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The Effects of Probiotic Supplementation on Depressive Symptoms: A Systematic Review

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Abstract

Major depressive disorder (MDD) is a common life-disrupting, highly recurrent mental disorder that is a leading source of disability worldwide. The connection between the gut-brain axis as it relates to neurological function, specifically depression, has increasingly become a topic of interest. Recent studies have confirmed that the microbial composition in MDD patients differs from that of non-depressed individuals. For the purpose of this review, probiotics are defined as "live microorganisms which when administered in adequate amounts confer a health benefit on the host." The beneficial effects not only localize in the gut but reach the whole microbiota-gut-brain axis. The purpose of this review was to evaluate randomized controlled trials (RCTs) assessing the effects of probiotic supplementation on depressive symptoms and depressive mood in healthy and clinically diagnosed patients. Specifically, to evaluate the hypothesis that probiotic supplementation in humans will lead to reduced depressive symptoms and a reduction in depressive mood occurrences. A systematic literature search was carried out using PubMed and MEDLINE databases. Of the final 4 RCTs selected, 2 evaluated the effect of probiotic supplementation on depressive symptoms or mood in healthy adults and 2 evaluated depressive symptoms or mood in clinical diagnosed samples (diagnosis of major depressive disorder). In each of the studies, the probiotic species administered were from Lactobacillus or Bifidobacterium strains (single strain and multi-strain). Results of these studies showed strong statistical significance for reductions in depressive symptoms across all 4 RCTs included. Additional research and increased sample size are required to confirm further and enhance the understanding of probiotic use to treat and prevent depression.

Keywords

Microbiome, Probiotic, Major Depressive Disorder, Gut-Brain Axis, Systematic Review

1. Introduction

Major depressive disorder is a common life-disrupting, highly recurrent mental disorder that is a leading source of disability worldwide, affecting approximately 21% of the global population, or 1 in 4 people [1-4]. Large genome-wide association studies projected the chances of heritability to be 37% to 48% for major depressive disorder [5-6]. This disorder presents with low mood, low self-esteem, and loss of interest in typically enjoyable activities [2]. Depression is a multifactorial disease mostly associated with genetic, biological, environmental, and social factors [2, 7]. According to current psychology and biology concepts, depression is not just a mental disorder but also a physiological disease. It has clear biological foundations, such as brain changes including unbalanced neurotransmitters, impaired neurogenesis, neuroplasticity decline, and abnormal neuronal circuitry [8-9].

The connection between the gut-brain axis as it relates to neurological function, specifically depression, has increasingly become a topic of interest. The gut-brain axis is a bidirectional communication system that not only provides GI homeostasis but can also affect motivation as well as higher cognitive functions [10]. The gastrointestinal tract is the largest organ in mammals, secreting dozens of different signaling molecules, including peptides. Gut peptides in the systemic circulation can bind cognate receptors on immune

cells and vagus nerve terminals enabling indirect gut-brain communication [11]. Evidence suggests that gut microbiota play an important role in central nervous system function through inflammation, the hypothalamic-pituitary-adrenal (HPA) axis or interference with neurotransmitter signaling [1, 12]. Recent studies suggest that the gut-brain axis may impact mood and behavior in various ways. Increased bacterial translocation in mood disorders, such as depression, has been demonstrated in some human studies [1]. These pathogenic bacteria influence the disease by interacting with the vagus nerve, directly changing the function of the central nervous system, affecting the intestinal nervous system, changing the plasticity of the brain, and activating the immune system [12-15].

The term microbiome refers to all microorganisms and their genetic material living in the body, and the term microbiota refers to populations of microorganisms present in the body's various ecosystems [16]. The gut microbiota is referred to as a "hidden organ" in the body and may be related to the pathogenesis of numerous diseases, such as cardiovascular disease, diabetes, and obesity [3]. The human gastrointestinal system hosts approximately 1,800 different phyla and 40,000 bacterial species, collectively known as microbiota [17]. Microbiota impact how humans think, perceive and experience the world [18]. The gut microbiota can also play a critical role in supporting homeostasis in health, immune function, nutrient processing, and other aspects of host physiology [12, 19-22]. Gut microbiota composition and function are influenced by genetics, age, sex, diet, life experiences, antibiotic use, chronic stress, and many other factors and must act as potential biomarkers of the gut-brain axis that could be used in psychiatry and co-morbid conditions [23-25]. Microorganisms living in the gut are in contact with epithelial and immune system cells and are involved in the development of numerous neuropsychiatric and metabolic disorders, particularly autoimmune diseases [26].

