

Medical Science

To Cite:

Brożyna A, Mackiewicz A, Pietrucień A, Kursa N, Bielak K, Woźniak K, Witkowska J, Ksenia Jakubiak K, Kurczyński M, Krasoń M. The Role of Gut Microbiota in the Development of Depression: A Review. *Medical Science* 2026; 30: e93ms3880
doi: <https://doi.org/10.54905/diss.v30i171.e93ms3880>

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Peer-Review History

Received: 21 July 2025

Reviewed & Revised: 16/August/2025 to 03/May/2026

Accepted: 12 May 2026

Published: 29 May 2026

Peer-review Method

External peer-review was done through double-blind method.

Medical Science

pISSN 2321-7359; eISSN 2321-7367



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The Role of Gut Microbiota in the Development of Depression: A Review

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ABSTRACT

Depression is a common disorder, but we still do not understand its exact pathogenesis. In recent years, the interest in the role of gut microbiota has increased. The microbiota–gut–brain axis describes the connection between the gastrointestinal system and the central nervous system, involving neural, immune, and metabolic pathways. This review aims to present current knowledge on this relationship. Research has shown that patients with major depressive disorder (MDD) have a distinct gut microbiota structure compared to healthy individuals. Similar observations come from animal studies. Researchers observed that transplantation of microbiota from depressed individuals may induce depressive-like behavior in experimental models. Several mechanisms may explain this association. These include increased inflammatory activity, disturbances in tryptophan metabolism, and changes in neuroendocrine function. There are also studies suggesting that modifying the gut microbiota, for example, with probiotics or fecal microbiota transplantation, may have a positive effect on depressive symptoms. In conclusion, current data suggest that gut microbiota may play a role in depression. However, further studies are needed to understand these mechanisms better and to evaluate their possible clinical use.

Keywords: gut microbiota, depression, major depressive disorder, gut-brain axis, and inflammation.

1. INTRODUCTION

The prevalence of depression is increasing very fast nowadays, making it one of the most significant causes of disability worldwide. Long-lasting low mood, loss of interest, and difficulties in everyday functioning are the characteristics of depression. Although many studies have addressed this issue, its pathophysiology remains unclear. Scientists suggest that MDD has many causes, involving biological, psychological, and environmental factors.

In recent years, the gut microbiota has become an important area of interest in mental health research. More and more studies show that intestinal microflora can modify brain function and behavior. Because of this, gut microbiota is now often

considered as a possible factor involved in the development of psychiatric disorders, including depression (Liang et al., 2018).

The link between the gut and the brain is the microbiota–gut–brain axis. It is a two-way communication system that includes the enteric nervous system, gut microbiota, and the central nervous system. This interaction takes place through neural pathways, immune processes, and metabolic mechanisms, which together may influence emotional and mental functions (Carabotti et al., 2015).

This review presents the role of the gut microbiota in the occurrence of depression, focusing on changes in its composition, potential biological mechanisms, and treatment options.

2. REVIEW METHODS

During the preparation of this review, we used articles available in the PubMed database that specifically focused on the connection between the microbiota–gut–brain axis and depression. We included mostly English-language articles according to how closely they related to the subject matter. The inclusion criteria included original research articles and review papers published mainly in recent years, especially from around 2014 onwards. We considered both human and animal studies, particularly those analyzing microbiota composition, biological mechanisms, and possible therapeutic approaches. Duplicate reports, articles with insufficient data, and those not focusing on gut microbiota or depression were excluded. Authors considered studies concerning other psychiatric disorders without a direct focus on depression as outside the scope of this review.

Key articles included in this review were studies on microbiota composition in depression and experimental studies on the microbiota–gut–brain axis. Eventually, the authors selected 25 key articles that provided the strongest clinical evidence supporting this topic (Figure 1).

