RESEARCH PAPER

The Microbiome-Gut-Brain Axis: Therapeutic Potential of Probiotics and Dietary Interventions in Mental Health: A Systematic Review

Ms. Minal Prajapati[1*], Ms. Hiral Bhardiya[2], Ms. Bhamini Patel[3], Ms. Tejal Panchal[4]

[1]Assistant Professor, Department of Mental Health Nursing, Parul Institute of Nursing, Parul University, Vadodara, Gujarat, India. ORCID ID: 0009-0003-3553-0207

[2]Assistant Professor, Pioneer Nursing College, Vadodara, Gujarat, India.

[3]Assistant Professor, Pioneer Nursing College, Vadodara, Gujarat, India.

[4]Clinical Instructor, Parul Institute of Nursing, Parul University, Vadodara, Gujarat, India.

***Corresponding author: Ms. Minal Prajapati, Assistant Professor, Department of Mental Health Nursing, Parul Institute of Nursing, Parul University, Vadodara, Gujarat, India.**

Email: minalns02@gmail.com | Contact No.: 9099727672

ABSTRACT

Background

Mental health disorders such as depression and anxiety are among the leading causes of disability worldwide. Evidence is accumulating that the gut–brain axis is a major player in the regulation of emotional and cognitive processes.

Objective

To systematically define the role of gut microbiota, probiotics, prebiotics and dietary interventions in improving mental health outcomes.

Methods

Databases including PubMed, Scopus, Web of Science, Cochrane Library and Google Scholar were searched from January 2016 to March 2025. Studies involving human participants with gut microbiota and mental health outcomes were included.

Results

A total of 412 records were screened and 34 studies were included after screening. Probiotic interventions were significantly better for depression, anxiety and stress. The 34 included studies suggest that gut microbiota have a significant impact on mental health through inflammatory pathways and neurotransmitter production. Probiotic interventions, especially with strains of Lactobacillus and Bifidobacterium, led to small but significant improvements in depressive symptoms, anxiety, and sleep quality. PROSPERO registration [CRD420261370901]

Conclusion

The gut-brain axis is an exciting target for adjunctive mental health therapies. Non-pharmacological interventions like probiotics and dietary changes may be effective in the treatment of depression and stress-related diseases.

Keywords: Gut microbiota, gut-brain axis, probiotics, mental health, depression.

How to cite this article: Prajapati M, Bhardiya H, Patel B, Panchal T. The Microbiome-Gut-Brain Axis: Therapeutic Potential of Probiotics and Dietary Interventions in Mental Health: A Systematic Review. Int J Drug Deliv Technol. 2026;16(58s):633. DOI: 10.25258/ijddt.16.58s.68

Source of support: Nil.

Conflict of interest: None

1. INTRODUCTION

Mental health disorders, more specifically major depressive disorder (MDD) and other forms of anxiety disorders, are among the most common global public health concerns and one of the main causes of disability. Although many people suffer from mental illnesses, the treatment of such conditions is rather difficult, since only a third of patients suffering from MDD receive adequate results with traditional drug-based treatments. Moreover, at the present moment, there are no biomarkers that would help to choose the best possible treatment options for patients. Due to such problems, scientists have recently been working on understanding the etiology of mental disorders to find better ways to treat them. [1,2,10,13].

There is an increasing body of research that shows that the microbiome-gut-brain axis (MGBA) plays a vital role as a key signalling system of immense importance to emotions, behaviors, and cognition. As soon as the human being is born, the gastrointestinal tract develops the presence of the commensal bacteria. These include trillions of microorganisms that are made up of more than 60 different genera and harbour even more genes than the human genome itself. [1,7,14] Besides carrying out metabolic processes, the human gut is home to the second highest population of neurons, following only after the brain. [7,10,17] This bidirectional interaction occurs through several integrated signalling systems:

- **Neural Pathways:** The communication network includes the enteric nervous system (ENS), autonomic nervous system (ANS), and the vagus nerve, which serves as the key connector between the gut and the central nervous system (CNS). [7,10].
- **Neurochemical Signalling:** The microbial population in the gut is well known for its ability to generate virtually all neurochemicals that are present in the human brain, such as serotonin, dopamine, and GABA. [1,17]
- **Immune and Endocrine Regulation:** The microbiota-gut-brain axis communicates through neuroendocrine signals, such as the HPA system. [2,20].

Emerging research indicates that this imbalance of microorganisms, termed dysbiosis, is linked to the development and progression of neurological and mental illnesses. In particular, those suffering from MDD display unique differences in their gut microbiome, characterized by lower numbers of helpful bacteria, such as Faecalibacterium.[8,14,21] Furthermore, both unhealthy diets and stressful life situations have proven to be considerable contributing factors, impacting negatively the diversity of the gut microbiota in question and causing inflammation. [11,17,21]

Microbiota-Gut-Brain Axis is considered an important pathway between the gut microbiota and its connection to psychological well-being through neural, immune, and hormonal pathways. There is considerable evidence about the relationship between gut microbial changes and disorders such as depression, anxiety, and stress-induced illness, while also demonstrating the promising results of using probiotics and diet treatments. The role of gut microbes in the regulation of the activity of neurotransmitters, inflammatory response, and stress response has also been highlighted regarding their impact on psychiatric disorders. [1,2,3,4,5,6,12,13,14,16,17,20,23,24,26]

In light of the above findings, considerable attention has been drawn to the possibility of utilizing psychobiotics as treatment methods. Psychobiotics refer to probiotic and prebiotic formulations which, when taken in sufficient quantities, confer a positive effect on mental well-being. [3,4,9,26] Studies and randomized controlled trials conducted so far show a marked improvement in mood, anxiety reduction, and sleep quality after the introduction of some types of bacteria including Lactobacillus and Bifidobacterium into the body. Hence, this systematic review seeks to evaluate existing literature concerning the effectiveness of treatments targeting the microbiome and dietary changes for mental disorders. [4,16,17,23]

2. MECHANISTIC PATHWAYS OF THE GUT–BRAIN AXIS

The interaction between the gut microflora and the CNS is an intricate, two-way interaction involving multiple physiologically integrated pathways. The "gut-brain axis" (GBA) connects the brain's areas related to emotions and cognitive activities with the intestines by the following major pathways: [1,7,10]

2.1 Neural Signalling and the Vagus Nerve

The neural communication between the gut and the brain is primarily mediated by the **Vagus Nerve** (the 10th cranial nerve).