Recent studies have confirmed that the microbial composition in MDD patients differs from that of non-depressed individuals. Analysis of fecal samples from MDD patients found a weak negative correlation between the amount of *Faecalibacterium* present and the severity of depressive symptoms experienced, and that the MDD patients had increased levels of Enterobacteriacaea and *Alistipes* but reduced levels of *Faecalibacterium* [17]. A variety of approaches have been used to study the effect of the microbiota on brain function, including antibiotic use, probiotic treatments, fecal microbiota transplantation, gastrointestinal infection studies, and germ-free studies [27].

Despite the fact that antidepressant medication is widely used to treat depressive symptoms, 30-40% of patients do not respond to current drug strategies [1]. Traditional treatment of major depressive disorder targets the brain through different drugs and psychotherapy. A large percentage of patients never receive any treatment at all [28]. For the purpose of this review, probiotics are defined as "live microorganisms which when administered in adequate amounts confer a health benefit on the host" [29]. The beneficial effects of probiotics not only reside in the gut but reach the whole microbiota-gut-brain axis; researchers call these probiotics "psychobiotics" to emphasize their capabilities to improve behavior and mind [19]. The term "psychobiotics" was initially used by Dinan and colleagues and denotes a live organism that produces health benefits in patients suffering from a psychiatric illness [27]. Research has shown that psychobiotic supplementation reduces depressive symptoms and achieves similar effects to traditional antidepressant treatments. The purpose of this review was to evaluate randomized controlled trials (RCTs) assessing the effects of probiotic supplementation on depressive symptoms and depressive mood in healthy and clinically diagnosed patients. Specifically, to evaluate the hypothesis that probiotic supplementation in humans will lead to reduced depressive symptoms and a reduction in depressive mood occurrences.

2. Methods

2.1. Search Strategy, Eligibility, and Inclusion/Exclusion Criteria

A systematic literature search was carried out using PubMed and MEDLINE databases. Search teams included probiotic supplementation* OR microbiota* OR gut-brain axis* AND depression* OR depressive symptoms*. Studies included in this review were of English language, peer-reviewed, and RCTs assessing the impact that probiotic supplementation has on depressive symptoms and depressive mood in healthy and clinical adult samples (age 20-60). Search results were evaluated for potentially relevant trials, and full-text versions of the studies were obtained and chosen for inclusion, which is outlined in Table 1. This review follows PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) guidelines for conducting systemic reviews and meta-analysis [30].

Participants with pre-existing health conditions were excluded from all studies. These health conditions consisted of chronic kidney disease [31-32], lung disease [31], chronic or acute inflammatory disease [31], hepatic [31-32] and thyroid disease [31], severe intestinal disease [31], cardiovascular disease [32-33], respiratory disease [32], and peptic ulcers [31]. Those using insulin [31], vitamin supplements [31], other nutritional supplements [31-32], antibiotics [31-32], and those who had used probiotics within the last 2 months before the study [32-33] were also excluded, as well as those who are pregnant [31-33] or lactating [32-33] and those with allergies [31], though types of allergies were not specified. Those who smoke cigarettes or use tobacco [32], those who use alcohol [32], or those with a past or current substance abuse issue [32-33] were also excluded in some studies. One study [32] also excluded anyone following a specific diet, those who made any significant diet or lifestyle changes before the study, or anyone participating in a different study within the 2 months before the study.

2.2. Data Extraction and Study Selection

Relevant information was obtained from the selected studies. This information included target population, age range, gender, probiotic source, probiotic strain, probiotic dose, and specific outcomes such as depressive symptoms. Informed consent was obtained from all individual participants included in all studies.

The Leiden Index of Depression Sensitivity – Revised (LEIDS-r) is a self-report questionnaire with 34 items, which assesses the extent to which dysfunctional thoughts are activated when experiencing mild dysphoria. LEIDS-r scores have been used in the past to predict depression. The Beck Depression Inventory II (BDI-II) is a 21-item multiple-choice self-report questionnaire that assesses the existence and severity of current depression symptoms that have occurred within the last 2 weeks. The General Health Questionnaire (GHQ) comprises 28-items consisting of four subscales; somatic symptoms, anxiety and insomnia, social dysfunction, and severe depression. The Depression Anxiety and Stress Scale (DASS) questionnaires comprise three 14-item self-report scales that measure depression, anxiety, and stress.