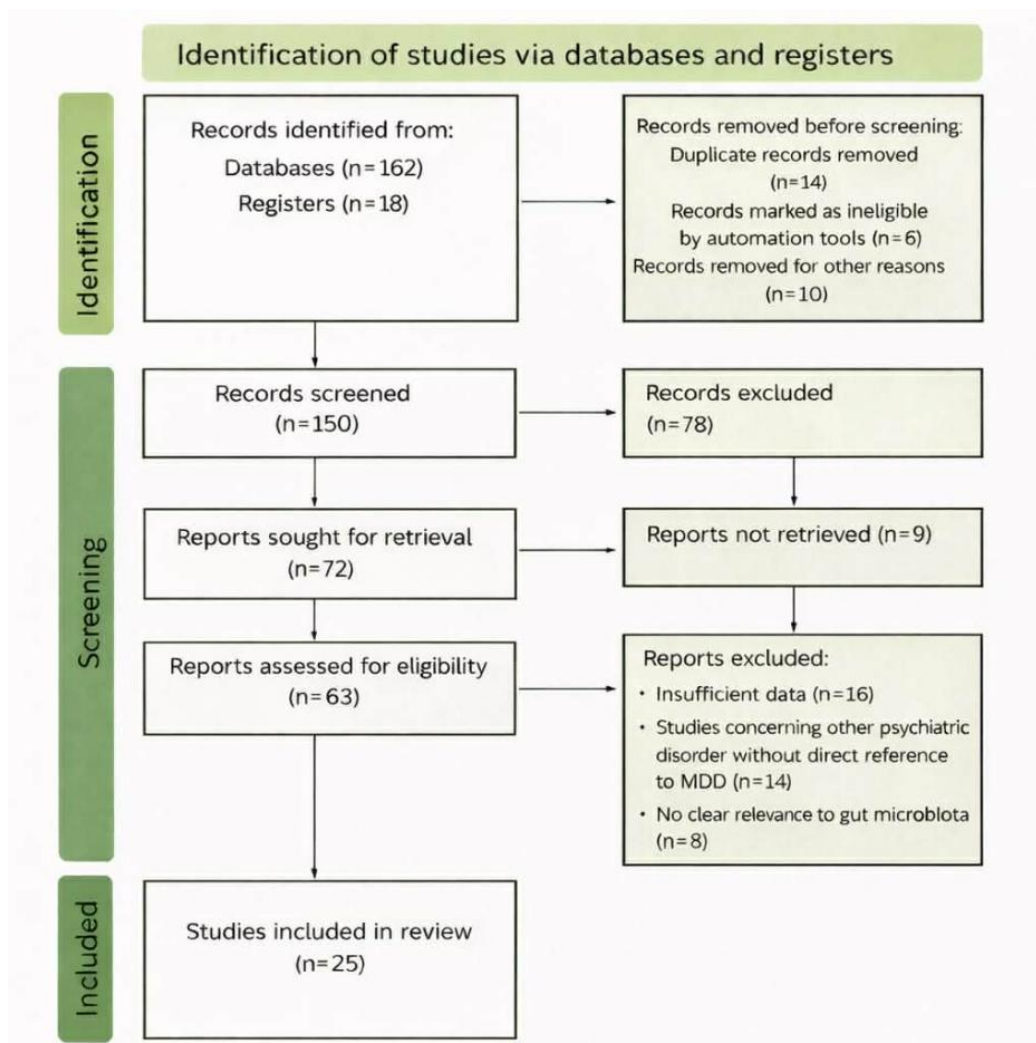


Figure 1. Flow chart

3. RESULTS AND DISCUSSION

Alterations of gut microbiota in depression

Studies support the idea that patients with MDD have a different gut microbiota than healthy people. These differences mainly concern the composition and proportions of the bacterial community. There are shifts in specific bacterial groups in depression (Jiang et al., 2015; Naseribafrouei et al., 2014). Some results indicate fewer beneficial bacteria and more linked to inflammation. A relatively low proportion of Firmicutes, along with increased levels of Bacteroidetes, such as Alistipes and Parabacteroides, was observed in patients with MDD. Since Alistipes are associated with inflammatory processes and the metabolism of tryptophan, many researchers find it particularly relevant (Jiang et al., 2015).

