIPLES AND PRACTICE OF CLINICAL RESEARCH
A Global Journal of Clinical Research

The Benefits of Probiotics on Depression: A Systematic Mini-Review

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Abstract

Introduction: *Evidence from randomized controlled trials investigating the effects of probiotics on depression published in the last four years has not yet been synthesized. The current systematic mini-review aimed to summarize the impact of probiotics in adults diagnosed with major depression with mild, moderate, or severe symptoms using studies published after May 2018.*

Methods: *A systematic literature search was conducted in PubMed, Web of Science, and Embase databases to identify randomized controlled trials that investigated the effect of any strain of probiotics alone or as an add-on therapy for the treatment of adult patients with mild, moderate, or severe symptoms of major depression and without other neurological and/or psychiatric disorders, published between May 2018 and August 2022. Data were extracted and qualitatively reviewed to determine the treatment effect. In addition, the quality of the methodology and risk of bias was assessed using the Cochrane risk-of-bias tool (RoB 2).*

Results: *Five studies met the inclusion criteria. All were randomized, parallel-group, placebo-controlled, double-anonymized trials with probiotics administered as an add-on therapy for treating mild and moderate symptoms of major depression only. In total, 303 patients (18–65 years) were randomized and treated with probiotics for 1–3 months. Four studies showed positive treatment effects, while one showed no difference between groups.*

Discussion: *There is encouraging evidence showing the potential beneficial effect of probiotics as an add-on treatment for patients with major depression with mild-to-moderate symptoms. However, future phase III trials are required to corroborate these results.*

Introduction

Major depression is a heterogeneous disorder characterized by persistent low or depressed mood or disinterest in pleasurable activities, in addition to feelings of guilt or worthlessness, fatigue, poor concentration, appetite changes, psychomotor impairment, sleep disturbances, or suicidal thoughts which severely reduce the quality of life (Gutierrez-Rojas et al., 2020; Otte et al., 2016) and is a significant risk factor for suicide (Moitra et al., 2021). The severity of major depression has been associated with short-term treatment outcomes, probability of recovery, and treatment response. The Diagnostic and Statistical Manual of Mental Disorders (DSM) (currently the DSM-V) categorizes the severity of major depression

*Corresponding author: rosario.caruso@unimi.it
Received: December 6, 2022 **Accepted:** March 29, 2023
Published: July 10, 2023
Editor: Felipe Fregni **Reviewers:** Monia Alcantara, Cecilia Sousa, Justyna Garnier, Frans Serpa, Marcio Kawano
Keywords: add-on, depression, probiotics, randomized controlled trial, a systematic review
DOI: http://dx.doi.org/10.21801/ppcrj.2023.91.6

into mild, moderate, or severe strata based on the aggregate of criteria symptoms, the intensity of the symptoms, and the level of functional disability and distress (Kendler, 2016).

The recent COVID-19 pandemic has led to a dramatic, widespread surge (27.6%) in depression globally. It remains the leading cause of disability worldwide, with 2,471 cases per 100,000 people, causing enormous individual and societal health-related burdens (Santomauro et al., 2021). Treatment options often include psychological or interpersonal therapies in conjunction with antidepressant pharmacotherapies. Despite ongoing treatment, approximately 60% of patients experience some depression symptoms (Nikolova, 2021). Many patients are concerned about medication-related side effects such as withdrawal, sexual dysfunction, weight gain, and feeling 'emotionally numb' (Cartwright, 2016) and have difficulties adapting to treatment (Berlim et al., 2007). The refractory nature of depression points to its clinical and etiological heterogeneity (Hasler, 2010).

Probiotics are living microorganisms that reconstitute the gastrointestinal barrier. Their potential therapeutic applications for treating psychiatric disorders have been tentatively explored in pre-clinical and clinical proof-of-concept studies (Schaub et al., 2022; Suneson et al., 2021). Probiotics may enhance standard therapies for treating depressive disorders by modulating neurotransmitters, proteins (Tian et al., 2022; Majeed et al., 2018), hormones, neuropeptides, short-chain fatty acids, and anti-inflammatory substances (Majeed et al., 2018). An advantage of probiotics is the low cost and accessibility of treatment, which may promote utilization in clinical practice and optimize the treatment of depression. As early as the intrauterine period, gut microbiota may critically influence multiple neurochemical and immunomodulatory pathways. Microbiota-gut-brain axis dysregulation is associated with gastrointestinal, metabolic, and neuropsychiatric disorders (Cheng et al., 2019). Many microbiota-based approaches are being investigated to elucidate and treat the etiopathogenesis of neuropsychiatric diseases, including depression (Evrensel, 2020).

