2-27-2024

Effectiveness of Probiotic Therapy on the Symptoms of Major Depressive Disorder (MDD)

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EFFECTIVENESS OF PROBIOTIC THERAPY ON THE SYMPTOMS OF MAJOR DEPRESSIVE DISORDER (MDD)

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School of Nursing, University of Maine, 2021

A Synthesis Paper

Submitted in Partial Fulfillment of the

Requirements for the Degree of

Master of Science in Nursing

(Individualized)

School of Nursing

The University of Maine

May 2024

Advisory Committee:

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PICO(T) In people diagnosed with major depressive disorder (MDD), (P) what effect does probiotic therapy (I) versus placebo (C) have on their symptoms of depression (O)?

Hypothesis: People diagnosed with MDD who are administered probiotic therapy will experience improved symptoms of depression when compared to those given a placebo.

Significance

Clinical depression, also called major depressive disorder (MDD), is a serious and common mental health condition affecting 264 million people worldwide (Wisevoter, 2023). With an average lifetime prevalence of 12%, MDD is a global health concern (Bains & Abdijadid, 2022). According to the World Health Organization (WHO), depression is the third key contributor to the global disease burden and is projected to become number one by 2030 (2023). Depression is currently the leading cause of disability worldwide (WHO, 2023). MDD is often classified as a chronic condition since the risk for recurrence with each subsequent major depressive episode (MDE), increases while the time between MDEs decreases (Lye et al., 2020). Individuals have a 60% chance of recurrence after their first MDE (Lye et al., 2020). This risk for recurrence increases to 70% for those who have experienced 2 MDEs and 90% for those with three or more MDEs (Lye et al., 2020). In addition, with each recurrence, patients report experiencing more severe symptoms with decreased treatment responses (Lye et al., 2020). On average, people with MDD experience four major depressive episodes, each lasting approximately twenty-five years in duration (Hasin et al., 2018). In the first year of the pandemic, worldwide depression rates rose by 25% (WHO, 2022). Researchers project that as newer data are collected and analyzed, they will see that the disease burden of MDD has only continued to climb (WHO, 2022). In the year 2020, 20.78% of adults living in the United States (US; 50 million people) had a severe mental illness diagnosis (Mental Health America, 2023).

Past-year depression rates in the US rose from 7.3% in 2015 to 8.6% in 2019 to 9.2% in 2020 (Goodwin et al., 2022). This significant increase occurred across all income, gender, and racial/ethnic subgroups, reflecting an escalating public health problem even before the onset of the pandemic (Goodwin et al., 2022). Despite the significant increase in levels of depression, there was no corresponding increase in mental health treatment (Goodwin et al., 2022). Depression costs US employers an estimated $187.8 billion yearly, with $134 billion due to health care costs, $20.9 billion due to absenteeism, and $32.9 billion due to lost productivity (Almendral, 2021).

MDD is associated with elevated morbidity and mortality rates across numerous domains. Depression is one of the most common comorbidities of many chronic medical conditions, including metabolic disorders such as diabetes mellitus (DM); cardiovascular diseases or related complications such as coronary artery disease, angina, hypertension, or myocardial infarction; chronic obstructive pulmonary disease; irritable bowel syndrome (IBS); cancer; and stroke (Bains & Abdijadid, 2022; Steffen et al., 2020). Steffen and colleagues (2020) explain that this comorbidity contributes further to poor quality of life, worse patient outcomes, higher medical costs, increased mortality, greater disability, and more extreme functional impairment compared to when depression or a physical condition occurs on its own. Not only does MDD impact the functional aspects of life, but according to Bains & Abdijadid (2022), it also harms interpersonal relationships, contributing to a further decrease in quality of life.