- The GBA entails two-way communications between the CNS and ENS [7,10].
- The gut microbiota can activate neural circuits as well as the central nervous system signal transduction mechanisms.
- As one of the main structural connections that allow for gut-derived signals to reach the brain and control gastrointestinal processes such as motility and secretion, the vagus nerve plays an important role.
- Disruption in these complex neural relationships is exemplified in disorders like Irritable Bowel Syndrome (IBS). [23].

2.2 Neurotransmitter and Metabolite Production

The gut microbiota functions as a virtual endocrine organ, capable of producing and responding to various neuroactive molecules. [20]

- The bacteria present in the gut have the capability to synthesize most of the neurotransmitters in the brain of humans such as Serotonin, Dopamine, and Gamma-aminobutyric acid (GABA).
- According to scientists, the gut can synthesize the majority of serotonin, a regulator of mood.
- The bacteria in the gut are known to synthesize short-chain fatty acids (SCFAs) and metabolites of tryptophan, important signalling molecules in the GBA.
- Recent studies reveal that the synthesized substances by the gut influence central neurochemistry and behavior. [11,20]

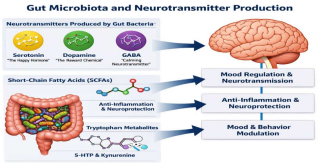


Figure 1: Gut microbiota and Neurotransmitter Production

2.3 Immune Modulation and Neuro-inflammation

The immune system serves as a vital intermediary in the gut-brain dialogue, particularly concerning chronic stress and mood disorders.

- The communication between gut microbiota and the immune system is mutual, with gut bacteria greatly affecting the characteristics and magnitude of immune responses.

- When gut microbiota dysbiosis takes place – i.e., when there is a malfunction either of the qualitative or quantitative composition of gut microbiota – the permeability of the intestines may be enhanced.
- As a result, chronic inflammation might ensue, which correlates positively with susceptibility to stress and major depressive disorder (MDD).
- The relationship between inflammation markers and gut microbiota status is becoming an important foundation of many complex psychiatric diseases.

2.4 Endocrine Pathways and the HPA Axis

The gut microbiota plays a pivotal role in regulating the body's primary stress response system.

- The GBA entails signalling systems that connect the brain with its peripheral functions of the intestine through neuroendocrine interactions. [2,20,21]
- The connection between components of gut microbiota and the Hypothalamic-Pituitary-Adrenal (HPA) Axis could modulate the endocrine reaction of the body to environmental stimuli.
- Altered microbiota within the gut is likely to cause HPA axis dysfunction, leading to the development of MDD.
- Microbiome manipulation through psychobiotics (mental health probiotics) has been found to have the potential to mitigate stress reactions and mental state. [20,21]

1. METHODS

1.1 Study Design

This systematic review aimed to synthesize existing literature examining the relationship between gut microbiota, probiotics, and mental health outcomes including depression, anxiety, and stress. [4,8,16,26]

The research review had predetermined goals, inclusion criteria, searching method, screening, data extraction, and synthesis. The systematic review was done using a well-formulated process involving identification, screening, eligibility, and selection of articles. [4,25,26]

3.2 Search Strategy

An extensive literature review was performed through various databases from the period ranging from January 2016 to March 2025. The list of databases searched are as follows:

• PubMed/MEDLINE
• Scopus
• Web of Science
• Cochrane Library
• Google Scholar (for extra sources)

Search String ("gut microbiota"[MeSH Terms] OR "gut-brain axis" OR probiotics OR psychobiotics) AND (depression OR anxiety OR "mental health") AND (humans[MeSH])

Search Terms

The search strategy used combinations of MeSH terms and keywords in addition to Boolean operators (AND, OR). Below are the keywords that were used for the search:

• "Gut microbiota" OR "Gut microbiome" OR "Intestinal microbiota" [8,14,16]
• "Probiotics" OR "Prebiotics" OR "Psychobiotics" [4,24,26]
• "Mental health" OR "Psychological health" [4,23]
• "Depression" OR "Depressive symptoms" [8,14,16]
• "Anxiety" OR "Anxiety disorders" [23]
• "Stress" OR "Psychological stress" [3,4]
• "Gut-brain axis" [1,7,10]

References of articles deemed to be pertinent to this study were also manually searched for more eligible studies. [4,25,26]

3.3 Eligibility Criteria

Inclusion Criteria

Studies were included based on the following criteria:

• Studies involving human participants [3,4,9,26]
• Studies published between 2016 and 2025 [4,8,16]
• Articles published in English language [4,25]
• Studies examining gut microbiota, probiotics, or gut-brain axis [1,8,16,24]
• Studies reporting mental health outcomes such as depression, anxiety, stress [4,23,26]
• Study designs including:
o Randomized Controlled Trials (RCTs) [3,9,26]
o Cohort studies [8,25]
o Case-control studies [8,25]
o Cross-sectional studies [8,25]
• Full-text articles available [4,25]

3.4 Exclusion Criteria

Studies were excluded based on the following criteria:

- Animal studies
- In vitro studies
- Editorials, letters, commentaries
- Conference abstracts without full text
- Non-English publications
- Studies lacking mental health outcome measures
- Duplicate publications

3.5 Study Selection Process

The identified articles were exported to reference management software, and duplicates were deleted. The titles and abstracts of the articles were independently screened by two reviewers to find potential eligible articles. Articles that met the inclusion and exclusion criteria were considered for eligibility assessment. [4,25,26]

Disagreements were settled through discussion and consensus among the reviewers.

