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ABSTRACT

Objective: To assess the effect of probiotic supplementation on clinical symptoms of major depressive disorder in adults. **Design:** Systematic literature review. **Methods:** Searches were performed on PubMed using the terms “adults with depression and probiotics”. The limits on PubMed were set to include randomized control trials, studies on adults, studies done within the last 10 years, studies done on patients that did not have depression, studies that did not use the Beck Depression Inventory, and studies that focused on other conditions. **Results:** Three studies were found that met search criteria: Reninghaus et al., Schaub et al., and Chahwan et al. **Conclusion:** The included studies showed a reduction in Beck Depression Index scores reflecting an improvement in clinical symptoms of depression. Therefore, probiotic supplementation should be considered as a possible adjuvant therapy for adults with major depressive disorder.

INTRO

Depression is a term that can both represent a transient emotional state as well as a clinical condition.[1] Unipolar major depression is a very common condition with estimated lifetime prevalence of about 21% in the United States.[1] In a study of over 36,000 adults in the US, the average age of onset of a first episode of major depression occurs at 29-years-old.[1] Diagnosing depression in adults requires the near daily presence of at least five of the following nine symptoms which include: depressed mood most of the day, little interest in doing things most of the day, insomnia or hypersomnia, significant weight loss or gain or appetite changes, psychomotor retardation or agitation that is noticed by others, fatigue or low energy, decreased ability to concentrate or make decisions, excessive or inappropriate thoughts of worthlessness or guilt, recurrent thoughts of death, suicidal ideation or attempt.[2]

Probiotics are living microorganisms and when taken in adequate amounts, interact with host microbiota to suppress pathogens exposed to the human body.[3] Probiotics often contain microorganisms such as bacteria including *Lactobacillus* and *Bifidobacterium* and yeasts such as *Saccharomyces boulardii* (NIH).[4] Probiotics work in a variety of ways, including helping to maintain the health of the microbiome, produce beneficial substances, and help the immune system (NIH).[4] Gut microbes play a large role in many psychiatric disorders as there is a bidirectional communication between the brain and gut called the microbiota-gut-brain axis (MGBA).[3]

Many studies have shown that bacteria are important for many different physiological processes and transmit and interpret information from the periphery of the body back to the

brain and vice versa.[3] It involves neural pathways such as the vagus nerve and enteric nervous system along with cytokine and endocrine pathways all of which are found to be altered in psychiatric disorders.[3] Once the microbiome senses stress, it influences the hypothalamic pituitary axis to release cortisol.[3] Therefore, stress induced cortisol can be altered by taking probiotics.[3]

While antidepressants may work for some people, there are others who say they have no effect on them with the effect of antidepressants being around 40-60%.[5] With the many different types of antidepressants available, there are also many side effects such as dry mouth, headache, dizziness, and sexual dysfunction.[5] It was found that there is a significant difference in the gut microbiota composition in those with depression and individuals without clinically diagnosed depression.[3] The aim of this literature review is to assess whether probiotic supplementation can improve clinical symptoms of depression in adults.