An estimated 1.2 million or 4.84% of US adults experienced serious thoughts of suicide in 2020, and while most people with MDD do not commit suicide, an estimated 60% of people who die by suicide are believed to have had MDD (Holmes, 2023; Mental Health America, 2023). Depression is the strongest risk factor for suicidal behavior, making MDD a potentially

lethal condition (Goodwin et al., 2022). Those with MDD are also at a greater risk of engaging in numerous destructive coping behaviors and are more likely to have a comorbid anxiety or substance use disorder, further increasing their likelihood of attempting to commit suicide (Bains & Abdijadid, 2022).

The contribution of depression to population health has been recognized as a significant public health concern. However, public health interventions have fallen short in targeting depression. Even though there are known, effective treatments for MDD, more than half of US adults (54.7%) with a mental health diagnosis do not receive treatment, and almost one-third of US adults (28.2%) report being unable to receive the treatment that they need (Mental Health America, 2023). In the US, there are an estimated 350 individuals requiring mental health services for every mental health provider, an alarming ratio of 350:1 (Mental Health America, 2023).

Emerging research suggests that digestional health may play a critical role in our mental health (Akkasheh et al., 2016; Appleton, 2018; Kazemi et al., 2019; Majeed et al., 2018; Métraux, 2022; Schaub et al., 2022; Tian et al., 2023; Yamanbaeva et al., 2023). While many studies support the importance of the microbiota-gut-brain axis or the back-and-forth communication pathways between the bacteria in our digestive system and our brain, little is known about the exact mechanisms responsible for their interconnectedness (Métraux, 2022). The gastrointestinal tract is responsible for the production and synthesis of 95% of the body's serotonin, the main target neurotransmitter of many antidepressant medications (Appleton, 2018). Researchers are now hypothesizing that the health state of the digestive system may play such a large role in one's mental health largely due to the high concentration of the "feel good hormone," serotonin, in the gastrointestinal tract (Appleton, 2018). However, research has yet to

determine which strains of gut microbiota exert the greatest effect on serotonin production and concentration in the gut. Future studies are needed to analyze and compare the effects of different microbiota/probiotic strains on the concentrations of serotonin in the gut with statistical comparisons performed on the resulting symptoms of depression.

As the understanding of the complex relationship between the gut microbiome and mental health unfolds, scientists hope also to determine if specific treatments for irritable bowel syndrome and related gastrointestinal conditions, such as probiotics, could serve a dual purpose in improving symptoms of depression (Métraux, 2022). Depression treatment with antidepressant medication does not work for everyone, and even when these pharmacological treatment modalities are effective, they often have troublesome side effects such as weight gain and sexual dysfunction (Métraux, 2022). The goal of the present review and the following proposed study is to investigate the potential for dietary supplementation, namely probiotic therapy (independent variable), to influence the microbiota-gut-brain axis and to exert effects on the symptoms of depression (dependent variable). In addressing this issue, the following PICOT question was asked: In people diagnosed with major depressive disorder (MDD), what effect does probiotic therapy versus placebo have on their symptoms of depression?

Methods

To obtain evidence-based data and information regarding the effectiveness of probiotic therapy versus placebo on the symptoms of depression in individuals diagnosed with MDD, searches were conducted within Science Direct, CINAHL, PubMed, and Google Scholar databases. The search terms and phrases used to locate chosen research articles included major depressive disorder, MDD, depression, probiotic, probiotic vs placebo, psychobiotics, randomized control trial, RCT, gut microbiota, serotonin, gut-brain axis, GBA, psychological

outcomes, and mental health. An asterisk (*) was placed after the root of search words and phrases to ensure that all possible suffixes were included within the search query.

