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Authors' Affiliation:
Collegium Medicum at Jan Kochanowski University in Kielce, Poland

***Corresponding author:**
Agnieszka Kowalska, Collegium Medicum at Jan Kochanowski University in Kielce, Poland;
e-mail: aga_kowalska1@onet.eu

Contact list:

Agnieszka Kowalska	aga_kowalska1@onet.eu
Milena Kędzierska	kedzierska.milena19@gmail.com
Michał Biernacki	michalbiernacki01@op.pl
Michał Wójcicki	michal.w953@gmail.com

Orcid list:

Agnieszka Kowalska	0009-0007-1298-7788
Milena Kędzierska	0009-0008-0980-3543
Michał Biernacki	0009-0009-8083-7129
Michał Wójcicki	0009-0008-1649-5024

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The Gut–Brain Axis in Depression: A Review of Current Evidence

Milena Kędzierska, Michał Wójcicki, Agnieszka Kowalska*, Michał Biernacki

ABSTRACT

Major Depressive Disorder (MDD) is no longer seen just as a problem with brain chemicals. Instead, it is a whole-body issue. A key part of this is the gut-brain axis, in which the brain and the digestive system communicate via nerves, hormones, and the immune system. This review looks at how an unhealthy balance of gut bacteria (dysbiosis) contributes to depression. This constant, low-level inflammation alters how the body processes amino acids; instead of producing serotonin (the "mood" chemical), the body produces toxins that can stress brain cells and reduce levels of growth factors like BDNF. Furthermore, signals from gut microbes can alter how the body responds to stress and how it produces calming neurotransmitters, such as GABA. Finally, this paper examines psychobiotics—specific probiotics that may improve mental health. Clinical trials show that certain strains of Lactobacillus and Bifidobacterium can reduce depressive symptoms and strengthen the gut barrier. While these results are encouraging, the studies are currently small and short-term. More standardized research is needed, but targeting gut health is clearly a promising new strategy for treating depression.

Keywords: gut-brain axis, depression, microbiota, inflammation, cytokines, short-chain fatty acids (SCFA), probiotics.

1. INTRODUCTION

For over two thousand years, we have lived with the idea that "all disease begins in the gut," a concept usually linked to Hippocrates (Cryan et al., 2019). Today, this old intuition is causing a major shift in how we understand neuroscience and psychiatry (Kelly et al., 2015). We no longer view depression simply as a chemical imbalance in the brain. Instead, we see it as a whole-body condition that causes persistent low mood, a loss of interest in life, and major changes in sleep and appetite (Cryan et al., 2019; Kelly et al., 2015). Recent research suggests these symptoms may actually originate in the microbiota-gut-brain axis- a two-way communication system in which the brain and the gut work together to keep the body healthy (Sarkar et al., 2016; Cryan et al., 2019).

This axis comprises several layers: the central nervous system, the nerves in our digestive tract, the immune system, and the trillions of bacteria living in our gut. These microbes are so important that scientists often refer to them as a "superorganism" that regulates how our bodies function (Kelly et al., 2015; Cryan et al., 2019). Over millions of years, humans and microbes have grown to depend on each other. These bacteria provide signals that enable our stress response (the HPA axis) to develop and our immune system to learn how to function (Cryan et al.,

2019; Sarkar et al., 2016). While our genes remain mostly the same throughout life, our microbiome constantly changes in response to what we eat and the stress we face. This makes it a great target for new medical treatments (Cryan et al., 2019).

This review focuses on the "leaky gut" theory. This idea suggests that when the gut lining breaks down, pieces of bacteria- like inflammatory toxins can leak into the blood (Kelly et al., 2015; Sarkar et al., 2016). This creates constant, low-level inflammation often seen in depressed patients. These inflammatory signals can reach the brain and directly change how we feel and behave (Kelly et al., 2015). In this paper, we will examine how the gut and brain remain connected, and whether psychobiotics (probiotics and prebiotics) can help manage depression.