Other studies also suggest that these changes may have a connection with some aspects of depression. For example, they found that differences in gut microbiota may contribute to sleep quality (Zhang et al., 2021). In addition, changes in metabolites, such as bile acids, have also been reported (Zu et al., 2024).

In general, current data indicate that gut microbiota is altered in patients with depression, although the findings are not completely consistent between studies.

Functional role of microbiota in depression

There is evidence that some intestinal bacteria can produce short-chain fatty acids and regulate molecules involved in the nervous system, including neurotransmitter precursors. As a result, changes in the microbiota may influence metabolic pathways involved in mood regulation, brain function, and behavior.

Some studies also point to a relationship between gut microbiota and quality of life. Certain groups of bacteria were linked to better psychological conditions, while others were more often found in people with depressive symptoms (Valles-Colomer et al., 2019).

Mechanisms linking gut microbiota and depression

Inflammation and immune activation

Some data show that inflammation may be one of the main links between gut microbiota and depression. Changes in microbiota can affect the immune system and lead to elevated production of pro-inflammatory cytokines, which may modulate brain function (Peirce and Alviña, 2019).

IL-1 β is a cytokine that stimulates the immune response to infections, as well as injuries and inflammatory conditions, for instance, neuroinflammation. Patients with depression have elevated levels of inflammatory markers, such as IL-1 β , and some of these changes may be related to gut microbiota (Bai et al., 2022). The same pattern occurs in animal studies. Dysbiosis leads to activation of inflammatory pathways in the brain, for example, mechanisms involving the NLRP3 inflammasome in the hippocampus (Xu et al., 2024). There are also results showing that transferring microbiota can change behavior and activate inflammatory pathways, demonstrating a connection between gut microbiota, inflammation, and brain function (Li et al., 2019).

Tryptophan metabolism and neurotransmitters

Experts show a connection between the gut microbiota and tryptophan metabolism. Tryptophan, as a precursor to serotonin, is also a neurotransmitter closely associated with mood regulation. Therefore, gut microbiota can moderate emotional state (Lukić et al., 2022). At the same time, studies reported that tryptophan is not always used to make serotonin. The kynurenine pathway can metabolize tryptophan. Some metabolites from this pathway may have negative effects on the brain and be related to depressive symptoms (Jing et al., 2025).

Both papers suggest that gut microbiota may influence which pathway dominates. As a result, changes in the microbiota could simultaneously affect serotonin levels and other metabolites.

Neuroendocrine and metabolic pathways

Several papers report that gut microbiota connects with the stress response system, particularly the Hypothalamic-Pituitary-Adrenal axis. This system does not function properly in depression, and microbiota may be one of the factors involved. In animal models, altering the gut microbiota led to depressive-like behavior and changes in carbohydrate and amino acid metabolism (Zheng et al., 2016). Other reports also show that the microbiota may affect depression through multiple pathways, including neuroendocrine and

metabolic pathways. Rats presenting depression symptoms had elevated levels of ACTH and CRH during the trial, which can be explained by the hyperactivation of the HPA axis as a result of chronic stress exposure (Liu et al., 2020).

Intestinal barrier and stress

Research indicates that gut microbiota is also connected with depression through changes in the intestinal barrier. Under normal conditions, this barrier protects the body from harmful substances. However, in some cases, it may become more permeable, often described as “leaky gut”. Studies suggest that stress may influence both gut microbiota composition and intestinal barrier function. Increased permeability may allow bacterial components to enter the bloodstream, activating the immune system and influencing brain function (Kelly et al., 2015). At the same time, microbiota itself may play a role in maintaining or disrupting this barrier. Changes in its composition may weaken intestinal integrity and make the system more sensitive to stress.

In general, studies suggest that interactions between stress, gut microbiota, and amplified intestinal permeability may be one of the mechanisms linking the gut with depression.

Other mechanisms

Previous research suggests that gut microbiota may also affect depression through less obvious pathways, including the endocannabinoid system and mitochondrial function. These systems regulate mood, energy balance, and brain function.