Nikolova and colleagues (2019) performed an informative but relatively small systematic review and meta-analysis (three studies with a total equal to n=229), including studies on the effect of probiotics on depression and/or depressive symptoms, published before May 2018. Although they found that probiotics had a favorable impact on depression symptoms, considerable heterogeneity was observed. The authors claimed "limited evidence for the efficacy of probiotics in depression" at the time of their report and called for further research in the field (Nikolova et al., 2019). Indeed, since their publication, interest in the intervention of probiotics on depression through the gut-brain axis has continued to gain momentum within the scientific community (Skowron et al., 2022). Thus, an exploration of the expanding literature in the field may be helpful to clinicians and researchers. Using studies published after May 2018, the current systematic mini-review sought to qualitatively summarize the effect of probiotics (any strain) versus any comparator on depressive symptoms in adults diagnosed with major depression and without neurological and psychiatric disorders.

Materials and Methods

The research question was developed following the systematic review and meta-analysis by Nikolova et al. (2019) and followed the same population, intervention, comparison, outcomes, and study (PICOS) framework (Amir-Behghadami & Janati, 2020). The primary research question was: "What is the evidence from the last five years showing the efficacy of probiotics in treating major depression in the general adult population?"

The protocol guiding this study shows the PICOS, medical subject headings terms, main concepts retained by each stratum, and search strategy (Caruso et al., 2022). In addition to the PubMed and Web of Science databases used in the reference study (Nikolova et al., 2019), we also searched the Embase database to extend our search results.

The inclusion criteria were as follows: the population was adults with diagnosed major depression and without neurological and psychiatric disorders; the intervention was the use of probiotics (any strain) as an add-on or stand-alone therapy; the comparator was placebo or other treatment; the outcome was an improvement of depressive symptoms; and the study design was randomized controlled trials (RCTs) published between May 2018 and August 2022.

To keep the focus of the literature review on the population diagnosed with major depression and to avoid including studies with additional conditions, such as psychiatric disorders, that require in-depth and further analysis, studies that included subjects with neurological disorders or other psychiatric conditions were excluded. Other exclusion criteria included the following: animal studies, case reports, nonprimary research with experimental design, and a lack of focus on major depression.

The search strategy developed the queries for each stratum of the PICOS, combining strata with the Boolean operator AND. The leading Medical Subject Heading (MeSH) terms used for the population were "adult" and "depression," which were searched with a broad combination of synonyms entered as text

words using the Boolean operator OR. The primary MeSH term for the intervention was "probiotics," to which 24 additional MeSH indicating the available strains were added by employing the Boolean operator OR. As no specific comparisons were identified, we did not develop a specific query for this stratum to enhance the sensitivity of the final query. Instead, the stratum of the outcome was searched by including the MeSH term "depressive disorder, major" and synonyms were added by employing the operator OR. Finally, the clinical query search tool available in the PubMed repository was used to identify RCTs. The final query was adapted from PubMed to the other searched databases.

We used the PRISMA 2020 flow diagram to guide a four-step approach for selecting articles (Page et al., 2021), as demonstrated in Figure 1. First, study selection was performed using Mendeley and Rayyan, a web-based app for systematic reviews (Ouzzani et al., 2016).

We screened the titles and abstracts of the remaining 108 studies; 85 articles were further excluded because the study design was not an RCT or the intervention was not a probiotic, and 25 were excluded due to lack of focus on major depression. In addition, eight full-text studies were retrieved to evaluate their eligibility, and a further three studies were excluded: one had an outcome different from depression, one had a nonprimary study design, and one did not include patients diagnosed with major depression as the study population. Finally, there were five studies included for review.