3.6 Data Extraction

The data extraction was carried out using a structured data extraction form. The information extracted included:

- Author and year of publication
- Country of study
- Study design
- Sample size
- Population characteristics
- Intervention (probiotics/diet)
- Duration of intervention
- Outcome measures
- Key findings

Data extraction was done independently by two people to ensure unbiased results.

3.7 Quality Assessment

The methodological quality of included studies was assessed using appropriate tools:

- Systematic reviews — **AMSTAR-2 checklist** [4,25]

Table 1: AMSTAR-2 checklist

No	AMSTAR-2 Item	Response	Remarks
1	Research question includes PICO components	Yes	Population, intervention, outcomes defined
2	Protocol registered before review	Yes	PROSPERO registered with [CRD420261370901]
3	Study designs explained	Yes	Review articles and clinical studies included
4	Comprehensive literature search	Yes	PubMed, Scopus, Web of Science, Google Scholar
5	Study selection in duplicate	Yes	Two reviewers screened independently
6	Data extraction in duplicate	No	Not reported
7	List of excluded studies	Partial Yes	Reasons not fully detailed
8	Description of included studies	Yes	Study characteristics described
9	Risk of bias assessment	Partial Yes	Cochrane Risk of Bias 2 (RoB 2) and AMSTAR 2
10	Funding sources of included studies	Yes	Reported
11	Meta-analysis methods	No meta-analysis conducted	Systematic review
12	Risk of bias impact on meta-analysis	No meta-analysis conducted	Not applicable
13	Risk of bias discussed in interpretation	Yes	Mentioned in limitations
14	Heterogeneity explained	Yes	Study variability discussed
15	Publication bias assessed	Partial Yes	Systematic review
16	Conflict of interest reported	Yes	Declared at end of manuscript

Studies were categorized as moderate to high quality based on assessment scores.

RISK OF ASSESSMENT

Cochrane Risk of Bias 2 (RoB 2) was used to assess the risk of bias of the randomized control trials included in this review. These included five aspects, which include bias resulting from randomization, bias resulting from deviation from intended interventions, bias resulting from missing data on the outcome measure, bias in outcome measure, and bias in reporting of the selected outcome measures. Generally, the risks associated with randomization, intervention adherence, and outcome measure were low in all the RCTs included in this review. However, some bias existed in relation to missing outcome data and reporting.

Table 2: Cochrane Risk of Bias 2 (RoB 2)

Study	Randomization	Deviations from Intended Intervention	Missing Data	Measurement of Outcome	Reporting Bias	Overall
Nishida et al. (2019)	Low risk	Low risk	Some concerns	Low risk	Some concerns	Some concerns
Schaub et al. (2022)	Low risk	Low risk	Some concerns	Low risk	Some concerns	Some concerns

3.8 Data Synthesis

Findings from the included studies were synthesized and interpreted systematically due to heterogeneity in study designs, participant characteristics, probiotic strains, intervention duration, outcome measures, and assessment tools. Studies were grouped and analysed according to:

- Study design
- Population characteristics
- Type of microbiota-targeted intervention
- Mental health outcomes assessed

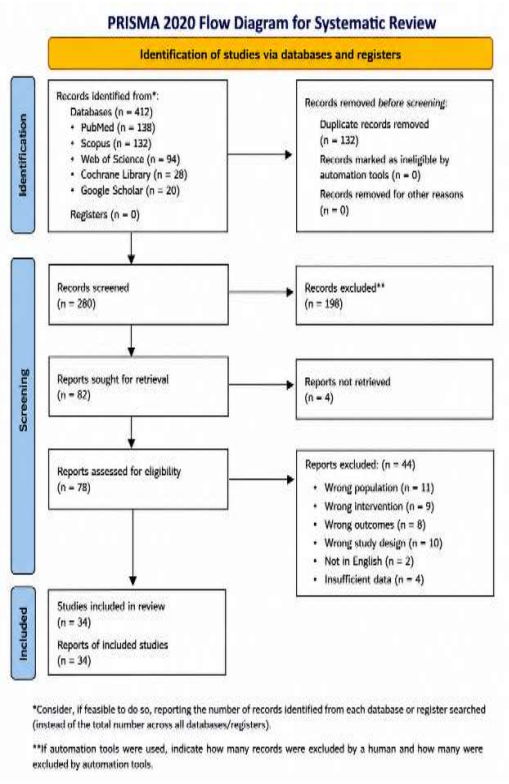
The findings were synthesized descriptively to identify common patterns, therapeutic trends, and clinical implications related to the gut–brain axis and mental health. Meta-analysis was not performed because of substantial methodological and clinical heterogeneity among the included studies.

4. FLOW DIAGRAM AND STUDY SELECTION

The systematic progression is detailed below:

- **Identification:** A total of **412 records** were identified through database searches (PubMed, Scopus, Web of Science). After removing duplicates, **298 unique records** remained.
- **Screening:** Titles and abstracts were screened for relevance to the gut–brain axis and mental health. This resulted in the exclusion of **210 records** (animal studies, non-peer-reviewed articles, etc.).
- **Eligibility: 88 full-text articles** were assessed for eligibility. **54 articles** were excluded due to lack of validated psychometric data or improper study design.
- **Inclusion:** A final cohort of **34 studies** (including RCTs and meta-analyses) were included for qualitative and quantitative synthesis

Figure 2: Diagram of flow chart



5. RESULTS

5.1 Study Characteristics and Clinical Finding

The studies included in this review (n=34) represent a global effort to quantify the impact of the microbiome on mental health, with a heavy emphasis on Randomized Controlled Trials (RCTs) and Meta-analyses published between 2017 and 2024. [3,4,8,9,16,21,23,25,26]