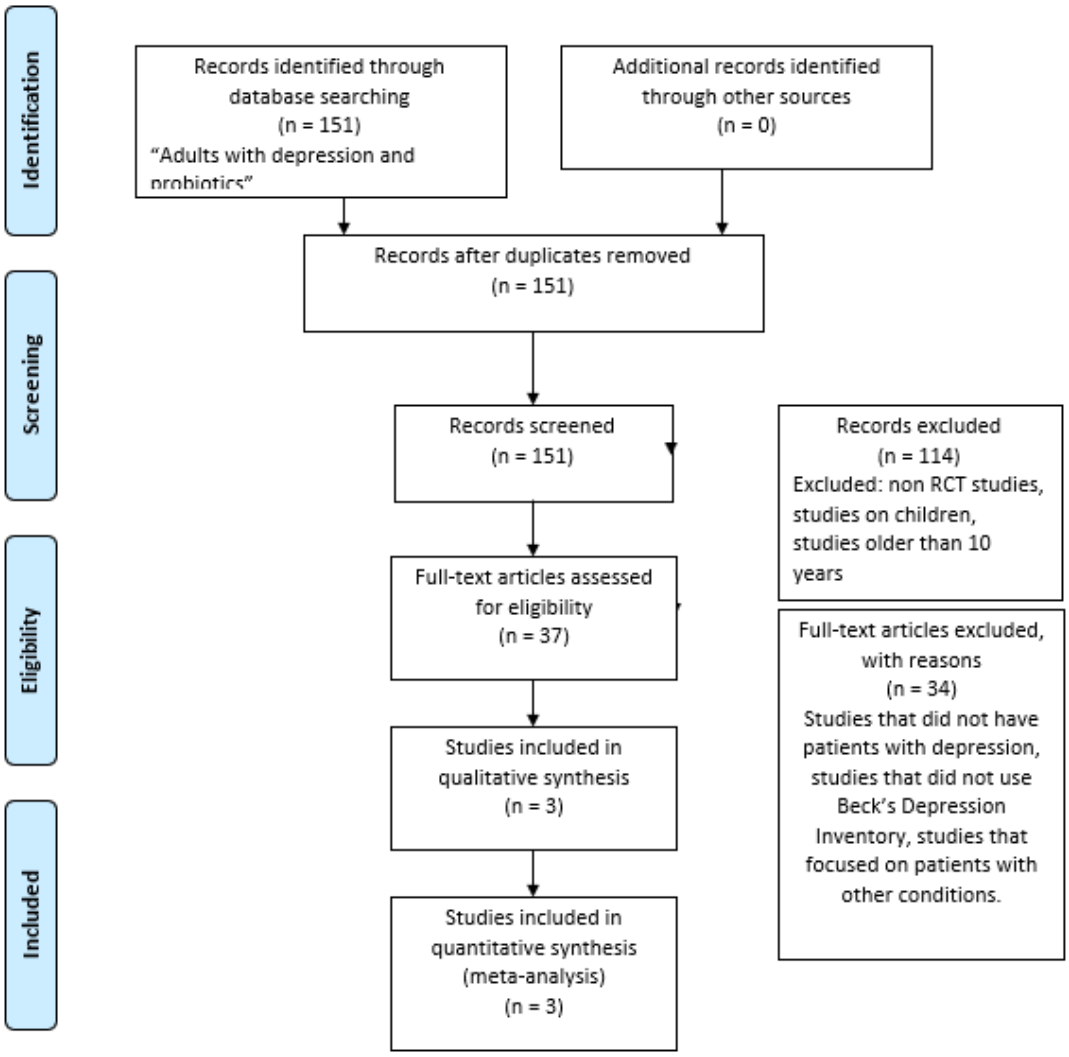
METHODS

An initial search was performed using the search engine PubMed in September 2022 with the terms “adults with depression and probiotics.” This initial search resulted in 151 articles. There were no other data sources used. There were no duplicates in the initial Pubmed search. Limits included “randomized controlled trial, published in the last 10 years, English.” This yielded 37 full text articles that we assessed for eligibility. Of the 37 articles, 34 were excluded because they did not meet the inclusion criteria (Table 1). The three remaining articles were included in this review after meeting the inclusion criteria (Table 1).

Table 1. Study Criteria

Inclusion Criteria	**Exclusion Criteria**
RCT Studies included major depressive disorder and use of probiotics as intervention	Study results did not use Beck Depression Inventory Articles older than 10 years

PRISMA 2009 Flow Diagram **Hayley Loiselle, Alexa Hammock**



RESULTS

Study #1: *PROVIT: Supplementary Probiotic Treatment and Vitamin B7 in Depression - A Randomized Controlled Trial. Reininghaus et al.*[6]

Objective:

To evaluate the effect of probiotic treatment plus keratin in depressed individuals both on clinical parameters and intestinal microbiota changes.

Study Design:

This study was a double blind, placebo controlled randomized control trial. The study included 82 patients who were in an inpatient facility for depression treatment. Table 2 outlines the exclusion criteria.