At least two independent researchers performed all the steps in this study. First, we extracted pertinent information using a data extraction tool adapted from the Cochrane data collection form (Appendix 1) (Sambunjak et al., 2017). We assessed the quality of the methodology employed and the risk of bias in each of the included articles using the Cochrane recommendations RoB version 2 (RoB 2; Higgins & Cochrane Collaboration, 2020). For each study, the magnitude of the effect of probiotics on depression compared to the control was summarized using Cohen's d coefficient.

Results

Among the 303 patients (18–65 years) included in the five studies, 217 were female (71.62%). Although we intended to include patients with major depression with mild, moderate, or severe symptoms, our search yielded studies that included only those with mild and moderate symptoms. All studies used probiotics as an add-on therapy. Each study tested different strains of probiotics. Two studies investigated single strains of probiotics (Bifidobacterium breve

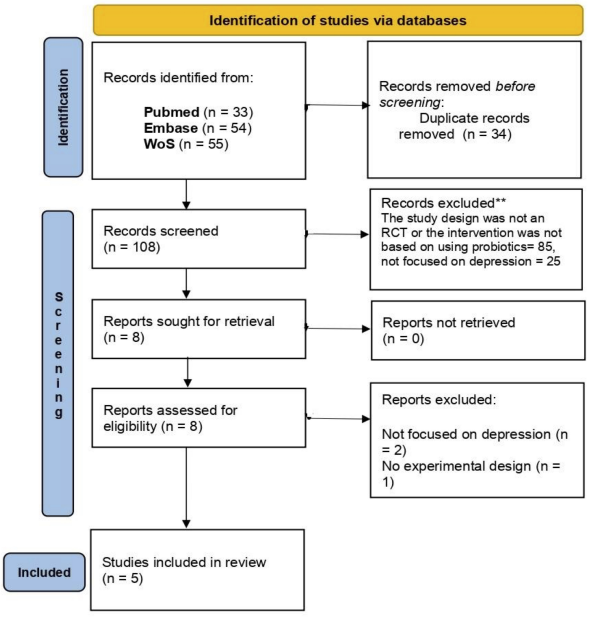

Figure 1: *Study selection flowchart.*

CCFM1025 and Bacillus coagulans MTCC 5856) (Majeed et al., 2018; Tian et al., 2022), and three studies investigated the effect of a blend of probiotics (Kazemi et al., 2019; Reininghaus et al., 2020; Schaub et al., 2022). All the blends had at least one strain of Lactobacillus and one strain of Bifidobacterium.

Patients taking probiotics reported significant improvement in depressive symptoms over the follow-up (1–3 months) compared to the placebo groups in four studies (Kazemi et al., 2019; Schaub et al., 2022; Tian et al., 2022; Majeed et al., 2018). At the last follow-up, within-subject improvement was shown in both groups, but the improvement was significantly more significant in the experimental arms. One study reported no significant difference between groups (Reininghaus et al., 2020).

All the RCTs had Level-1 evidence (meaning they included three or more 'good quality' RCTs with similar results) (Wright et al., 2003). Table 1A displays the characteristics of the included studies. To quantify symptoms of depression, two studies (Schaub et al., 2022; Tian et al., 2022) used the Hamilton Depression (HAMD) scale alone, and one (Kazemi et al., 2019) used the Beck Depression Inventory (BDI) alone. One study (Reininghaus et al., 2020) used both the HAMD and BDI and other scales, and one study (Majeed et al., 2018) used the HAMD and multiple other scales. Because various tools were used to assess depression symptoms (Table 1B), we estimated the magnitude of the effects using Cohen's d. The effects of probiotics were significant in three studies: Cohen's d coefficients were respectively 1.54 ($p < .001$), 1.17 ($p < .001$), and