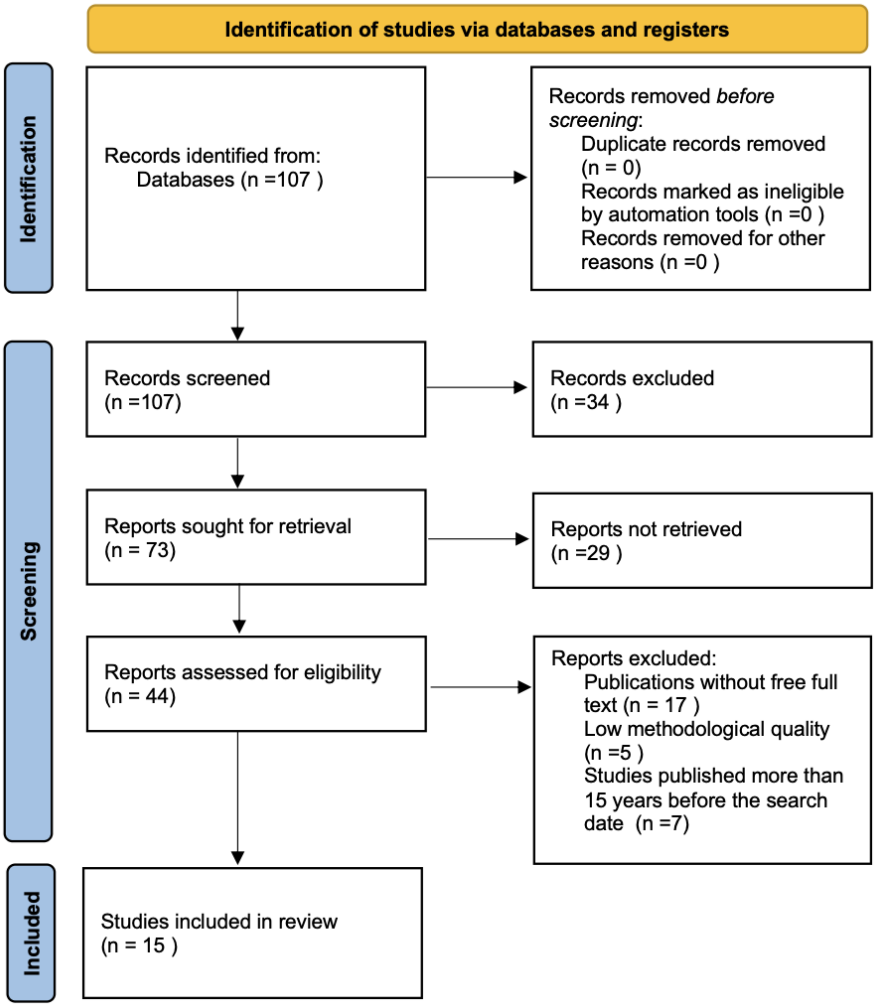

Figure 1. Entire selection process is illustrated in the PRISMA diagram

2. REVIEW METHODS

The search strategy utilized keywords: "gut-brain axis", "depression", "microbiota", "inflammation", "cytokines", "short-chain fatty acids" (SCFA), and "probiotics". Databases were searched to cover the biological and physiological basis of psychiatric and neurodevelopmental disorders, with a specific focus on how the resident microbiota influences host behavior.

Inclusion & Exclusion: We reviewed full-text articles in English published over the last 15 years (2011 to 2025). This timeframe was chosen because most major discoveries about the gut-brain axis occurred during this period. We focused on high-quality evidence, such as systematic reviews, meta-analyses, and randomized controlled trials (RCTs). We also included important animal studies- like those involving germ-free mice or fecal transplants- to help explain how these processes work.

Our search focused on "psychobiotics," which are probiotics or prebiotics that can improve mental health. We excluded any articles that did not explain the actual science behind how the gut and brain communicate. We also excluded studies that were not available in full or that did not focus on the direct relationship between the host and its gut bacteria.