Table 1

Databases Used and Terms/Phrases Searched

Databases	Terms/Phrases Searched
• Science Direct • CINAHL • PubMed • Google Scholar	• major depressive disorder • MDD • depression • probiotic • probiotic vs placebo • psychobiotics • randomized control trial • RCT • gut microbiota • serotonin • gut-brain axis • GBA • psychological outcomes • mental health

All research articles utilized were required to be full-text and peer-reviewed. All articles still under review were excluded. Quantitative, randomized control trials (RCTs), the gold standard of research, were the only study design considered for this review to ensure that the data analyzed represented the highest level of evidence. All meta-analyses and systematic reviews of

RCTs were excluded, as were studies that used a qualitative or mixed-methods design. In addition, all studies had to be placebo-controlled and double-blind. Single-blind RCT studies were excluded. Study participants were required to have a diagnosis of MDD according to DSM-5 or International Classification of Disease, tenth revision (ICD-10) criteria. Any RCTs published before 2016 were excluded from the review. This ensured that no studies used MDD diagnostic criteria based on earlier revisions of the DSM or ICD. DSM-5 was released in 2013 and ICD-10 took effect in 2015. Studies published between 2016 and 2023 were included in this review. All studies with conflicts of interest were excluded, as were studies without explicit mention of participants' informed consent or ethical approval of the study. To be considered for analysis in this review, probiotic therapy was required to be an isolated intervention compared with the placebo. Any study examining the effectiveness of prebiotic or combined prebiotic and probiotic therapy was excluded. Studies were chosen regardless of whether or not participants were receiving antidepressant medications or another therapy before their start. Participants could not have been taking any type of psychobiotic preparation at the onset of the trial, however. The assumption was made that as long as all participants continued with their treatment as usual (TAU), any influence that the placebo or probiotic had on their symptoms of depression would still be observable.

Table 2

Inclusion and Exclusion Criteria for Studies Reviewed

Inclusion Criteria	Exclusion Criteria
Full-text	Abstract only
Peer-reviewed	Still under review

Quantitative, randomized control trials (RCTs)	Meta-analyses, systematic reviews of RCTs, studies that used a qualitative or mixed-methods design
Placebo-controlled, double-blind	Single-blind RCT studies
Participants diagnosis of MDD according to DSM-5 or ICD-10 criteria	No participant diagnosis of MDD according to DSM-5 or ICD-10 criteria
Studies published between 2016 and 2023 were excluded	RCTs published before 2016
Studies with no identified conflicts of interest	Studies with conflicts of interest
Studies explicitly mention participants' informed consent or ethical approval of the study	Studies without explicit mention of participants' informed consent or ethical approval of the study
Probiotic therapy is an isolated intervention compared with the placebo	Any study examining the effectiveness of prebiotic or combined prebiotic and probiotic therapy
Participants continue TAU with the agreement to not consume probiotic products during the study duration	

Synthesis

Significant research has been conducted studying the benefits of probiotics on gut health (Akkasheh et al., 2016). Recent research has found the benefits of microflora in the intestine reach well beyond the gut (Akkasheh et al., 2016). Preclinical data suggest that gut microbiota influence brain functions, including depression (Kazemi et al., 2019). Six research articles related to the use of probiotics in the treatment of depression and its symptoms, specifically for those diagnosed with MDD, were analyzed for this review and will be discussed under five primary themes: study design and participant demographics; strains of probiotic used; depression scales for primary outcome measures: effects on symptoms of depression; secondary outcome measures: gastrointestinal effects; and secondary outcome measures: neuroimaging.

All six of the articles stated that the impetus for their study was the accumulating evidence that gastrointestinal health and mental health have an integral connection, suggesting the possibility that alterations to the gut microbiota may prove to be a successful treatment for depression (Akkasheh et al., 2016; Kazemi et al., 2019; Majeed et al., 2018; Schaub et al., 2022; Tian et al., 2023; Yamanbaeva et al., 2023). While different scales were used to measure participants' symptoms of depression between studies, all six of the articles found that symptoms of depression improved in those who underwent probiotic therapy when compared with those who received a placebo (Akkasheh et al., 2016; Kazemi et al., 2019; Majeed et al., 2018; Schaub et al., 2022; Tian et al., 2023; Yamanbaeva et al., 2023). In addition, different strains of probiotics were used for each study, necessitating further research to determine which single or combined probiotic strains are the most successful, beneficial, and effective in increasing gut concentrations of serotonin and reducing symptoms of depression in patients diagnosed with MDD. These evidence-based interventions can then be actively implemented across all sectors for the largest possible populations and for the most desired and optimal outcomes to be achieved.