	Reference	Country	Sample (sex)	Age	Probiotics (strains)
1	Reininghaus et al., 2020	Austria	Total: n=61 Probiotics: n=28 (20 females) Placebo: n=33 (27 females)	Probiotics: 43.0 ±14.31 Placebo: 40.1 ± 11.45	OMNi-BiOTiC® Stress Repair (*Bifidobacterium bifidum* W23, *Bifidobacterium* lactisW51, *Bifidobacterium* lactis W52, *Lactobacillus acidophilus* W22, *Lactobacillus* casei W56, *Lactobacillus*. paracasei W20, *Lactobacillus* plantarum W62, *Lactobacillus*. salivarius W24 and *Lactobacillus lactis* W19) + 125 mg D-Biotin (vitamin B7), 30 mg of common horsetail, 30 mg of fish collagen and 30 mg of keratin
2	Kazemi et al., 2019	Iran	Total: n=110 Probiotic: n=38 (27 females) Prebiotic: n=36 (29 females) Placebo: n=36 (23 females)	Probiotics: 36.1 ± 7.86 Prebiotics: 37.4 ± 7.9 Placebo: 36 ± 8.5	Probiotic: *Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175 (CNCM strain I-3470) bacteria Prebiotic: Galactooligosaccharide and 0.2% Plum flavor
3	Schaub et al., 2022	Switzerland	Total: n=47 (27 females) Probiotics: n=21 (14 females) Placebo: n=26 (13 females)	Probiotics: 39.4 ± 11.45 Placebo: 38.8 ± 10.3	Probiotic supplement (Vivomixx®): Streptococcus thermophilus NCIMB 30438, *Bifidobacterium breve* NCIMB 30441, *Bifidobacterium longum* NCIMB 30435 (Re-classified as *Bifidobacterium lactis*), *Bifidobacterium infantis* NCIMB 30436 (Re-classified as *Bifidobacterium lactis*), *Lactobacillus acidophilus* NCIMB 30442, *Lactobacillus plantarum* NCIMB 30437, *Lactobacillus paracasei* NCIMB 30439, *Lactobacillus delbrueckii* subsp. Bulgaricus NCIMB 30440 (Re-classified as *Lactobacillus helveticus*)
4	Tian et al., 2022	China	Total: n=45 Probiotics: n=20 (14 females) Placebo: n=25 (16 females)	Probiotics: 51.32 ± 16.11 Placebo: 48.15 ± 13.96	*Bifidobacterium breve* CCFM1025 powder
5	Majeed et al., 2018	India	Total: n=40 Probiotics: n= 20 (17 females) Placebo: n=20 (17 females)	Probiotics: 40.36 ± 10.28 Placebo: 43.88 ± 9.85	*Bacillus coagulans* MTCC 5856

	Reference	Study Design	Treatment and Follow-up	Main Findings
1	Reininghaus et al., 2020	Randomized, double-blind, placebo-controlled trial	Add-on therapy 1-month follow-up	Both probiotic-treated and control groups showed improvement in depression symptoms over time (HAMD, BDI-II, MSS, GSI, and PSDI). There were no significant differences between groups.
2	Kazemi et al., 2019	Randomized, double-blind, placebo-controlled trial	Add-on therapy 2-month follow-up	Probiotics decreased depressive symptoms (BDI) when compared to placebo. The change in the prebiotic group was not significant when compared to placebo or to probiotics.
3	Schaub et al., 2022	Randomized, placebo-controlled trial	Add-on therapy 2-month follow-up	Probiotic-treated group showed decreased depressive symptoms (HAMD) along with changes in the gut microbiota and brain, compared to the control group
4	Tian et al., 2022	Randomized, double-blind, placebo-controlled trial	Add-on therapy, 1-month follow-up	Probiotics showed a better antidepressant-like effect than placebo, based on the HAMD.
5	Majeed et al., 2018	Randomized, multi-center, double-blind, placebo-controlled trial	Add-on therapy, 3-month follow-up	*Bacillus coagulans* showed robust efficacy for major depressive disorder, measured by HAMD, MADRS, and CES-D in patients with Irritable Bowel Syndrome.

BDI, Beck Depression Inventory; BDI-II, Beck Depression Inventory version II; CES-D, Center for Epidemiological Studies Depression Scale; GSI, Global Symptom Index; HAMD, Hamilton Depression Scale; MADRS, Montgomery-Asberg Depression Rating Scale; MSS, Mania Self Rating Scale; PSDI, Positive Symptom Distress Index; PST, Positive Symptom Total

Table 1: *1A.Characteristics of included studies; 1B.Efficacy of probiotics for depression.*

0.94 (p =.005) in the RCTs reported by Kazemi et al. (2019), Schaub et al. (2022) and Majeed et al. (2018). The effects were moderate (Cohen's d = 0.64; p =.036) in the study reported by Tian et al. (2022). One study reported significant treatment effects in placebo and probiotic groups in 28 days (Reininghaus et al., 2020).