The groups were randomized and were given either Omnibiotic Stress Repair (containing *B. bifidum* W23, *B. lactis* W51, *B. lactis* W52, *L. acidophilus* W22, *L. casei* W56, *L. paracasei* W20, *L. plantarum* W62, *L. salivarius* W24 and *L. lactis* W19) plus biotin and matrix (containing maize starch, maltodextrin, inulin, potassium chloride, magnesium sulfate, fructooligosaccharides (FOS), enzymes (amylases) and manganese sulfate) or a placebo plus the same biotin and matrix. Over the course of 28 days, participants were given either supplement in the morning and received other treatments including standard antidepressant treatment at the facility which included physical therapy, occupational therapy, psychopharmacological therapy and psychotherapy. Clinical symptoms and gut microbiome were analyzed at the beginning of the study and after one week and after 4 weeks. Clinical visits consisted of fasting blood samples, stool samples, psychological and cognitive testing, and clinical interview regarding side effects and symptoms.

Table 2. Patient Exclusion Criteria

Acute suicidality	Known florid tumor disease
Lack of consent	Congenital/infantile mental disability
Pregnant/breastfeeding	Moderate/severe dementia
Active severe drug dependence	Severe florid autoimmune diseases
Other active severe cerebral organic diseases	Current immunosuppression
Severe skull/brain trauma or surgery	Antibiotic therapy within the last month
Intake of other probiotics and prebiotics or butyrate preparations during the entire trial or within the last month	Chronic laxative abuse
	Acute infectious diarrheal disease
	Regular intake of butyrate-containing or probiotic supplements in the last year
Intake of antibiotics or prebiotics during the entire trail or within the last month	

Results:

Patients results from the 61 individuals who completed the study were recorded on many different psychiatric scales including Hamilton Depression Scale (HAM-D), Beck's Depression Inventory II (BDI-II), Mania Self Rating Scale (MSS), Global Symptom Index (GSI), Positive Symptom Total (PST), Positive Symptom Distress Index (PSDI) and Gastrointestinal Quality of Life (GIQL) at the time of admission and after 4 weeks. The study found that there were significant improvements in both groups concerning psychiatric symptoms but not a significant

difference between the treatment and placebo group on the psychiatric scales. The probiotic intervention differed from placebo only in microbial diversity. Results revealed elevated *Ruminococcus gauvreauii* and *Coprococcus 3* levels in the probiotics group after 28 days and upregulated vitamin B6 and B7 synthesis.

Critique:

The study groups had no significant differences in demographics with the exception of the placebo group having significantly more cigarette smokers in the group (19 in the placebo group and 9 in the treatment group). Another critique is that the study was only 28 days which may not have been a long enough time to see more improvements in clinical symptoms reflected in changes on psychiatric scales. Lastly, patients were also receiving many other inpatient therapies and since they were inpatient they were not eating foods that they normally would, and they were not on their normal routines.

Study #2: *Clinical, gut microbial and neural effects of a probiotic add-on therapy in depressed patients: a randomized controlled trial. A.-C. Schaub et al.*[7]

Objective:

Evaluation of probiotics and the efficacy in reducing depressive symptoms when added to prescribed antidepressants.

Study Design:

This study used a double blind RCT of a probiotic add on therapy for 4 weeks in patients with depression. Inclusion and exclusion criteria are outlined in Table 3. A total of 60 patients were included in this study with 47 completing the study.

Over 4 weeks, patients took a probiotic supplement that contained eight different strains (*Streptococcus thermophilus* NCIMB 30438*, Bifidobacterium breve* NCIMB 30441*, Bifidobacterium longum* NCIMB 30435 (Re-classified as *B. lactis), Bifidobacterium infantis* NCIMB 30436 (Re-classified as *B. lactis), Lactobacillus* acidophilus NCIMB 30442*, Lactobacillus plantarum* NCIMB 30437*, Lactobacillus paracasei* NCIMB 30439*, Lactobacillus delbrueckii subsp.* and *Bulgaricus* NCIMB 30440 *(*Re-classified as *L. helveticus))* in addition to their prescribed treatment as usual (TAU). Each dose of the probiotic contained 900 billion CFU per day and could be mixed with any cold, non-carbonated drink. The control group received a placebo containing maltose with no bacteria. The intervention was given by nursing personnel and participants who were no longer inpatient were instructed to continue the intervention at home. Patients were randomized into two different study groups and all inpatient participants

received the same diet of standardized amount of fibers and starch. Stool samples were taken by participants and stored at -80C until available for DNA extraction in which calprotectin and fecal moisture were recorded. Enterotyping, microbiome diversity measures, and bacteria taxa were recorded.