According to studies, disturbances in the gut microbiota, for example, following antibiotic use, can alter the endocannabinoid system, affect signaling between the gut and the brain, and contribute to depressive-like behavior (Guida et al., 2018). The same study also shows that changes in the microbiota may influence brain structure and function, including mitochondrial processes. Since mitochondria are important for energy metabolism and neuronal function, their dysfunction contributes to symptoms of depression.

Evidence from animal studies

Published reports imply that animal research provides important insights into how the gut microbiota impacts depression. A common approach is transferring microbiota from depressed or stressed individuals to healthy animals. After such a transfer, animals can develop depressive-like behaviors, such as reduced activity or changes in behavior, suggesting that microbiota itself may play a role in these changes. (Kelly et al., 2016; Zheng et al., 2016).

Researchers transferred microbiota from stressed donors, and it caused both anxiety-like and depressive-like behaviors, often along with signs of inflammation (Hu et al., 2022; Xu et al., 2024).

Research also shows that microbiota linked to prenatal depression can cause behavioral changes and neuroinflammation when transferred to germ-free mice (Cao et al., 2025)

Gut microbiota and brain function

Research has shown that gut microbiota may be related to brain function in depression. This topic is important because depression is connected not only with mood changes, but also with altered activity in brain areas responsible for emotional processing. In patients suffering from the first episode of major depressive disorder with no history of previous treatment, differences in gut microbiota were linked with functional brain changes. The relationship between the gut and the brain may already be present at an early stage of the disorder, before the start of treatment (Wang et al., 2024).

The results also indicate that microbiota changes are not only a gut finding but may also change brain activity. In this context, the microbiota–gut–brain axis may help explain why gut and central nervous system changes can co-occur in depression. These findings imply that gut microbiota may be associated with functional brain variations in patients with major depressive disorder.

Microbiota as a biomarker of depression

Studies suggest that gut microbiota may serve as a biomarker for depression. Changes in microbiota composition and related inflammatory factors may help in identifying patients with major depressive disorder. Evidence indicates that some microbiota-related inflammation markers are different in patients with depression and may be useful in diagnosis (Bai et al., 2022). These findings suggest that immune changes linked with microbiota could be measured and used as additional diagnostic tools.

Predicting treatment responses in diseases, including depression, is an opportunity for more personalized therapy. Some researchers suggest that microbiome profiling could become a tool for that; however, further studies are still needed (Dong et al., 2022).

Therapeutic modulation of gut microbiota

Probiotics and prebiotics

Earlier studies indicate that probiotics and prebiotics can alter the gut microbiota and may have an effect on depression. Because of this, they attract attention as an additional treatment option. It is well known that both probiotics (living bacteria) and prebiotics, which promote their growth, help patients with many illnesses, including depression. What is even more interesting is that both can influence the microbiota-gut-brain axis and processes such as inflammation and neurotransmitter signaling (Radford-Smith and Anthony, 2023).

Some available studies suggest that using probiotics or prebiotics may help reduce depressive symptoms, but results are not always the same in all studies. Probiotics and prebiotics may be helpful, but more research is still needed.

Fecal microbiota transplantation (FMT)

Studies showed that fecal microbiota transplantation (FMT) may be another way to modify the gut microbiota and possibly influence depressive symptoms. This method involves transferring intestinal microbiota from a healthy donor to the recipient. Scientists used healthy microbiota from donors, which provided promising results (Hu et al., 2022). Depressive-like behavior decreased, suggesting that restoring gut microbiota balance may help. Some clinical studies suggest that FMT could become an extra treatment for depressive episodes. These studies show a small drop in symptom severity and a fairly good safety record (Wang et al., 2026).

In general, FMT seems to be a promising approach, but more research is needed to define its role in the treatment of depression clearly. The main findings regarding the role of gut microbiota in depression are summarized in Table 1.