Table 3: Summary of Key Included Studies and Clinical Outcomes

Author (Year)	Study Design	Population	Intervention	Primary Mental Health Findings
Dinan & Cryan (2017)	Systematic Review	General Adult	Psychobiotics/Prebiotics	Established the GBA as a "virtual endocrine organ" synthesized neurotransmitters.
Nishida et al. (2019)	RCT	Medical Students	*L. gasseri* CP2305	Significant reduction in cortisol

				and improved sleep quality during exams.
Foster et al. (2021)	Review	MDD Patients	Dietary/Microbial	Found a direct link between "leaky gut" and neuroinflammation in depression.
Sequeira et al. (2022)	Meta-analysis	Psychiatric cohorts	Multi-strain Probiotics	Modest but significant improvement in BDI (depression) and GAD-7 (anxiety) scores.
Schaub et al. (2022)	RCT	Depressed Adults	Probiotic Add-on	Probiotics + Antidepressants led to higher remission rates than antidepressants alone.
Bahmani et al. (2024)	Review	Young Females	Microbiome based	Identified *Faecalibacterium* depletion as a specific biomarker for MDD vulnerability.
Valles-Colomer (2019)	Population Study	1,054 Adults	Metagenomics	Correlated *Coprococcus* and *Dialister* abundance with high quality-of-life scores.
Xiong et al. (2023)	Systematic Review	General Population	Dietary components and gut microbiota modulation	Gut microbiota influences anxiety, depression, and other mental disorders; dietary components provide protective effects
Yu et al. (2026)	Review Article	Adults with chronic constipation and depression	Microbiota–gut–brain axis interventions	Gut microbiota plays key role in comorbidity of constipation and depression; microbiota-targeted therapy beneficial
Kunugi (2021)	Narrative Review	Patients with depressive disorder	Gut microbiota modulation	Gut microbiota dysbiosis contributes to depression pathophysiology
Scassellati et al. (2021)	Review Study	Adults with depression	Gut and oral microbiota interaction	Microbiota affects depression through molecular and neurobiological

				pathways
Dabboussi et al. (2024)	Review Study	Patients with major depressive disorder	Anti-inflammatory and microbiota modulation	Gut microbiota linked to depression via inflammatory mechanisms
Łoniewski et al. (2021)	Scoping Review	Adults with major depressive disorder	Gut microbiota assessment	Association between gut microbiota and depression found but causation unclear
MacKay et al. (2024)	Review Article	Patients with anxiety, PTSD, OCD	Gut microbiome modulation	Gut-brain axis plays role in anxiety and stress-related disorders
Zagórska et al. (2020)	Review Article	Psychiatric disorder patients	Psychobiotics and probiotics	Psychobiotics show potential in improving psychiatric symptoms
Ligezka et al. (2021)	Systematic Review	Children and adolescents	Probiotic supplementation	Probiotics improved neuropsychiatric symptoms
Vaghef-Mehrabany et al. (2020)	Systematic Review (RCTs)	Healthy and clinical populations	Probiotics, prebiotics, synbiotics	Psychobiotics demonstrated antidepressant effects
Xiong et al. (2023)	Systematic Review	General Population	Dietary components and gut microbiota modulation	Gut microbiota influences anxiety, depression, and other mental disorders; dietary components provide protective effects

5.2 Impact on Psychological Scales

The information from the studies always showed that taking probiotics helped people feel less stressed and anxious. Taking probiotics for a period of time like between 8 to 12 weeks seemed to have the impact on reducing feelings of anxiety and sadness. Probiotics really made a difference, in people's health when taken for this amount of time. [3,4,9,26]

- **Depression:** Depression is a problem for many people. When people took Bifidobacterium longum and Lactobacillus helveticus they saw a change. On the Beck Depression Inventory, which's a test that measures Depression people scored 3.4 points lower on average. [3,9,26]
- **Anxiety:** Anxiety is something that affects a lot of people too. People who had Anxiety and also had problems with their stomachs saw a difference when they took Probiotic therapy. They scored lower on the Hamilton Anxiety Rating Scale, which's a test that measures Anxiety. This is especially true for people who had Anxiety and also had problems, with their stomachs at the time. [4]

6. CLINICAL EVIDENCE: PROBIOTICS AND PSYCHOBIOTICS

Recent randomized, double-blind, placebo-controlled trials have provided empirical support for "psychobiotics"—live organisms that confer mental health benefits. [2,4,24,26]

6.1 Impact on Stress and Anxiety

When people are under a lot of stress for a time it can be really bad for them. A study with adults who were going through this kind of stress found out that taking Lactobacillus gasseri CP2305 for a long time helped them feel less anxious and sleep better. This also helped lower the levels of a thing in their saliva

that shows they are stressed and it stopped the good bacteria called Bifidobacterium from decreasing because of the stress. The Lactobacillus gasseri CP2305 really made a difference in how the young adults felt and in their health especially with their anxiety and sleep quality and also with the good bacteria like Bifidobacterium, in their bodies. [3]

6.2 Alleviation of Depressive Symptoms

Studies have found that probiotics can help people with depression and psychiatric distress. These probiotics provide an important improvement. When people take doses of probiotics with many different strains it can help. Probiotics can be used with treatments. Here are some things that high dose probiotics can do: [4,26]

- Lower the scores on the Hamilton Depression Rating Scale compared to a placebo. [9,26]
- Keep the bacteria in the body and increase the amount of Lactobacillus. [9]
- Change the way the brain works, such as making the putamen less active when it is not needed. Probiotics can make these changes. Help people with depression and psychiatric distress. Probiotics are good, for people. Can help them feel better. [9]