Table 3. Study Criteria

Inclusion Criteria	Exclusion Criteria
Current depressive episodes according to ICD-10 diagnosis code Inpatient status Hamilton Rating Scale for Depression (HAM-D) score of >7 18 years of age or older Treatment as usual (TAU) for depression Able to read and understand information and give informed consent	Immunosuppressed patients Patients with dietary restrictions and medical conditions such as acute infectious diseases Pregnancy Breast-feeding Comorbid psychiatric disorders including addiction, bipolar disorder, schizophrenia

Results:

Primary outcome was recorded by changes in the HAM-D. Other outcomes were measured by the German version of Beck Depression Inventory (BDI), Gastrointestinal Symptom Rating Scale (GSRS), and the State-Trait Anxiety Inventory 1 (STAI1). There was a decrease in the HAM-D scores over time with a stronger decrease in the intervention group. Treatment response was indicated by HAM-D changes in > 57% of the total participants. Eighty percent of those patients who reported changes were in the intervention group and 48% of them were in the placebo group. Stool samples did not show any differences between calprotectin, fecal moisture, or cell counts. There was no change in enterotype composition in the study groups. There were no significant changes in the microbiome diversity in the study groups. Participants who received the intervention had increased *Lactobacillus*. As the abundance of *Lactobacillus* increased, there was a negative association with the HAM-D and BDI but a positive association with the GSRS. Overall, there was a remission rate of 55% in the intervention group and a 40% remission rate in the placebo group indicating that probiotic supplementation to TAU has a beneficial effect on the clinical progression of depressive symptoms.

Critique:

Compliance was high because the participants were monitored in an inpatient setting and interventions were given by professional personnel which is not indicative of real-world situations. The sample size was relatively small starting with 60 participants and ending the study with 47. This indicated a 30% drop out rate in the probiotics group and 13% in the placebo group. TAU in place was not specified meaning there was no correlation of probiotics with specific antidepressants.

Study #3: *Gut feelings: a randomised, triple-blind, placebo-controlled trial of probiotics for depressive symptoms. B. Chahwan et al.*[8]

Objective:

To determine whether an 8-week supplementation of a probiotic leads to reduced symptoms of depression.

Study Design:

This study was a triple blinded parallel, placebo-controlled randomized clinical trial in which participants were randomly assigned to a control and study group. The randomization was performed by a computerized randomizer in blocks of four. A total of 71 participants were recruited and screened with the Beck Depression Index-Second Edition (BDI-II). The minimum cut off score for the BDI-II was 12 indicating a depression severity of mild. Other inclusion criteria included age of 18 years or above, willingness to travel to The University of Technology Sydney (UTS), Ultimo campus, ability to provide stool samples, and no consumption of probiotic rich foods and drinks that may skew results. Prior to the study, participants submitted a stool sample**,** completed the Mini International Neuropsychiatric Interview (MINI), the Depression Anxiety Stress Scale - 21 (DASS-21), BDI-II, and Beck Anxiety Inventory (BAI). They each attended weekly checkups to complete the BDI-II, DASS-21 and weekly checkup questionnaire. Patients were given information on how to prepare and consume their eight-week supplement. The intervention group was given two pouches for each day of the study which contained 2g of freeze-dried probiotic powder (Ecologic®Barrier; Winclove probiotics, The Netherlands). This contained nine bacterial strains including *Bifidobacterium bifidum* W23, *Bifidobacterium lactis* W51, *Bifidobacterium lactis* W52, *L. acidophilus* W37, *Lactobacillus brevis* W63, *Lactobacillus casei* W56, *Lactobacillus salivarius* W24, *Lactococcus lactis* W19 and *Lactococcus lactis* W58 (total cell count 1 × 1010 CFU/day). The placebo group was given two pouches for each day of the study which contained 2g of freeze-dried maize starch and maltodextrins.