Study Selection & Data Extraction: The selection process was carried out by three independent authors, who evaluated titles and abstracts against pre-established criteria. In case of discrepancies, decisions were made by consensus. All data presented in this paper come from peer-reviewed scientific studies that met the above criteria. A preliminary database search identified 107 records. 44 articles were selected for full-text evaluation. Based on inclusion and exclusion criteria, 15 publications were included in the final synthesis. The entire selection process is illustrated in the PRISMA diagram (Figure 1).

3. RESULTS AND DISCUSSION

The Influence of Enteric Microorganisms on the Etiology of Depressive Disorders

The trillions of microbes in our gut form a complex ecosystem that is vital to maintaining healthy metabolism and immune function (Liu et al., 2023). When these bacteria are stable and balanced- a state called eubiosis- the communication between the gut and the brain works exactly as it should (Mhanna et al., 2024). However, in people with depression, this balance is often disrupted. This "dysbiosis" means the gut loses its healthy variety, with certain types of bacteria becoming either too common or too rare.

What is actually happening is a fight for survival within the gut. Pro-inflammatory strains move in and dominate the environment, physically displacing the "good" bacteria that the body relies on to keep inflammation in check (Liu et al., 2023). The disappearance of these beneficial, butyrate-producing microbes is particularly damaging, as their absence directly feeds into depressive symptoms (Liu et al., 2023; Reyes-Martínez et al., 2023). This "microbial signature" of depression is typically defined by an overgrowth of specific groups- such as Bacteroides, Eggerthella, and Streptococcus- while the host sees a sharp decline in essential commensals like Blautia, Faecalibacterium, Coprococcus, and Bifidobacterium (Liu et al., 2023; McGuinness et al., 2022).

Mechanisms of How Inflammation Affects the Brain

It is a mistake to think that inflammation stays only in the body. In reality, pro-inflammatory cytokines can enter the central nervous system. They can also be produced directly in the brain by activated glial cells, such as microglia and astrocytes, which can lead to neuroinflammation (Kouba et al., 2024). This process usually happens through several main pathways.

First, small proteins called cytokines (such as IL-2, TNF-α, and IFN-γ) alter brain function. They turn on a special enzyme called IDO. This enzyme forces the body to make a chemical called kynurenine instead of serotonin. This creates two big problems. One, the brain does not have enough serotonin to feel happy. Two, the body produces harmful toxins, such as quinolinic acid. These toxins are like poison; they hurt brain cells and damage the brain. The data presented in Table 1 illustrates that the gut-brain axis relies on both direct neural connections and complex biochemical shifts to influence emotional states.

Table 1. Physiological Pathways Linking Gut Microbiota to Depressive Pathophysiology

Pathway	Biological Mechanism	Impact on Depression	Citations
Neurotransmitter Synthesis	Bacterial genera such as Lactobacillus and Bifidobacterium possess the metabolic capacity to synthesize key neurotransmitters including GABA and serotonin, although a significant portion of serotonin is produced peripherally in the gastrointestinal tract.	Dysbiosis can limit the availability of essential precursors like tryptophan, shifting metabolism toward the kynurenine pathway and leading to impaired serotonin synthesis, which is a central factor in depressive pathophysiology.	Mhanna, et al., 2024; Reyes-Martínez, et al., 2023; Sarkar, et al., 2016
Neuroendocrine & HPA Axis	Increased intestinal permeability, often referred to as "leaky gut," allows the translocation of bacterial products like lipopolysaccharides (LPS) into the bloodstream, triggering systemic inflammation.	Chronic inflammation and microbial signals activate the HPA axis, resulting in excessive cortisol secretion. This creates a vicious cycle where elevated cortisol further degrades the intestinal barrier and exacerbates pathology.	Liu, et al., 2023; Reyes-Martínez, et al., 2023; Kelly, et al., 2015

Neural Transmission	The vagus nerve serves as one of the most critical direct physical highways for communication between the enteric environment and the central nervous system.	Microbes send signals via the vagus nerve that influence depressive-like behaviors. Experimental evidence shows that a vagotomy can inhibit the development of depressive phenotypes induced by microbial changes, confirming the pathway's necessity.	Mhanna, et al., 2024; Liu, et al., 2023; Reyes-Martínez, et al., 2023; Cryan, et al., 2019

How Inflammation Changes the Brain

It is a common mistake to think that inflammation stays trapped in the body. In reality, inflammatory signals (cytokines) can cross into the brain. They can also be produced directly inside the brain by "activated" glial cells, such as microglia and astrocytes. When these cells stay switched on, it leads to chronic neuroinflammation (Kouba et al., 2024).