3. Results

3.1. Study Selection & Study Characteristics

Search results, as shown in Figure 1, resulted in a total of 82 citations across all databases used. 6 studies were removed for duplicates and 68 were excluded based on thorough review of title and abstract, leaving 8 for further analysis. Of the final 4 RCTs selected, 2 evaluated the effect of probiotic supplementation on depressive symptoms or mood in healthy adults [31, 34] and 2 evaluated depressive symptoms or mood in clinical diagnosed samples (diagnosis of major depressive disorder) [32-33]. In each of the studies, the probiotic species administered were from Lactobacillus or Bifidobacterium strains (single strain and multi-strain). (See Table 1 for specific strains). 2 RCTs [32-33] also reported assessments of relevant physiological indicators along with assessments of depressive symptoms. All evaluations of mood were conducted through self-report measures that are frequently referenced in the literature.

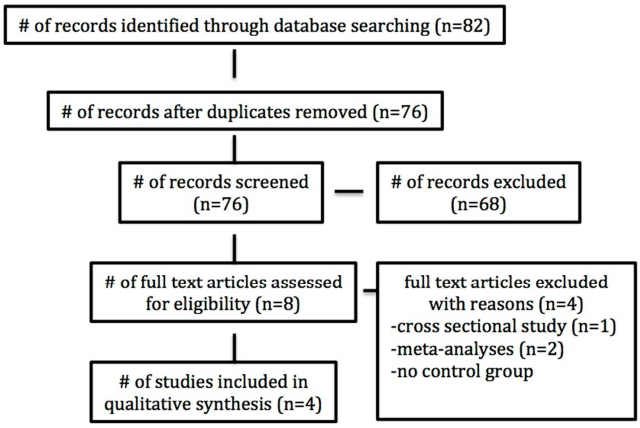

Figure 1. *PRISMA Flow Chart.*

Table 1. *Characteristics of Selected Trials Included in this Review.*

Author, year	Sample (age range)	No. of participants (completed)	Intervention (weeks)	Comparison	Bacterial species and daily dose (CFU)	Mood-related results
Akkasheh G, 2015	Major depressive disorder patients (20-55)	40 (37)	Capsule (8)	Placebo	L. acidophilus, L. casei, B. bifidum (6 x 10^9)	Statistically significant reductions in mean BDI post-intervention compared to the placebo group.
Kazemi A, 2017	Major depressive disorder (18-50)	110 (81)	Powder (8)	Placebo	L. helveticus, B. longum (>10 x 10^9)	Statistically significant reductions in mean BDI score post-intervention compared to the placebo group.
Mohammadi A, 2015	Healthy adults (20-60)	75 (70)	Yogurt or capsule (6)	Yogurt	Probiotic yogurt L. acidophilus LA5 B. lactis BB12 (1 x 10^7) Probiotic capsule L. casei, L. acidophilus, L. rhamnosus, L. bulgaricus, B. breve, B. longum, S. thermophiles	Statistically significant reductions in mean GHQ and DASS post-intervention compared to regular yogurt. No significant between-group differences as all experienced reduction in symptoms.
Steenbergen L, 2015	Healthy adults (NR)	40 (40)	Powder (4)	Placebo	B. bifidum W23, B. lactis W52, L. acidophilus W37, L. brevis W63, L. casei W56, L. salivarius W24, L. lactis (W19 and W58) (2.5 x 10^9)	Statistically significant reductions in mean total LEIDS-r post-intervention compared to placebo, but not BAI or BDI.

3.2. Quality Assessment and Risk of Bias

Potential bias was evaluated using the Cochrane Collaboration Tool for Assessing Bias (Table 2). Table 2 shows the risk of bias for the studies reviewed according to the Cochrane Collaboration Criteria.

Table 2. *Risk of Bias Assessment (Cochrane Risk of Bias Assessment Tool).*

	Akkasheh et al., 2015	**Kazemi et al., 2017**	**Mohammadi et al., 2015**	**Steenbergen et al., 2015**
Selection Bias (Random Sequence Generation)	Low	Low	Unclear	Low
Selection Bias (Allocation Concealment)	Low	Low	Unclear	Low
Performance and Detection Bias/Binding	Low	Low	Low	Low
Attrition Bias (Incomplete Outcome Data)	Low	Low	Low	Low
Reporting Bias (Selection Reporting)	Low	Low	Low	Low
Other Bias	Low	Low	Unclear	Unclear

3.3. Probiotic Supplementation and Depressive Symptoms in Healthy Adults

2 RCTs [31, 34] focused on the effects of probiotic supplementation on anxiety or depressive symptoms in healthy adults (see Table 1). All 4 of the studies reported benefits (reductions in depressive symptoms or mood post-intervention) of supplementation, but only 3 studies [32-34] demonstrated statistically significant reductions between probiotic treated and placebo control groups.