Study Design and Participant Demographics

Table 3

Synthesis of Research Articles

Study	Measures for Depression	Biomarkers & Measures for GI / Metabolic Health	Intervention: probiotic stain used	Intervention Duration	Results/Findings	Design	Population
Akkasheh et al., (2016).	DSM-5 BDI	Lipid Profile HOMA-IR HOMA-B QUICKI	3 Strains: -*B. bifidum* -*L. acidophilus* -*L. casei*	56 days (2 months)	Probiotic administration in patients with MDD for 8 wk had beneficial effects on BDI, insulin, HOMA-IR,	randomized, double-blind, placebo-controlled trial (RCT)	n=40 40 patients with MDD whose ages range between 20 and 55 years.

Study	Measures for Depression	Biomarkers & Measures for GI / Metabolic Health	Intervention: probiotic stain used	Intervention Duration	Results/Findings	Design	Population
		hs-CRP GSH TAC Insulin FPG			hs-CRP, and GSH levels, but did not influence FPG, HOMA-B, QUICKI, lipid profiles, and TAC levels.		participants were randomized 1:1 to receive placebo (n=20) or intervention (n=20)
Kazemi et al., (2019)	BDI	Biomarker Levels: -Tryptophan -Kynurenine -BCAA -Isoleucine	2 Strains: -*B. lactis* -*L. helveticus*	2 months	In patients with MDD, probiotic supplementation resulted in an improvement in BDI score compared with placebo whereas no significant effect of prebiotic was observed.	three-arm parallel design, placebo-controlled, double-blind, RCT	n=110 110 patients with mild-to-moderate MDD whose ages ranged between 18 and 50 years. participants were randomized 1:1:1 to receive placebo (n=36), prebiotic intervention (n=36), or probiotic intervention (n=38)
Majeed et al., (2018)	DSM-5 Subject diaries HAM-D MADRS CES-D	IBS-QOL GI-DQ Serum myeloperoxidase	1 Strain: -*B. coagulans* 600 mg (2 billion spores) daily	90 days with follow-up screening at day 105 Day 0: baseline Day 30: screening Day 60: screening Day 90: screening Day 105: screening	*B. coagulans* may be a new and alternative approach for the management of MDD in patients with comorbid IBS.	randomized, double-blind, placebo-controlled, multi-center, pilot clinical study	n=40 40 patients diagnosed with comorbid MDD and IBS. participants were randomized 1:1 to receive a placebo (n=20) or intervention (n=20)
Schaub et al., (2022)	ICD-10 HAM-D BDI	GSRS	8 Strains:' -*B. breve* -*B. lactis* -*L. acidophilus* -*L. delbrueckii* -*L. helveticus* -*L. paracasei* -*L. plantarum* -*S. thermophilus*	4 weeks	An add-on probiotic treatment improves depressive symptoms and maintains healthy enterotypes, species richness, and increases specific health-related bacterial taxa.	double-blind RCT	n=47 47 patients with current depressive symptoms and a diagnosis of MDD. participants were randomized to receive placebo (n=26) or intervention (n=21)
Tian et al., (2023)	MADRS	GSRS	3 Strains:	4 weeks	Probiotic treatments can	two-arm parallel design,	n=28