Risk of Bias Assessment

Figure 2. shows the assessment of the risk of bias. Based on the RoB 2 criteria (Higgins & Cochrane Collaboration, 2020), two studies were classified as having a low risk of bias (Kazemi et al., 2019; Majeed et al., 2018), whereas one study was classified as having a high risk of bias (Schaub et al., 2022). The remaining two studies were classified as having 'some concerns' owing to deviations from the intended interventions (Reininghaus et al., 2020) and possible bias due to missing data (Tian et al., 2022).

Discussion

This systematic mini-review investigated the effect of probiotics on depression by summarizing the results of RCTs investigating probiotics for the treatment of depression, published between May 2018 and September 2022. The current study focused on a population with significant depression without other neurological or psychiatric conditions. For this reason, despite the publication of more recent systematic reviews on broader people in 2021 (Nikolova et al., 2021), we selected the study by Nikolova et al. (2019) as the launch point for our review because it included our specific population of interest. Also, restricting the period to only studies published from 2021 to 2022 is unlikely to depict the current state of the evidence accurately. Therefore, we decided to conduct the literature search from the publication date of the last primary study included in the Nikolova et al. (2019) systematic review (May 2018).

Five studies were included in the review with a combined sample size of 303 patients. All five studies investigated the use of probiotics as an add-on therapy. Each study had a limited sample size (40–110 patients) and a short follow-up period (1–3 months). Four of these studies (Kazemi et al., 2019; Schaub et al., 2022; Tian et al., 2022; Majeed et al., 2018) reported positive findings. The effect magnitudes ranged from moderate (Tian et al., 2022) to large (Kazemi et al., 2019; Schaub et al., 2022; Majeed et al., 2018).

Collectively, five different depression scales were used to measure depression. Three studies used a single scale (Kazemi et al., 2019; Schaub et al., 2022; Tian et al., 2022), and two used multiple scales (Majeed et al., 2018; Reininghaus et al., 2020). The most frequently used scale was the HAMD, used by four studies. The use of different measurement scales may have led to statistical heterogeneity, primarily caused by the diverse psychometric performance of the tools and, therefore, additional reliability in the outcome measurements.

Before 2018, some RCTs investigated probiotics as a stand-alone treatment for depression (Nikolova et al., 2019). However, all studies in the current review investigated probiotics as an add-on therapy to standard antidepressant treatment. We hypothesize that this reflects safety and ethical concerns about denying participants with diagnosed depression access to standard treatment.

Four studies (Kazemi et al., 2019; Schaub et al., 2022; Tian et al., 2022; Majeed et al., 2018) demonstrated reduced depression scores in patients treated with probiotics to placebo. These findings mirror the distinct trend favoring probiotics in treating psychological disorders reported by earlier studies. El Dib et al. (2021) conducted a systematic review and meta-analysis focusing on probiotics for treating depression and anxiety. Hofmeister et al. (2021) performed a large meta-analysis of the effects of all interventions targeting the gut microbiota. Both studies reported positive treatment effects in subgroup analyses targeting probiotics in depressed patients.

We believe that the non-significant findings of this study are probably due to heterogeneous study methodology rather than different treatment effects. One study reported improvements in probiotic and control groups, showing no significant difference between group comparisons (Reininghaus et al., 2020). This study was conducted on a sample of newly hospitalized patients with depression. There are several potential reasons for their non-significant results, including (a) limited power to detect effects in newly hospitalized patients, (b) short follow-up period (1 month), which may have been unable to detect add-on effects, (c) sudden change to hospital diet, (d) possible interactions with co-administered biotin and other nutrients, and (e) baseline differences in nutrition and smoking status between groups. There is also a possibility of Berkson's bias because patients were sampled from new hospital admissions rather than the community.