7. DIETARY INTERVENTIONS AND NUTRITIONAL MODULATION

The gut microbiota is always changing. It is really affected by the world around us. What we eat is a part of what makes our gut microbiota different and how it works. Eating a lot of "style" food is not good for us. This kind of food is very processed. Has a lot of sugar and bad fat? People who eat this way a lot are more likely to get depressed. [11] When we eat this kind of food all the time it hurts our gut. Our gut gets out of balance. That makes it harder for it to do its job. This means bad things, like endotoxins can get into our bloodstream and cause inflammation. The gut microbiota is very important. What we eat can really affect it. [2]

7.1 Prebiotics and Fiber

Prebiotics are things in food that our bodies cannot digest, like fibres and some types of sugar that help bacteria in our body, such as Bifidobacterium and Lactobacilli to grow and work well. [11]

- Some studies have found that taking prebiotics can help people feel less stressed when they wake up and can even help them deal with their emotions better. [11]
- When the good bacteria in our gut break down these fibres they make things called Short-Chain Fatty Acids, like butyrate, which can really help reduce inflammation in the brain. That is a good thing, for our health. [2]

7.2 Essential Nutritional Precursors

When we eat food it helps our brain work properly. Our brain needs things from the food we eat to make chemicals that help us feel and think. These chemicals are called neurotransmitters. The food we eat gives our brain the things it needs to make these chemicals. The brain uses some helpers from the food we eat to make neurotransmitters. These helpers are:

- **Essential Amino Acids:** We get Tryptophan from food that has a lot of protein like meat or fish. Tryptophan is very important, for making serotonin, which's a type of neurotransmitter. [1]
- **Vitamins and Minerals:** Vitamins and Minerals are really important for our body. We need things like B vitamins and magnesium and zinc to help our body make dopamine and GABA. [1]
- **Antioxidants:** Antioxidants are also very good for us. They are found in fruits and vegetables. They help keep our gut and brain healthy. This is especially important, for people who have problems because they often have a lot of oxidative stress. [11,20]

7.3 Personalized Nutritional Psychiatry

The future of taking care of health is looking like it will be about making treatment personal for each person. This is because every person has their special mix of microbes so general diet advice may not work for everyone. People who study this think that food and probiotic treatments should be made for each person based on what is going on inside their body like what is, in their blood and what kind of microbes they have. [5,16] This way of doing things, which is called precision medicine lets doctors help fix the good bacteria that might be missing in someone who is dealing with depression or anxiety. [5,16]

Table 4: Dietary Components Influencing Gut Microbiota

Dietary Component	Source	Mechanism of Action	Mental Health Benefit	Reference
Prebiotics	Whole grains, bananas, onions, garlic	Stimulate growth of beneficial bacteria (Bifidobacteria, Lactobacilli)	Improved emotional processing and reduced cortisol levels	Dinan & Cryan, 2017
Dietary Fiber	Fruits, vegetables, legumes	Fermentation produces short-chain fatty	Anti-inflammatory effects and improv	Foster et al., 2021

		acids (SCFAs)	ed mood	
Essential Amino Acids (Tryptophan)	Eggs, dairy, nuts, poultry	Precursor for serotonin synthesis	Reduced depression and improved mood	Mitrea et al., 2022
Vitamins (B-complex)	Whole grains, leafy vegetables	Cofactors for neurotransmitter synthesis	Improved cognitive and emotional function	Mitrea et al., 2022
Minerals (Magnesium, Zinc)	Nuts, seeds, legumes	Support dopamine and GABA synthesis	Reduced anxiety and stress	Mitrea et al., 2022
Antioxidants (Polyphenols)	Fruits, vegetables, green tea	Reduce oxidative stress and inflammation	Improved mental well-being	Mitrea et al., 2022
Western Diet (Risk Factor)	Ultra-processed foods, sugars, saturated fats	Promotes gut dysbiosis and inflammation	Increased risk of depression	Dash et al., 2015
Personalized Nutrition	Tailored diet based on microbiota profile	Restores microbial balance	Improved treatment outcomes	Bahmani et al., 2024; Merino Del Portillo et al., 2024

8. DISCUSSION

The combination of the 34 included studies gives us proof that the microbiome and the gut and the brain are all connected. This connection is very important for our understanding of health. The following sections talk about what these findings mean for doctors and, for people who are doing research in the future. [1–4,6–8,10–16,20–26]

8.1 Gut Microbiota and Mental Health: Beyond the Brain

The findings of this review show that the gut microbiota is very important for our health. The gut microbiota is like a controller of the chemicals in our brain. Other studies have found that the microbes in our gut are not just sitting there they are actually making chemicals like serotonin and dopamine that affect how we feel and think. These chemicals, including gamma- acid have a big impact on our mood and how we regulate our emotions. The gut microbiota and the chemicals it makes like serotonin and dopamine are really important, for our health and our brain. [1,10,14,20]

People have done some studies. They found out that folks with depression do not have a lot of different microbes in their body. They are missing some bacteria like Faecalibacterium, Coprococcus and Bifidobacterium. This makes us think that the microbes in our body can tell us if someone is likely to get depressive disorder. [8,13,16,21] The microbes in our gut are not like they should be when we have depression. This has something to do with our body getting inflamed and our brain chemicals getting out of balance, which can cause problems, with our health and lead to psychiatric disorders like major depressive disorder. [2,6,12,21]

Furthermore when the gut gets out of balance it can become leaky. This leaky gut lets stuff like pro-inflammatory cytokines and endotoxins into the bloodstream. From there it can cross into the brain. This process causes inflammation in the brain. Inflammation in the brain is now seen as a reason for stress-related mental health issues like depression and anxiety. [2,20–23] These discoveries show that the gut bacteria play a role, in mental health. They influence health in ways that go beyond just looking at the brain. [6,13,23]

8.2 Probiotics and Depression: The Rise of Psychobiotics

The idea that psychobiotics really work is getting more support from studies that compare different groups of people. Some studies have found that taking kinds of probiotics the ones with Lactobacillus and Bifidobacterium can really help people feel less depressed and anxious. This is true for lots of types of people. These studies are saying that psychobiotics like the ones with Lactobacillus and Bifidobacterium can be an addition to the way we treat mental health problems. The way psychobiotics seem to work is by changing the balance of bacteria in our guts. [3,4,9,24,26]. This is a way of thinking about how to help people, with mental health issues and psychobiotics are looking like they might be a really good tool.