Study	Measures for Depression	Biomarkers & Measures for GI / Metabolic Health	Intervention: probiotic stain used	Intervention Duration	Results/Findings	Design	Population
	HAM-D	Gut Motility Tests Faecal 16SrRNA sequencing and bioinformatic analyses: -Endocrine hormones -Stool moisture -BDNF -5-HT turnover -qRT-PCR -SCFAs	-*B. breve* -*B. lactis* -*P. acidilactici*		mitigate psychiatric symptoms and comorbid gastrointestinal symptoms in patients with MDD.	placebo-controlled, double-blinded, RCT	28 participants aged over 18 years with mild to moderate MDD participants were randomized to receive placebo (n=13) or intervention (n=15)
Yamanbaeva et al., (2023)	HAM-D	n/a	8 Strains:' -*B. breve* -*B. lactis* -*L. acidophilus* -*L. delbrueckii* -*L. helveticus* -*L. paracasei* -*L. plantarum* -*S. thermophilus*	4 weeks with TAU for depression	Probiotics affect brain structure and function in the fronto-limbic network and these effects are partly associated with a decrease in depressive symptoms.	double-blind RCT	n=32 32 patients from Switzerland with a diagnosis of MDD. participants were randomized into two groups: control (n=18; placebo) and intervention (n=14)

BDI, Beck Depression Inventory; BCAA, branched-chain amino acids; BDNF, brain-derived neurotrophic factor; CES-D, Center for Epidemiological Studies Depression Scale; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; FPG, fasting plasma glucose; GI-DQ, gastrointestinal discomfort questionnaire; GSH, total glutathione; GSRS, gastrointestinal symptom rating scale; HAM-D, Hamilton Rating Scale for Depression; HOMA-B, homeostatic model assessment of beta cell function; HOMA-IR, homeostasis model of assessment of insulin resistance; hs-CRP, high-sensitivity C-reactive protein; IBS, irritable bowel syndrome; IBS-QOL, irritable bowel syndrome quality of life questionnaire; MADRS, Montgomery-Asberg Depression Rating Scale; MDD, major depression disorder; qRT-PCR, quantitative reverse transcription polymerase chain reaction; QUICKI, quantitative insulin sensitivity check index; SCFS, short-chain fatty acids; TAC, total antioxidant capacity; TAU, treatment as usual; 5-HT turnover, serotonin turnover

While all six of the studies (Akkasheh et al., 2016; Kazemi et al., 2019; Majeed et al., 2018; Schaub et al., 2022; Tian et al., 2023; Yamanbaeva et al., 2023) required participants to be diagnosed with MDD, one study (Kazemi et al., 2019) required the participant to be taking an antidepressant drug. Another research article (Schaub et al., 2022) noted that regular medications could be taken as usual. Majeed et al., (2018) required participants not to use any medication, including prescription, over-the-counter, vitamins, or minerals, or eat yogurt during the study. Akkasheh et al., 2016 allowed no supplements or medications during the study. Kazemi et al., 2019 excluded using other probiotics, alcohol, and tobacco. Those with an opioid addiction were also excluded. The other two articles had no medication specifications (Tian et al., 2023; Yamanbaeva et al., 2023). The only study to require participants to have IBS symptoms was Majeed et al., 2018.

All six of the studies (Akkasheh et al., 2016; Kazemi et al., 2019; Majeed et al., 2018; Schaub et al., 2022; Tian et al., 2023; Yamanbaeva et al., 2023) required participants to be at least 18 years of age. However, Akkasheh et al., 2016 and Majeed et al., 2018 set a minimum age of 20. Three studies (Schaub et al., 2022; Tian et al., 2023; Yamanbaeva et al., 2023) stated maximum age in the research articles. However, Kazemi et al., 2019 set a maximum participant age of 50. Akkasheh et al., 2016 set a maximum age of 55, and Majeed et al., 2018 allowed participants up to age 65. The mean age of the studies in ascending order is 36.07 ∓ 5.84 standard deviation (SD) (Schaub et al., 2022), 36.5 ∓ 8.03 SD (Kazemi et al., 2019), 37.25 ∓ 10.38 SD (Akkasheh et al., 2016), 37.6 ∓ 10.51 SD, (Yamanbaeva et al., 2023), 42.21 ∓ 10.1 SD (Majeed et al., 2018), 43.5 ∓ 18.1 SD (Tian et al., 2023).