Table 4. Study Criteria	
Inclusion Criteria	Exclusion Criteria
18 years old or older Could provide informed consent Willing and able to travel to UTS Ultimo campus weekly Could provide stool samples at the start and end of the trial Could not consume probiotic-rich foods or drinks during the trial Relatively healthy apart from depression diagnosis Not on any medications (including antidepressants)	Diagnosis of HIV/AIDS, Crohn's disease, ulcerative colitis, lactose-intolerance, gluten intolerance Diagnosis of cancer or undergoing chemotherapy Currently experiencing severe depressive symptoms (>57 on BDI-II) Actively suicidal or self-harming Diagnosis of bipolar disorder, personality disorder, psychiatric disorder or experiencing psychosis High-risk alcohol consumption (20 standard drinks per week for males, 12 for females) Currently receiving psychological or pharmacological treatment for mental health issues Currently or having taken antibiotics or probiotic supplements within two weeks of the trial Pregnant or planning to become pregnant during the course of the trial Currently participating in another research trial

Results:

The results revealed a reduction in depressive symptoms over the course of the trial in both the probiotic and placebo groups. The depression symptoms were quantified using the BDI-II. The reduction in scores in both groups was attributed to having a routine of taking a probiotic and having regular appointments as well as seeking improvement in depressive symptoms. As the results did not show a significant difference between the treatment and placebo groups in clinical symptoms of depression, the study authors concluded that probiotics alone are not an effective treatment to manage depression, anxiety or stress symptoms. The significant difference between the two groups was a measure of cognitive reactivity towards sad mood which is a vulnerability marker of depression. Those in the probiotic group were found to have a lower cognitive reactivity to sad mood than those who were in the placebo group. This finding suggests that probiotics may act on cognitive processes that contribute to and are associated with depression. Follow up analyses of both groups also revealed that those in the

probiotic group were more likely to have improved from a diagnosis of subclinical depression to no depression diagnosis than those who were in the placebo group.

The study did not find any significant differences between the fecal microbiota between the probiotic and placebo groups before or after the trial. The authors of the study mention that this may have been because the dosage of the probiotic was too low to have a change reflected in the stool samples. The authors also note that these findings may be due to differences in the geography and diet of the study participants.

Critique:

The attrition rate of this study was 34% which could be due to the requirement to attend weekly monitored visits which can be difficult for patients with depression. A strength of the study is excluding participants who are on antidepressants or other medications that have been shown to be anti-microbial or alter the gut microbiota.

DISCUSSION

Table 5: Overview of Studies

	Reninghaus et al	Schaub et al	Chahwan et al
Patients, N	82	60	91
Population	In patient, depression diagnosis	In patient, depression diagnosis	Outpatient, depression diagnosis and non-depressed (20 without depression)
Gender	M - 22% W - 78%	Not reported	M - 30% W - 70%
Taking antidepressants	Yes	Yes	Yes, for those in the depression group
Intervention BDI pre	30.75	Not reported	28.91
Placebo BDI pre	32.69	Not reported	27.97
Intervention BDI post	15.11	22.38	19.8
Placebo BDI post	18.2	22.33	19.25

Bacterial strains used	B. bifidum W23 B. lactis W21 B. lactis W52 L. acidophilus W22 L. casei W56 L. paracasei W20 L. plantarum W62 L. salivarius W24 L. lactis W19	Streptococcus thermophilus NCIMB Bifidobacterium breve NCIMB Bifidobacterium lonbum NCIMB Bifidobacterium infantis NCIMB Lactobacillus acidophilus NCIMB Lactobacillus plantarum NCIMB Lactobacillus paracasei NCIMB Lactobacillus delbruekii subsp. Bulgaricus NCIMB	Bifidobacterium bifidum W23 Bifidobacterium lactis W51 Bifidobacterium lactis W52 L. acidophilus W37 Lactobacillus brevis W63 Lactobacillus casei W56 Lactobacillus salvarius W24 Lactococcus lactis W19 Lactococcus lactis W58

BDI = Beck Depression Inventory

Major depressive disorder is a common mental health issue seen throughout the population.[5] Even with clinically prescribed medications, 40-60% of the population on antidepressants do not see any decrease in their depressive symptoms.[5] With the many different antidepressants we offer to patients, the side effects can be detrimental to their mental health causing patients to stop taking medications on a regular basis. The purpose of this review is to determine whether or not probiotics enhance the effects of antidepressant medications and lead to reduced symptoms of depression.