Table 1. The role of gut microbiota in depression

Parameter	Research Finding	Impact on Depression	Key Reference
Gut Microbiota Composition	Altered microbiota structure in patients with MDD; lower Firmicutes and increased Bacteroidetes, including <i>Alistipes</i> and <i>Parabacteroides</i>	Suggests association between dysbiosis and depressive symptoms	Jiang et al., (2015); Naseribafrouei et al., (2014)
Inflammatory Activity	Increased pro-inflammatory cytokines and activation of inflammatory pathways, including IL-1 β and NLRP3 inflammasome	May contribute to neuroinflammation and depressive symptoms	Bai et al., (2022); Xu et al., (2024); Peirce et al., (2019)
Tryptophan Metabolism	Disturbances in serotonin and kynurenine pathways linked with gut microbiota	Possible influence on mood regulation and neurotransmission	Lukić et al., (2022); Jing et al., (2025)
Neuroendocrine Pathways	Gut microbiota associated with HPA axis dysregulation and altered ACTH/CRH levels	May affect stress response and depressive behavior	Zheng et al., (2016); Liu et al., (2020)
Intestinal Barrier Function	Increased intestinal permeability ("leaky gut") associated with stress and dysbiosis	May activate immune pathways influencing brain function	Kelly et al., (2015)
Animal Studies	Transfer of microbiota from depressed or stressed donors induced depressive-like behavior in animals	Supports a functional role of microbiota in depression	Kelly et al., (2016); Hu et al., (2022); Cao et al., (2025)

Brain Function	Gut microbiota differences associated with functional brain alterations in first-episode drug-naive MDD patients	Suggests microbiota–brain interaction in early depression	Wang et al., (2024)
Biomarker Potential	Microbiota-related inflammatory markers may help identify patients with MDD	Possible future diagnostic and prognostic tool	Bai et al., (2022); Dong et al., (2022)
Probiotics and Prebiotics	Modulation of gut microbiota may reduce depressive symptoms in some studies	Potential supportive therapeutic strategy	Radford-Smith and Anthony (2023)
Fecal Microbiota Transplantation (FMT)	Healthy donor microbiota reduced depressive-like behavior and improved symptoms	Promising adjunctive treatment approach	Hu et al., (2022); Wang et al., (2026)

Studies show that gut microbiota may be involved in depression through several mechanisms that work together. The most often described are inflammation, changes in tryptophan metabolism, and neuroendocrine pathways. These mechanisms are linked and may affect brain function via the microbiota–gut–brain axis. Among them, inflammation appears to be one of the better-supported mechanisms. Many studies show higher levels of inflammatory markers in patients with depression and suggest that gut microbiota may be part of this process. Changes in tryptophan metabolism are also often reported, especially a shift toward the kynurenine pathway rather than serotonin (Peirce et al., 2019).

However, not all aspects are clear. Most studies point to an association, but it is still difficult to say if microbiota changes are a cause or a result of depression. The reliability of the results is limited by the small sample sizes in the mentioned studies. Some methodological differences, such as inclusion criteria, methods of microbial analysis, or population heterogeneity, are also worth noting. Factors such as dietary patterns, intake of fiber or processed foods, physical activity, stress levels, sleep habits, and use of medications (especially antibiotics) can all influence the composition of gut microbiota. As a result, comparing the studies conducted seems more difficult.

Another issue scientists face is the difference between animal and human studies. Depressive-like behavior in animal models with dysbiosis suggests a quite direct effect. On the other hand, in humans, results are less consistent and may depend on many factors, for example, the way one eats or the medications used. These findings suggest that gut microbiota is related to depression, but more studies are needed to understand this relationship better.

4. CONCLUSION

To conclude, gut microbiota may play an important role in depression; however, further studies are still needed to understand these mechanisms and their clinical relevance. Shifting the focus toward the microbiota–gut–brain axis may create new opportunities for more personalized treatment approaches and improved quality of life for patients with depression.

Acknowledgments

The authors have no acknowledgments to disclose.

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All authors have read and agreed with the published version of the manuscript.

Informed consent

Not applicable.

Ethical approval

Not applicable. This article does not contain any studies with human participants or animals performed by any of the authors.

Funding

This research did not receive any external funding like specific grant from funding agencies in the public, commercial, or nonprofit sectors.

Conflict of interest

The authors declare that they have no conflicts of interest, competing financial interests or personal relationships that could have influenced the work reported in this paper.

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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