All six research studies (Akkasheh et al., 2016; Kazemi et al., 2019; Majeed et al., 2018; Schaub et al., 2022; Tian et al., 2023; Yamanbaeva et al., 2023) excluded patients who were

pregnant or lactating or any participants with current medical conditions such as acute infectious diseases, or serious physical illnesses. Three studies (Schaub et al., 2022; Tian et al., 2023; Yamanbaeva et al., 2023) also excluded participants with comorbid mental health conditions. Two research articles (Schaub et al., 2022; Tian et al., 2023) also excluded immunosuppressed participants. Tian et al. (2023) was the only research article that specified the exclusion of those with neurodegenerative diseases.

Studies differed in their duration. Three studies (Schaub et al., 2022; Tian et al., 2023; Yamanbaeva et al., 2023) were performed over four weeks. One study (Akkasheh et al., 2016) spanned 56 days. Another study (Kazemi et al., 2019) lasted two months, and the longest study (Majeed et al., 2018) spanned 90 days with a follow-up on day 105. Therefore, more studies are needed to explore the effect of probiotics in larger-scale trials over a longer period of time with extended follow-up and ensure compliance by any participant used in the resulting data.

Strains of Probiotics Used

All six studies utilized probiotics as the primary trial intervention for symptoms of depression compared with a placebo in the control group. However, the number and type of probiotic strains varied for each study with some overlap. One of the studies (Majeed et al., 2018) used only one strain, *B. coagulans*, and another used two probiotic strains, *L. helveticus and B.* lactis (Kazemi et al., 2019). *L. helveticus* was used in combination with other probiotic strains in two other studies (Schaub et al., 2022; Yamanbaeva et al., 2023). Similarly, *B. lactis* was common in four studies (Kazemi et al., 2019; Schaub et al., 2022; Tian et al., 2023; Yamanbaeva et al., 2023). Tian et al., 2023 used three stains, *B. breve*, also used in two other studies (Schaub et al., 2022; Yamanbaeva et al., 2023), *B. lactis*, mentioned previously, and *P. acidilactici*. Akkasheh et al. (2016) also used three strains of probiotics: *L. acidophilus, L. casei,*

and *B. bifidum.* Two of the studies (Schaub et al., 2022; Yamanbaeva et al., 2023) used the same eight probiotic strains, *S. thermophilus, B. breve, B. lactis, L.* acidophilus, *L. plantarum, L. paracasei*, *L. delbrueckii, L. helveticus*. However, a gap in the literature remains. More research is needed to determine the specific strains of probiotics that are most effective in increasing gut concentrations of serotonin and improving symptoms of depression. The research should employ each of the strains used in the present studies individually to evaluate their beneficial effects on symptoms of depression and metabolic status in patients with MDD.

Depression Scales for Primary Outcome Measures: Effects on Symptoms of Depression

All six articles utilize symptoms of depression as a primary outcome measure, though not all of the studies utilized the same scales. The participants' symptoms of depression were measured both before and after any intervention (probiotic or placebo) occurred. Though the measurement scales differed between the six studies analyzed, there was great consensus regarding the positive effects of probiotic therapy on the symptoms of depression. Every depression rating scale across all six studies found a significant decrease in depression symptoms between pre- and post-analysis in the probiotic group when compared with the placebo group. These results are promising and offer hope for the potential to utilize probiotic therapy as a treatment for depression, either alone or in combination with existing therapy.

Two of the six studies (Akkasheh et al., 2016; Kazemi et al., 2019) measured the effects of probiotic treatment on symptoms of depression using only Beck's Depression Inventory (BDI). Akkasheh et al. (2016) found that study participants in the study group who received probiotic therapy had significantly decreased BDI scores ($p=0.001$) compared with those who only received a placebo. Similarly, Kazemi et al. (2019) reported a significant decrease in BDI scores between experimental (probiotic) and control (placebo) groups ($p=0.042$).