This review has some limitations. Our results provide an overall picture of the efficacy of probiotics in the population with mild-to-moderate levels of depression, but they should be interpreted cautiously. First, we included only RCTs published in the last four years, which limits generalizability. In this review, we intended to include patients with mild, moderate, and severe symptoms of major depression. However, we did not find studies including

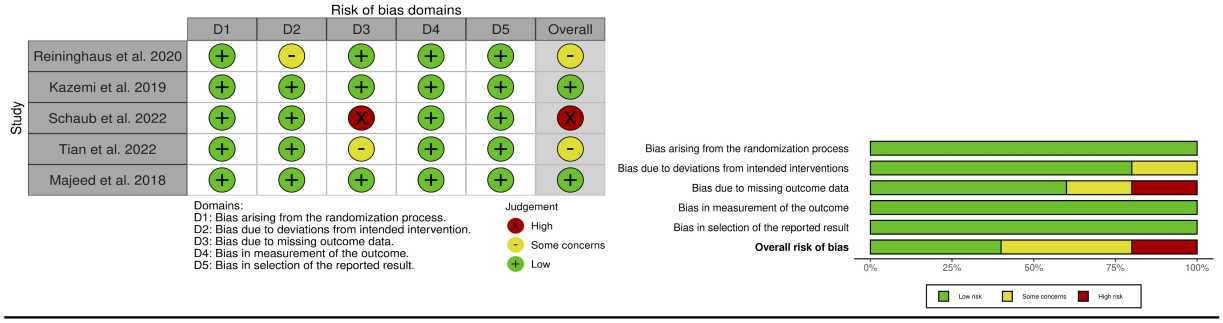

Figure 2: *Assessment of risk of bias of each study using the RoB version 2. (A) Graphical of risk of bias and (B) summary of the risk of bias.*

patients with severe depression symptoms, and thus, the full spectrum of the disorder is not represented in the study population. Even combined, the studies had a relatively small sample size, which also decreases the generalizability of this review. It was also noted that all studies had short follow-up periods, which may limit the likelihood of probiotics reducing symptoms of depression. The concentration and strains of probiotics used in each study differed, which may have introduced treatment heterogeneity and limited the internal validity of the included studies and this review. Furthermore, probiotics were added to a diversity of antidepressants which may have led to population heterogeneity. Finally, we cannot exclude the risk of publication bias because it is likely that studies with negative results have not been published.

The findings of the current review pave the way for future meta-regressions that will provide effect estimates of probiotics in treating specific subgroups of patients stratified by depression severity, age, comorbidities, anxiety levels, and others. In addition, studies should include categorical moderators such as the class of antidepressant and specific probiotic strains, blends, and concentrations.

An exciting advantage of probiotics is the low cost and accessibility of treatment, which may facilitate broad utilization in clinical practice and optimize the treatment of depression worldwide. However, the role of probiotics in mitigating depressive symptoms requires phase III research to clarify their effects and allow researchers to develop evidence-based clinical guidelines and inform clinical decision-making.

Conclusions

RCTs published in the last four years support the argument that probiotics used as an add-on treatment may positively affect patients with mild-to-moderate symptoms of major depression. Future phase III studies are needed to corroborate these results and facilitate the development of evidence-based clinical guidelines. Given the limited sample sizes, the risk of bias, and the short-term follow-up periods of the current evidence, discretion is advised when using probiotics to treat patients with major depression.

Author Contributions

All authors contributed to the conceptualization, study design, search strategy development, writing, reviewing, and editing of the manuscript. Arturo Tamayo oversaw the project. Rosario Caruso and Karen Fernandes developed the initial protocol, and Aimee Mercado, Ibrahim Radi, Mariana Checo, and Rosario Caruso performed protocol revision and registry. Angelica Jaldin, Jose Chamba, Celso Vespasiano, and Lauren Nirta performed the literature search and study selection. Lilia Oliveira, Prakrity Urja, Takuro Nishizawa, and Joyce Meza performed data extraction. Giovani Farina, Ibrahim Mohamed, Karen Fernandes, and Naira Link performed the qualitative review of data and risk of bias assessment.

Funding

This research received no external funding.

Data Availability Statement

The authors confirm that the data supporting the findings of this systematic mini-review are available within the article.

Conflicts of Interest

The authors declare no conflict of interest.

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