This inflammation sets off a chain reaction in your brain. First, it messes with the HPA axis, which is basically your body's "command center" for handling stress. When this center gets out of whack, your cortisol levels (the stress hormone) stay stuck on high. This makes it really hard for your brain to ever "switch off" the feeling of being stressed (Poletti et al., 2024; Kouba et al., 2024). To make matters worse, cytokines make the brain's stress receptors less sensitive, which keeps this cycle going. Inflammation also hits neuroplasticity,the brain's ability to change and heal. By lowering levels of BDNF (a protein essential for cell growth), inflammation prevents the brain from repairing itself (Poletti et al., 2024; Kouba et al., 2024). They increase the activity of an enzyme called IDO, which forces the body to use tryptophan to create kynurenine instead of serotonin. This shift creates two problems: it leads to a serotonin shortage and produces harmful substances like quinolinic acid. These toxins damage brain cells by overstimulating glutamate receptors. Long-term inflammation also messes with the HPA axis, the system that controls how you deal with stress. When this happens, your body stays flooded with cortisol because your brain loses the ability to "switch off" its stress mode (Poletti et al., 2024; Kouba et al., 2024). To make things harder, certain chemicals (cytokines) make your brain's stress sensors less sensitive. It's almost like your brain becomes "deaf" to its own signals to calm down. It's like the brain becomes deaf to its own signals to calm down. This creates a self-sustaining cycle of dysfunction that is difficult to break (Poletti et al., 2024).

Beyond stress regulation, neuroinflammation actively damages neuroplasticity. It lowers the production of BDNF, a protein that acts like "fertilizer" for brain cells. Short-chain fatty acids, often called SCFAs, are important small molecules that play a huge role in keeping our bodies healthy. When researchers refer to SCFAs, they usually mean three main types: acetate, propionate, and butyrate. These compounds are not just found in food; instead, they are produced in our gut by bacteria. These helpful bacteria feed on dietary fiber that our bodies cannot digest by themselves. Through a natural process called fermentation, the bacteria turn this fiber into SCFAs (Chudzik et al., 2021). The amount and type of SCFAs produced mostly depend on what exact types of bacteria live in our gut and how much fiber we eat in our daily diet.

Once produced, these fatty acids have several major biological functions. First of all, SCFAs have a strong ability to stop or reduce inflammation in the body. Butyrate is especially known for its anti-inflammatory properties, which help calm down the immune system and protect the gut. Secondly, these acids help repair and seal the gut barrier, which stops a harmful problem commonly known as "leaky gut". Studies have shown that giving a mix of different SCFAs can fix gut permeability issues that are caused by chronic stress (Harsanyi et al., 2022). Finally, SCFAs have a big impact on brain function and neuroplasticity. They can control how open the blood-brain barrier is and can even cross directly into the brain. They affect brain cells and increase the levels of BDNF, which is a key protein needed for brain growth, learning, and neuroplasticity.

Recent studies clearly show that SCFAs also play a major role in depression (Wu et al., 2024). Researchers noticed that people suffering from depression usually have fewer bacteria that produce these helpful SCFAs, especially butyrate (McGuinness et al., 2022). A lack of these anti-inflammatory molecules in the gut is often linked to the development and severity of depressive symptoms. Interestingly, experiments have shown that giving subjects a mix of acetate, propionate, and butyrate can actually reduce depression-like behaviors caused by severe stress. This discovery suggests that restoring the natural balance of SCFAs in the gut could offer hope for new and effective ways to treat depression in the future.