Mohammadi randomly assigned 70 adults for 6 weeks to 1 of 3 groups: (a) probiotic yogurt (PY) containing *Lactobacillus acidophilus LA5* and *Bifidobacterium lactis BB12* (1×10^7 CFU per day), and placebo capsule; (b) probiotic capsule (PC) containing a combination of *Lactobacillus casei* (3×10^3 CFU per gram), *Lactobacillus acidophilus* (3×10^7 CFU per gram), *Lactobacillus rhamnosus* (7×10^5 CFU per gram), *Lactobacillus bulgaricus* (5×10^8 CFU per gram), *Bifidobacterium breve* (2×10^{10} CFU per gram, *Bifidobacterium longum* (1×10^5 CFU per gram) and *Streptococcus thermophiles* (3×10^8 CFU per gram), and conventional yogurt, and (c) convention yogurt (CY) containing *Streptococcus thermophiles* and *Lactobacillus bulgaricus* starter cultures, and placebo capsule. While significant pre and post reductions in depressive symptoms were observed in the experimental probiotic groups (PC and PY), no significant between-group differences post-intervention were reported. All 3 groups had reductions in the mean scores on the General Health Questionnaire (GHQ) (-4.5 in PY, -7.1 in PC, -3.3 in CY) and the Depression Anxiety Stress Scale (DASS) (-10.3 in PY, -9.5 in PC, -6.7 in CY). A further review also revealed no significant differences in total bacterial counts between the PY and the CY groups.

Steenbergen utilized a Mini International Neuropsychiatric Interview (M.I.N.I.) to screen potential participants for potential neuropsychiatric disorders. Participants with no psychiatric or neurological disorders and no personal or family history of depression were considered appropriate to participate in the study. At the pre and post-intervention assessments, participants filled out questionnaires to assess cognitive reactivity to sad mood and questionnaires that assessed symptoms of depression. Steenbergen showed a significant post-intervention reduction between groups on the total Leiden Index of Depression Sensitivity (LEIDS-r) (-9.4 in the probiotic group vs -2.4 in placebo control, $P < .001$) after 4 weeks of receiving supplementation using a probiotic combination (5.0×10^9 CFU per day) containing *Bifidobacterium bifidum W23, Bifidobacterium lactis W52, Lactobacillus acidophilus W37, Lactobacillus brevis W63, Lactobacillus casei W56, Lactobacillus salivarius W24, and Lactobacillus lactis (W19 and W58).*

3.4. Probiotic Supplementation and Depressive Symptoms in Clinical Samples

Two RCTs [32-33] evaluated probiotic supplementation effects on depressive symptoms or depressive mood in clinical populations, specifically those clinically diagnosed with major depressive disorder.

Kazemi randomly assigned 110 clinically diagnosed (major depressive disorder) patients to 8 weeks of either a probiotic blend containing *Lactobacillus helveticus* and *Bifidobacterium longum* (10×10^9 CFU per 5 gram), a prebiotic (galactooligosaccharide) or placebo. In the end, 81 patients completed the trial successfully (28 in the probiotic group, 27 in the prebiotic group, 26 in the placebo group). Probiotic supplementation resulted in a significant decrease in BDI score (17.39-9.1) compared to placebo (18.18-15.55) and prebiotic (19.72-14.14) supplementation.

Akkasheh randomly assigned 40 clinically diagnosed (major depressive disorder) patients to 8 weeks of either a probiotic blend containing *Lactobacillus acidophilus* (2×10^9 CFU per gram), *Lactobacillus casei* (2×10^9 CFU per gram), and *Bifidobacterium bifidum* (2×10^9 CFU per gram) or placebo. A significant between-group difference in Beck Depression Inventory (BDI) in favor of the probiotic-treated group (-5.7 in probiotics vs. -1.5 in the placebo, $P = .001$) was reported.

3.5. Secondary Outcomes/Physiological Changes

3 RCTs [31-33] included physiological assessment in addition to the assessment of psychological symptoms. Mohammadi evaluated the effects of probiotic supplementation on serum neuropeptide Y, tryptophan, cortisol, and adrenocorticotropic hormone and reported no significant between-group differences [31]. Other secondary outcomes reported were a significant decrease in the kynurenine/tryptophan ratio [32], a significant decrease in serum insulin [33], and a significant rise in plasma glutathione (GSH) levels [33].

3.6. Adverse Impacts, Potential Dietary Medication Interactions, and Adherence

One trial [33] did not attempt to assess potential adverse

impacts from probiotic supplementation. However, when formally assessed, 3 studies [31, 33-34] reported no indications of adverse events resulting from supplementation. In one study [32], some participants who were receiving the probiotic reported adverse impacts; 2 participants reported having GI complaints, 1 participant reported nausea, 1 participant reported fever, 5 participants reported increase appetite, and 2 participants claimed worse mental state than before the study - however, this was ruled out as unrelated to study participation.