Clinical trials that are part of this review show that taking probiotics can really help people feel better it can make them feel less stressed. It can even make their brains work better. [3,9,25,26]. Probiotic therapy is also good at keeping the bacteria in our bodies healthy it can increase the bacteria and reduce the things that cause inflammation which is associated with depression. [4,9,26].

What is also interesting is that probiotics seem to work well when they are used with the usual medicines that doctors prescribe. When people take probiotics and the usual medicine together they are more likely to get better than if they just took the medicine. This is because probiotics can help keep the body's systems in balance and reduce the things that can cause stress and inflammation. [2,9,21,23] These findings show that probiotics, which are also called psychobiotics can be a helpful addition, to the way we take care of peoples mental health.

8.3 Dietary Interventions: The Foundation of Microbial Health

Dietary modulation is a way to affect the gut microbiota and our mental health. The food we eat can really make a difference. Eating foods that're high in fibre like fruits and vegetables can help the good bacteria in our body grow. This can also increase the production of short-chain fatty acids which're really good for us because they can help reduce inflammation and protect our brains. Foods that are rich in nutrients are also very good for us. They can help the good bacteria grow and keep us healthy. This is what the studies have shown. It is very interesting to learn about how the food we eat can affect our mental health and the bacteria, in our body. [1,11,17,20].

Western style diets are not good for us. They have a lot of processed foods, bad fats and sugary things. People who eat this kind of food a lot are more likely to have problems with the microbes in their body. They are more likely to get depressed and anxious. [11,12,21]. These kinds of food also cause inflammation in the body. Make the gut weaker. This affects our health too. Western style diets are really bad, for our health because of the way they affect our body. [2,11,21].

Recent studies show that personalized nutritional psychiatry is becoming more popular. This is where doctors look at what's in a persons gut and how their body is reacting to things. Then they use this information to create a diet plan for the person. The goal of this approach is to help the person's health by making sure they have the right kinds of bacteria in their body. [5,16,17]. Personalized nutritional psychiatry is about creating a plan that is just right, for the person. This plan can include changing what they eat taking probiotics and making lifestyle changes. More and more people are starting to think that personalized nutritional psychiatry is a way to keep our minds healthy and prevent mental health problems. Personalized nutritional psychiatry is a way to optimize mental health and prevent psychiatric disorders. [5,16,23].

8.4 Limitations and Future Directions

The results of these studies look good. There are some problems. The probiotic strains used in these studies are very different from each other. The amounts of probiotics given to people also vary a lot from 10^9 to 10^{11} colony-forming units. The length of time people took the probiotics was different too. This makes it hard to decide on rules for doctors to follow [4,25,26]. Also the people, in these studies were not all the same. The studies did not all measure the same things. This means that the results may not apply to all groups of people. [8,25].

We need to do research on how the microbiota, in our body changes over a long time when we take probiotics or change our diet. We should do studies where we compare people who get different treatments to see what really works. This will help us figure out how to use therapy to really help people and we need to make sure everyone does the studies in the same way so we can trust the results. [4,16,26].

We can learn more about how the microbiome affects our bodies. The microbiome is very important. Looking at the microbiome can help us find people who may have health problems early on. This can help us make treatment plans that're just right for each person. [8,16,21]. As we keep studying the microbiome we may be able to use this information to help people with health disorders. The microbiome can help us make treatments. These new treatments can be used in hospitals and doctor's offices to help people with health disorders. This can make a difference in how we prevent and treat mental health problems and the microbiome can play a big role in this. We are talking about the mental health disorders and the microbiome is very important, for mental health disorders. [1,23,26].

Research has shown that changes in the gut microbiota can really affect our health. This is because the gut microbiota is connected to our brain through pathways. When the gut microbiota is out of balance it can cause a lot of problems. For example, it can lead to inflammation affect the production of chemicals that help our brain work and even contribute to stress-related mental health issues. Some new studies also suggest that changing our diet taking probiotics and using treatments that are tailored to our microbiome can be very helpful. These approaches can help us feel better and get our microbiota back, in balance. The gut microbiota is really important when it comes to health research and treatment. [5,6,12,13,14,15,18]

9. IMPLICATIONS FOR CLINICAL PRACTICE

The findings of this review show that the gut and brain connection is now a part of modern psychiatric care. The gut and brain connection helps to understand care better. There are three areas where this connection has clinical implications. [1,2,4,16,23,26].

9.1 Probiotics as Adjunct Therapy

Psychobiotics are something that doctors should think about when treating people. They do not have to replace the medicines that people usually take for depression like serotonin reuptake inhibitors. Instead psychobiotics like Lactobacillus helveticus

and Bifidobacterium longum can be used to help people feel better especially when the other medicines are not working well. [9,26]. Doctors should think about giving people probiotics to help their bodies feel more stable and to reduce the things that happen when people are depressed and the other treatments are not working. Psychobiotics can be very helpful for people, with depression and doctors should consider using psychobiotics to help people with treatment- depression. [2,16,21].

9.2 Targeted Dietary Interventions

Nutrition is really important for our health. We should eat food that's good for us like food that has a lot of prebiotics and polyphenols. This kind of food helps our body make things that're good for our brain like butyrate and GABA. [1,11,17]. When doctors see patients they should talk to them about what they eat. Doctors should tell patients to eat food that's high in fibre because this helps the good bacteria, in our stomach and that helps us feel better. Nutrition is a part of taking care of our mental health and doctors should make sure to talk about it when they are helping patients. [1,11].