One study (Schaub et al., 2022) used BDI combined with the Hamilton Depression Rating Scale (HAM-D). However, BDI was considered a secondary measure in this study. Schaub et al. (2022) found that the decrease in HAM-D scores observed in participants throughout the study was significantly greater in the probiotic group compared with the placebo group ($p<0.002$). In addition, Schaub et al. stated that they found a significant decrease in the symptoms of depression in the probiotic group when compared with the placebo group according to pre-and post-BDI scores. However, they did not provide a p-value to indicate the level of significance.

Another study (Yamanbaeva et al., 2023) only used the HAM-D as a measure of symptoms of depression before and after the intervention. They found a significantly greater decrease in HAM-D score between baseline and follow-up for the probiotic group compared to the placebo group (Yamanbaeva et al., 2023).

One of the six studies (Tian et al., 2023) utilized both HAM-D and Montgomery-Asberg Depression Rating Scale (MADRS). Tian et al. (2023) found a statistically significant difference in the decrease in HAM-D scores between the probiotic group ($p<0.001$) and the placebo group ($p=0.553$) as well as in MADRS scores between the probiotic ($p<0.001$) and placebo groups ($p=0.679$). The final study analyzed (Majeed et al., 2018) also utilized MADRS and HAM-D as well as the Centre for Epidemiological Studies-Depression Scale (CES-D) to measure symptoms of depression before and after probiotic/placebo intervention. A statistically significant change was found in HAM-D ($p=0.005$), MADRS ($p=0.007$), and CES-D ($p=0.009$) scores in the probiotic group between baseline analysis and the end of the study compared with the change in scores seen in the placebo group (Majeed et al., 2018). Further study is needed to determine valid and reliable MDD self-report rating scales for research. Once reliability is determined, these

evidence-based subjective questionnaires and depression rating scales can be used for data pooling and replication alongside objective neuroimaging and comparison measurements.

Secondary Outcome Measures: Gastrointestinal Effects

Three out of the six studies (Majeed et al., 2018; Schaub et al., 2022; Tian et al., 2023) addressed gastrointestinal effects in some regard. Two studies (Majeed et al., 2018; Tian et al., 2023) found that subjects receiving the probiotic reported a significant decrease in IBS toward the end of the study, while no reduction of IBS symptoms was experienced in the placebo groups. Tian et al., (2023) concluded that changes in the serotonergic system within the gastrointestinal system were key to the probiotic' benefits, both in regards to reduced depression symptom severity and in improved digestive health. Schaub et al. (2022) more specifically reported that probiotics helped regulate gut microbiota, improving their diversity and richness. Schaub et al. (2022) also found that the healthy *Prevotella* enterotype decreased in the placebo group but not in the probiotic group and that the healthy *Lactobacillus* increased in the probiotic group but not in the placebo group. These results support the possibility of there being a direct link between decreased depression symptoms and improved microbiota after treatment with probiotics. Therefore, further study is needed understand the gut-brain axis and the part it may play in the treatment of depression.

Secondary Outcome Measures: Neuroimaging

Two of the six articles in this review (Schaub et al., 2022; Yamanbaeva et al., 2023) used brain imaging evaluations and other measures. Both of these studies had patients continue TAU for their depression during the research study, and through neuroimaging, both saw increased positive results for probiotic users that were not observed for those who only received a placebo (Schaub et al., 2022; Yamanbaeva et al., 2023). Schaub et al. (2022) reported that probiotics