All studies used a patient population who were already diagnosed with major depressive disorder and currently taking prescribed antidepressant medications. An overview of the studies is provided (Table 5). The Reninghause et al and Chahwan et al studies were more similar to each other in their patient participation, and gender populations. Reninghaus et al and Chahwan et al both had similar pretest Beck Depression Inventory (BDI) scores categorizing their patients into moderate to severe depression before any intervention. The Reninghaus et al had a higher decrease in BDI scores after the study with the intervention group having a mean score of 15.11 which categorized them into the mild mood disturbance BDI score and the placebo group having a mean score of 18.2 which categorized them into the borderline clinical depression BDI score.

While the study performed by Schaub et al did not record their participants' pretest BDI scores, both groups ended in the moderately severe depression BDI category with the intervention group having a mean score of 22.38 and the placebo group having a mean score of 22.33. Both groups in the Chahwan et al study fell into the borderline clinical depression BDI

score with the intervention group having a mean score of 19.8 and the placebo group having a mean score of 19.25.

Reninghaus et al and Chawhan et al used similar strains of bacteria leading to lower BDI scores than Schaub et al. Some of the similar bacterial strains of Reninghaus et al and Chowhan et al included B. bifidum, B. lactis, L. acidophilus, L. casei, L. salvarius, and L. lactis. This may indicate that probiotics containing the previously listed strains of bacteria may be more effective as an adjunct supplement to antidepressant medications.

CONCLUSION:

For adults previously diagnosed with major depressive disorder, does probiotic supplementation improve clinical symptoms? Probiotics are microbial supplements that help to maintain gut health. Some studies have shown that adding a probiotic supplement to concurrent treatment for major depression can improve clinical symptoms as reflected in improved depression severity scale scores. Based on the research studies evaluated, probiotic supplementation can be considered as a cost effective, non-pharmaceutical adjuvant therapy in those with major depressive disorder. Future researchof longer duration is needed to further evaluate the benefit of probiotic supplementation on major depressive disorder.

References

1. Uptodate. Accessed October 10, 2022. https://www.uptodate.com/contents/unipolar-depression-in-adults-epidemiology?search=depression%20in%20adults&topicRef=1721&source=see_link

2. Uptodate. Accessed December 1, 2022.

https://www.uptodate.com/contents/unipolar-depression-in-adults-assessment-and-diagnosis?search=depression%20in%20adults&source=search_result&selectedTitle=2~150&usage_type=default&display_rank=2#H644629723

3. Mörkl S, Butler MI, Holl A, Cryan JF, Dinan TG. Probiotics and the microbiota-gut-brain axis: focus on psychiatry. *Curr Nutr Rep*. 2020;9(3):171-182. doi:10.1007/s13668-020-00313-5

4. Probiotics: what you need to know. NCCIH. Accessed October 11, 2022. https://www.nccih.nih.gov/health/probiotics-what-you-need-to-know

5. *Depression: How Effective Are Antidepressants?* Institute for Quality and Efficiency in Health Care (IQWiG); 2020. Accessed October 10, 2022. https://www.ncbi.nlm.nih.gov/books/NBK361016/

6. Probiotics: what you need to know. NCCIH. Accessed October 11, 2022. https://www.nccih.nih.gov/health/probiotics-what-you-need-to-know

7. Schaub AC, Schneider E, Vazquez-Castellanos JF, et al. Clinical, gut microbial and neural effects of a probiotic add-on therapy in depressed patients: a randomized controlled trial. *Transl Psychiatry*. 2022;12(1):1-10. doi:10.1038/s41398-022-01977-z

8. Chahwan B, Kwan S, Isik A, van Hemert S, Burke C, Roberts L. Gut feelings: A randomised, triple-blind, placebo-controlled trial of probiotics for depressive symptoms. *Journal of Affective Disorders*. 2019;253:317-326. doi:10.1016/j.jad.2019.04.097