The Role of Probiotics in Depression

The Role of Probiotics in Modulating the Gut-Brain Axis in the Course of Depression. Probiotics are defined as live microorganisms that, when administered in adequate amounts, confer health benefits on the host. In the context of mental disorders, including depression, particular importance is attributed to so-called psychobiotis—bacterial strains that exert a beneficial effect on mental health. The strains most commonly used in clinical trials belong to the Lactobacillus and Bifidobacterium genera (Chudzik et al., 2021; Alli et al., 2022).

The way probiotics actually help with depression mostly comes down to their influence on the gut-brain axis- that two-way communication line that links our gut bacteria to the brain through nerves, hormones, and the immune system (Alli et al., 2022; Chudzik et al., 2021). Essentially, probiotics tweak our internal chemistry. They play a role in regulating how the body produces key neurotransmitters like GABA and serotonin, and they can even help bring down cortisol levels- changes that often lead to real, noticeable improvements in how someone feels and acts (Chudzik et al., 2021).

Clinical Efficacy and Limitations

We haven't reached a definitive conclusion yet on how well probiotics work for depression, but the data is starting to look more and more promising. According to meta-analyses, probiotics seem to offer small but statistically significant improvements in depressive symptoms. Research indicates that the beneficial effect is more noticeable in clinical and medical groups compared to healthy populations (Liu et al., 2019). For example, supplementation with Lactobacillus helveticus R0052 and Bifidobacterium longum R0175 was associated with improved mood and reduced anxiety in MDD patients (Chudzik et al., 2021). Similarly, the use of Bacillus coagulans MTCC 5856 in patients with irritable bowel syndrome and comorbid depression resulted in a significant reduction in depressive symptoms (Chudzik et al., 2021).

However, significant limitations of current probiotic therapy must be emphasized. Primarily, the literature is characterized by a large number of studies conducted on healthy populations, where the potential for reducing depressive symptoms is limited (Liu et al., 2019). One major hurdle is that we still don’t have enough long-term follow-up data or direct "head-to-head" comparisons between probiotics and traditional antidepressants (Alli et al., 2022). However, the evidence for probiotics is not yet conclusive due to several methodological flaws in clinical trials- most notably, the small number of participants (Liu et al., 2019; Chudzik et al., 2021). Although probiotics show promise as an additional treatment for depression, it is still too early to make final conclusions. Many current findings are limited because the clinical trials often involve too few people, making the results less certain (Liu et al., 2024; Chudzik et al., 2021). To fully confirm how effective these treatments are, we need larger studies that follow the same strict, standardized rules across the board (Liu et al., 2019; Alli et al., 2022).

4. CONCLUSION

Looking at the big picture, the microbiota-gut-brain axis is a major breakthrough in how we view depression- not just as a mental struggle, but as a systemic inflammatory disorder. When the gut is out of balance and becomes "leaky," it opens the door for neuroinflammation and throws the HPA axis off course. This is where "psychobiotics" come in; they offer a really promising way to reset the microbial balance and ease depressive symptoms. Still, we have to be realistic- the clinical results are still complicated by inconsistent study methods. To truly make these interventions a standard part of psychiatric care, we need more rigorous, long-term research to support them.

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Authors’ Contributions

Conceptualization: Agnieszka Kowalska, Michał Wójcicki.
Methodology: Milena Kędzierska, Michał Biernacki.
Formal Analysis: Agnieszka Kowalska.
Resources: Milena Kędzierska, Michał Biernacki, Michał Wójcicki.
Writing-original draft: Agnieszka Kowalska, Milena Kędzierska, Michał Biernacki, Michał Wójcicki.
Writing-review and editing: Michał Biernacki, Michał Wójcicki.

Visualization: Agnieszka Kowalska, Milena Kędzierska.
All authors have read and agreed with the published version of the manuscript.

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Data and materials availability
All data associated with this study will be available based on the reasonable request to corresponding author.

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