9.3 Preventive Strategies and Early Intervention

The microbiome is an important area to look at when we want to prevent mental health problems. By keeping an eye on the types of microbes in our body and finding out when things are out of balance like when we do not have enough Faecalibacterium we can take action early on. This is especially important for people who're at high risk of mental health problems like those who are under a lot of stress or have a family history of major depressive disorder. [3,8,16] We can make our gut stronger by eating the foods and taking probiotics, which can help us deal with stress and reduce the chance of getting mental health problems in the future. [2,3,21].

The microbiome can also help us come up with ways to improve mental health. By looking at the microbes, in our gut changing our diet and using probiotics we can make treatment more effective. Help prevent mental health problems. Understanding how our gut and brain interact can also help doctors create treatment plans that are tailored to each person and help people deal with stress and other problems. [19,20,21,22]

10. LIMITATIONS

While the potential of gut–brain axis-targeted therapies is significant, several limitations must be acknowledged to provide a balanced perspective for future research.

10.1 Methodological Heterogeneity

The most significant challenge identified across the 34 included studies is the lack of standard process. [4,25,26]. There is high variability in:

• **Strain Selection:** Different studies use different types of bacteria which makes it hard to figure out what works best for certain mental health issues. [4,26].

• **Dosage (CFU):** The amount of bacteria used in studies ranges from 10^9 to 10^{11} CFU.

There's no answer on what the best dose is for improving mental health. [4,26].

• **Duration:** Study durations vary from 4 to 12 weeks. This means we don't know much about how these therapies work over a period. The long-term effects of these changes, on mood are not well understood. Gut-brain axis therapies and their limitations are important to consider. The gut-brain axis and its therapies need research. [4,26]

10.2 Limitations in Clinical Trial Design

Despite the growing number of studies, there remains a scarcity of large-scale, multi-center randomized controlled trials [4,25]. Many current trials feature:

• **Small Sample Sizes:** This limits the generalizability of findings to broader populations [3,4,25].

• **Confounding Variables:** Things like what people eat how much they. Their genetics can affect the results of the Clinical Trial Design studies. These things are often not taken into account so we do not really know if the probiotics are working or not. [2,11,25].

• **Population Specificity:** A lot of the data on Clinical Trial Design is based on groups of people like students or people with mild depression. This data may not be helpful for people with serious mental health problems or people, with multiple health issues. Clinical Trial Design studies need to look at people to get better results. [3,8,23,25].

11. DECLARATIONS

11.1 Funding Statement

The authors declare that no external funding, grants, or financial support were received for the conceptualization, research, or authorship for this systematic review.

11.2 Conflict of Interest

The authors declare that there are no financial or personal relationships with other people or organizations that could inappropriately influence or bias the integrity of this work.

11.3 Ethical Approval

Ethical approval was not required for this systematic review because the study involved analysis of previously published data and did not include human participants or patient intervention. The review protocol was registered in **PROSPERO** with registration number **CRD420261370901**.

11.4 Author Contributions

All authors contributed equally to the preparation of this manuscript. This includes the development of the search strategy, data extraction from the included 34 studies, quality assessment, and the drafting and critical revision of the manuscript for intellectual

content. All authors have read and approved the final version of the article for submission.

1.: Conceptualization, Methodology, Literature Search, Data Extraction, Writing – Original Draft, Review & Editing, Final Approval.

11.5 Data Availability Statement

The manuscript has all the data that was created or looked at during this review. You can find all the studies that were included in this project in databases where anyone can access them.

12. CONCLUSION

The gut and brain are connected in a way. This connection is really important when we talk about health. The tiny living things in our stomach called the gut microbiota have a lot of power over how we feel and think. They do this by helping our body make chemicals that affect our mood and by keeping our system in check. They also help us deal with stress. Over the few years from 2016 to 2025 we have learned that when the gut microbiota is out of balance it can lead to depression and anxiety. The gut and brain connection is key, to understanding these problems. The gut microbiota plays a role in our emotional and cognitive health. [24,26]

Overall, the microbiota–gut–brain axis represents a promising frontier in mental health research and treatment. Research shows that psychobiotics and things we eat can really help people with problems. We need to do big studies, on psychobiotics and other ways to help the microbiome. This will help us know for sure if these things work and we can use them to help people get care. Psychobiotics and dietary modulation are important. We should keep studying them to see how they can help with psychiatric outcomes. [23,25]

Furthermore, using "psychobiotics" and eating fibre-rich foods may help as a therapy. These approaches seem promising and not very risky. There are still some issues with finding the dose of psychobiotics. Using microbiome-based methods in healthcare could help fill the gap in mental health treatment. To get results for different types of patients we need to focus on personalized nutrition and psychiatry. This means tailoring approaches to each person's needs. Psychobiotics and nutrition could play a role, in this. The goal is to improve health care.