modified the negativity bias and emotional valence in emotional face processing typically observed in patients diagnosed with MDD, meeting the main requirement of successful MDD treatment. These findings were only observed in the probiotic group and not in the placebo group (Schaub et al., 2022). Yamanbaeva et al. found that the mean diffusivity (MD) increased in the right uncinate fasciculus (UF), indicating atrophy and broad cellular damage for those in the placebo group, while MD remained stable throughout brain regions for the probiotics group (2023). A positive correlation was found between this stabilization and improved depression symptoms (Yamanbaeva et al., 2023). Yamanbaeva et al. also found decreases in resting-state functional connectivity (rsFC) in the probiotic group, which correlates positively with the reduction in symptoms of depression and indicates that probiotics may prevent further neurodegeneration (2023). Future research is needed to investigate the potential for probiotic therapy to reverse the negative structural and functional changes in the brain caused by chronic depression or MDD.

Summary & Recommendations

MDD affects a significant portion of the population, causing profound negative effects on all aspects of the lives of those with the diagnosis. Although rates of MDD have persistently increased, safe, effective, and affordable treatment approaches have not. Many patients who suffer from MDD do not find adequate relief from their symptoms through psychotherapy or antidepressant medication. When these treatments are effective, they take significant time to take effect or show beneficial results. In addition, many antidepressant medications cause distressing side effects, causing a lack of adherence.

Research has shown a connection between gut health and the brain, known as the gut-brain axis, though little is known about the precise mechanisms that contribute to their

interconnectedness. Considering that 95% of the body's serotonin is produced and stored in the gut and that much of its synthesis is dependent on the gut microbiome, researchers have suggested that manipulation of the microbiome health and composition may lead to an increase in serotonin levels with associated improvement in symptoms of depression (Appleton, 2018). Preliminary studies have found evidence that probiotic supplements may reduce symptoms of depression, though once again, the exact mechanism behind their effectiveness is still unknown.

Further research is warranted to gather more definitive evidence of the positive effects of probiotics on MDD. Previous studies have utilized small, unvaried sample sizes that are not representative of true population demographics (see Table 3). Future research should utilize large and diverse sample sizes that are representative of those suffering from MDD living on every continent. In addition, studies should have a longitudinal nature, observing patients over a longer period of time so that changes that may take time can be observed. While previous RCTs have demonstrated participants' symptoms of depression, studies have failed to isolate and measure the effectiveness of different probiotic strains on the symptoms of depression. Determination of which strain or strains of probiotics are the most efficacious in the symptom improvement of depression in patients diagnosed with MDD will be instrumental in ensuring the best outcomes for those who undergo treatment.

For the study design and implementation plan proposed below, an updated PICOT question has been made to address better the research gaps noted after analysis of the existing literature. The goal of the following proposed study is to investigate the effect of different strains of probiotic therapy to influence different aspects of the microbiota-gut-brain axis, and to exert effects on the symptoms of depression. In addressing this issue, the following PICOT question was asked: In people diagnosed with major depressive disorder (MDD), what is the effect of

different strains of probiotic therapy versus placebo on gut microbiome diversity, gut serotonin concentrations, neuroimaging results, and subjective symptoms of depression? The hypothesis was also amended and states: “People diagnosed with MDD taking various probiotic strains will experience statistically significant improvements (changes) in their gut microbial diversity, concentrations of gut serotonin, neuroimaging results, and subjective symptoms of depression after one year of treatment.”

Conclusion

The incidence and prevalence rates for MDD are on the rise. Discovering exactly what strains of probiotics are most efficacious in improving the symptoms of depression in people with major depressive disorder is necessary in ensuring the best treatment outcomes for this population. A better understanding of the mechanisms responsible for the interconnectedness between the gut microbiome and mental health will be essential in determining potential future treatments for both depression and gastrointestinal issues, such as IBS. Increasing the knowledge base regarding this phenomenon will allow for the implementation of evidence-based interventions that have the potential to improve the quality of life for the 264 million people worldwide diagnosed with major depression (Mental Health America, 2023). Considering that more than half of US adults go without mental health treatment (Wiswvoter, 2023), more safe, effective, accessible, and affordable treatment options are warranted!

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