3 of the 4 studies [31-33] prohibited participants from consuming any probiotics, antibiotics, or other fermented products during participation. All trials also rejected participants with specific health conditions that could potentially influence study findings, as mentioned previously. These protocols limited the possibility for potential dietary or medication interactions. 3 trials formally assessed dietary habits using a 3-day dietary record [31-33] and reported no significant changes from baseline or differences between groups in dietary habits, macronutrient, or micronutrient composition.

Adherence to supplementation regimens was monitored and confirmed via counting the number of returned pills [32-33], weekly phone interviews [31], and using a daily text message to remind participants [34]; all studies reported high rates of compliance.

4. Discussion

In summary, the results of these studies showed strong statistical significance for reductions in depressive symptoms across all 4 RCTs included. While the findings from these studies exhibit progressive first steps in understanding the clinical potential of probiotic supplementation, significant limitations associated with the current research practices act as a barrier. Study sample sizes were small, and only 3 trials [31-33] included a formal assessment of the food intake or supplementation adherence. Also, there were differences in probiotic formulations, dosage, and the duration of supplementation in all studies, demonstrating a need for studies to utilize consistent probiotic formulations to avoid discrepancies from differing strain characteristics. In the future, research on strain-specific effects is necessary to solidify the findings and the current focus on combined multispecies formulations. Only strain-specific studies will shed light on the impact that probiotic supplementation has on the specific neural, endocrine, and immune pathways. Attempting to determine the overall impact of probiotic supplementation may be premature given the variations in probiotic effects, mechanisms, and psychoactive capabilities. Assessments of between-group differences on a study-by-study basis allow for vital discoveries, regardless of statistical significance. For instance, while Mohammadi did not show a statistically significant between-group reduction in mean depressive symptoms, all 3 groups in that study (PY, PC, CY) demonstrated reductions in mean GHQ (-4.5 in PY, -7.1 in PC, -3.3 in CY) and the DASS (-10.3 in PY, -9.5 in PC, -6.7 in CY) [31].

Study-specific limitations existed due to some studies not requiring participants to stop all other probiotic/fermented food use [34], not further confirming compliance (for example by collecting a stool sample) [32, 34], not equally studying both genders [34], and relying on self-reported cognitive reactivity [34]. In one study [32], the recruitment phase lasted almost one calendar year, causing the intervention phase to be conducted at different times of the year. Conducting the study at different times of the year could present an issue related to the connection between vitamin D availability and physical activity during certain times of the year as they relate to mental health. One study [32], which evaluated clinical samples, allowed participants to continue taking their prescribed antidepressant drugs. A limitation to allowing this practice is that all medications were not identical and each has different effects and interactions.

5. Conclusion and Future Directions

There are four main effective methods to recover normal microbiota, which are probiotics, prebiotics, a healthy diet, and fecal microbiota transplantation [28]. Alterations in the human diet can dramatically alter the composition of the gut microbiota, and these changes have been shown to contribute to the development of gastrointestinal disease [35]. It is well recognized that poor diet, such as the Western Diet, the refined-food diet, and industrially processed foods, which contain excessive amounts of saturated fat, sugar, and food additives, destroy normal gut microbiota and act as a risk factor for depression [28]. Poor diet may perpetuate changes in the gut microorganisms and drive depressive symptoms, whereas a nutrient-rich diet may prevent depressive symptoms [36]. Dietary changes could be prescribed for patients with mild symptoms as an alternative to drug therapy. It is recommended to consume a predominantly plant-based diet and limited red meat. A diet high in plant-based foods will provide essential nutrients and act as a food source for microbes, which will increase the abundance of microbes and minimize gut immune activation [36]. In addition to probiotic use and dietary changes, clinicians are studying the effectiveness of fecal microbiota transplants as an alternative treatment option. Fecal microbiota transplantation is being evaluated as a possible way to manipulate the gut microbiome in a way that could potentially relieve diseases, like depression, related to abnormalities in the microbial community of the gut [36].

In summary, probiotic supplementation had a positive impact on depressive symptoms and depressive mood, despite limitations in current research. These current findings must be considered as tentative until future trials address the complexities of GI microbiota/gut-brain axis/CNS interactions, particularly in relation to specific probiotic strains and mediating biochemical pathways.

Conflict of Interest

The authors declare that they have no conflict of interest.

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Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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