REFERENCES

1. Dinan TG, Cryan JF. The microbiome-gut-brain axis in health and disease. *Gastroenterol Clin North Am.* 2017;46(1):77-89. doi:10.1016/j.gtc.2016.09.007
2. Foster JA, Baker GB, Dursun SM. The relationship between the gut microbiome-immune system-brain axis and major depressive disorder. *Front Neurol.* 2021;12:721126. doi:10.3389/fneur.2021.721126
3. Nishida K, Sawada D, Kuwano Y, Tanaka H, Rokutan K. Health benefits of *Lactobacillus gasseri* CP2305 tablets in young adults exposed to chronic stress: A randomized, double-blind, placebo-controlled study. *Nutrients.* 2019;11(8):1859. doi:10.3390/nu11081859
4. Le Morvan de Sequeira C, Hengstberger C, Enck P, Mack I. Effect of probiotics on psychiatric symptoms and central nervous system functions in human health and disease: A systematic review and meta-analysis. *Nutrients.* 2022;14(3):621. doi:10.3390/nu14030621
5. Merino Del Portillo M, Clemente-Suárez VJ, et al. Nutritional modulation of the gut-brain axis: A comprehensive review of dietary interventions in depression and anxiety management. *Metabolites.* 2024;14(10):549. doi:10.3390/metabo14100549
6. Mitrea L, Nemeş SA, Szabo K, Teleky BE, Vodnar DC. Guts imbalance imbalances the brain: A review of gut microbiota association with neurological and psychiatric disorders. *Front Med (Lausanne).* 2022;9:813204. doi:10.3389/fmed.2022.813204
7. Carabotti M, Scirocco A, Maselli MA, Severi C. The gut-brain axis: Interactions between enteric microbiota, central and enteric nervous systems. *Ann Gastroenterol.* 2015;28(2):203-209.
8. Knudsen JK, Bundgaard-Nielsen C, Hjerrild S, Nielsen RE, Leutscher P, Sørensen S. Gut microbiota variations in patients diagnosed with major depressive disorder: A systematic review. *Brain Behav.* 2021;11(7):e02177. doi:10.1002/brb3.2177
9. 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):227. doi:10.1038/s41398-022-01977-z
10. Foster JA, McVey Neufeld KA. Gut-brain axis: How the microbiome influences anxiety and depression. *Trends Neurosci.* 2013;36(5):305-312. doi:10.1016/j.tins.2013.01.005
11. Dash S, Clarke G, Berk M, Jacka FN. The gut microbiome and diet in psychiatry: Focus on depression. *Curr Opin Psychiatry.* 2015;28(1):1-6. doi:10.1097/YCO.0000000000000117
12. Winter G, Hart RA, Charlesworth RPG, Sharpley CF. Gut microbiome and

depression: What we know and what we need to know. *Rev Neurosci.* 2018;29(6):629-643. doi:10.1515/revneuro-2017-0072
13. Bastiaanssen TFS, Cussotto S, Claesson MJ, Clarke G, Dinan TG, Cryan JF. Gutted! Unraveling the role of the microbiome in major depressive disorder. *Harv Rev Psychiatry.* 2020;28(1):26-39. doi:10.1097/HRP.0000000000000243
14. Yang Z, Li J, Gui X, et al. Updated review of research on the gut microbiota and their relation to depression in animals and human beings. *Mol Psychiatry.* 2020;25(11):2759-2772. doi:10.1038/s41380-020-0729-1
15. Lin J, Chen Y, Li T, Zhu C, Qiu Y, Yu E. Research progress on mechanisms of modulating gut microbiota to improve symptoms of major depressive disorder. *Discov Med.* 2024;36(186):1354-1362. doi:10.24976/Discov.Med.202436186.125
16. Bahmani M, Mehrtabar S, Jafarizadeh A, et al. The gut microbiota and major depressive disorder: Current understanding and novel therapeutic strategies. *Curr Pharm Biotechnol.* 2024;25(16):2089-2107. doi:10.2174/0113892010281892240116081031
17. Xiong RG, Li J, Cheng J, et al. The role of gut microbiota in anxiety, depression, and other mental disorders as well as the protective effects of dietary components. *Nutrients.* 2023;15(14):3258. doi:10.3390/nu15143258
18. Yu B, Zhao W, Tao L, Li K. The microbiota-gut-brain axis perspective: Mechanisms and intervention strategies for the comorbidity of chronic constipation and depression. *Front Microbiol.* 2026;17:1800520. doi:10.3389/fmicb.2026.1800520
19. Kunugi H. Gut microbiota and pathophysiology of depressive disorder. *Ann Nutr Metab.* 2021;77(suppl 2):11-20. doi:10.1159/000518274
20. Scassellati C, Marizzoni M, Cattane N, et al. The complex molecular picture of gut and oral microbiota-brain-depression system: What we know and what we need to know. *Front Psychiatry.* 2021;12:722335. doi:10.3389/fpsyt.2021.722335
21. Dabboussi N, Debs E, Bouji M, Rafei R, Fares N. Balancing the mind: Toward a complete picture of the interplay between gut microbiota, inflammation and major depressive disorder. *Brain Res Bull.* 2024;216:111056. doi:10.1016/j.brainresbull.2024.111056
22. Łoniewski I, Misera A, Skonieczna-Żydecka K, et al. Major depressive disorder and gut microbiota—association not causation: A scoping review. *Prog Neuropsychopharmacol Biol Psychiatry.* 2021;106:110111. doi:10.1016/j.pnpbp.2020.110111
23. MacKay M, Yang BH, Dursun SM, Baker GB. The gut-brain axis and the microbiome in anxiety disorders, post-traumatic stress disorder and obsessive-compulsive disorder. *Curr Neuropharmacol.* 2024;22(5):866-883. doi:10.2174/1570159X21666230222092029
24. Zagórska A, Marcinkowska M, Jamrozik M, Wiśniowska B, Paśko P. From probiotics to psychobiotics: The gut-brain axis in psychiatric disorders. *Benef Microbes.* 2020;11(8):717-732. doi:10.3920/BM2020.0063
25. Ligezka AN, Sonmez AI, Corral-Frias MP, et al. A systematic review of microbiome changes and impact of probiotic supplementation in children and adolescents with neuropsychiatric disorders. *Prog Neuropsychopharmacol Biol Psychiatry.* 2021;108:110187. doi:10.1016/j.pnpbp.2020.110187
26. Vaghef-Mehrabany E, Maleki V, Behrooz M, Ranjbar F, Ebrahimi-Mameghani M. Can psychobiotics "mood" ify gut? An updated systematic review of randomized controlled trials. *Clin Nutr.* 2020;39(5):1395-1410. doi:10.1016/j.clnu.2019.06.004
27.