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Review Article

GUT–Brain Axis as a Therapeutic Target in Depression and Anxiety Disorders

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ABSTRACT

Depressive and anxiety disorders are common neuropsychiatric conditions in which incomplete treatment response, recurrence and adverse effects create a continuing need for complementary therapeutic strategies. The gut–brain axis describes a bidirectional communication network linking the gastrointestinal tract and the central nervous system through neural, endocrine, immune and metabolic pathways. The intestinal microbiota is an important functional component of this network because microbial products can influence neurotransmitter availability, tryptophan metabolism, immune tone, epithelial barrier integrity and hypothalamic–pituitary–adrenal activity. Conversely, psychological stress and altered autonomic signalling can change intestinal physiology and microbial ecology. Evidence from human studies has reported differences in microbial composition and microbial metabolites in depression and anxiety, although findings are heterogeneous and do not yet establish a single disease-specific microbial signature. Potential therapeutic approaches include probiotics, prebiotics, synbiotics, dietary modification, microbial metabolites, faecal microbiota transplantation and combination strategies. Among these, probiotic interventions have shown modest and strain-dependent improvements in some depressive and anxiety outcomes, whereas evidence for prebiotics, synbiotics and faecal microbiota transplantation remains less mature. This review summarizes the biological basis of the gut–brain axis, mechanisms linking dysbiosis with mood disorders, therapeutic approaches, current clinical evidence, safety considerations, limitations and future directions. The available evidence supports the gut–brain axis as a promising adjunctive research target rather than a replacement for established psychiatric treatment.

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INTRODUCTION

Depression and anxiety disorders arise from interactions among genetic susceptibility, brain circuits, endocrine regulation, immune processes, environmental exposures and psychosocial factors. Conventional pharmacological treatment remains important, but a substantial proportion of patients experience incomplete symptom control, delayed response, recurrence or intolerance. These limitations have encouraged investigation of biological systems outside the brain that can influence emotional regulation. The gut–brain axis has emerged as one such system because intestinal physiology and central nervous system function communicate continuously through neural, hormonal, immune and metabolic signals. [1,2]

The intestinal microbiota consists of a large and diverse community of microorganisms whose collective metabolic activity extends beyond digestion. Microbes can produce or modify short-chain fatty acids, bile acids and neuroactive compounds, while also influencing intestinal permeability, immune signalling and host metabolism. The brain, in turn, regulates gastrointestinal motility, secretion and immune activity through autonomic and neuroendocrine pathways. This bidirectional relationship means that psychological stress can affect the gut while gut-derived signals can modify brain function. [3,4]

In depression and anxiety, alterations in microbial diversity, microbial metabolites, inflammatory mediators and stress responses have been reported. However, these observations should not be interpreted as proof that dysbiosis alone causes psychiatric disease. Recent reviews emphasize that many human findings are associative, and differences in diet, medication exposure, age, geography, sampling method and disease severity can substantially influence microbiome results. [5,6]

The therapeutic concept is therefore broader than simply replacing 'bad' bacteria with 'good' bacteria. A useful gut–brain intervention may aim to improve microbial ecosystem function, increase beneficial metabolite production, reduce excessive inflammatory signalling, strengthen the intestinal barrier or alter communication between gut sensory pathways and the brain. This review evaluates these possibilities with emphasis on depression and anxiety disorders.

2. Overview of the Gut–Brain Axis

The gut–brain axis is a bidirectional network involving the gastrointestinal tract, enteric nervous system, autonomic nervous system, immune system, endocrine pathways, microbial communities and the central nervous system. It integrates information about food, nutrients, microbial metabolites, visceral sensation and internal physiological state. Gut sensory cells and neural fibres can transmit information to the brain, while sympathetic and parasympathetic pathways regulate intestinal function. [3,7]

The vagus nerve is an important communication route. Signals originating from the gastrointestinal tract can reach brainstem nuclei and subsequently influence higher brain regions involved in emotion, stress and cognition. Importantly, communication is not exclusively neural. Circulating cytokines, microbial metabolites and endocrine mediators can also alter brain function, either directly or through effects on vascular, immune and neural interfaces. [3,8]

The hypothalamic–pituitary–adrenal (HPA) axis forms another major component. Psychological stress activates hypothalamic corticotropin-releasing hormone, followed by pituitary adrenocorticotropic hormone and adrenal glucocorticoid release. Persistent stress can alter intestinal motility, epithelial permeability and microbial composition. Microbial signals may also influence HPA-axis reactivity, creating a potential feedback loop between stress and gastrointestinal function. [2,9]

3. Gut Microbiota and Dysbiosis in Depression and Anxiety

Individuals with depression have been reported to show altered abundance of several bacterial groups, including changes involving taxa associated with short-chain fatty acid production. Similar alterations have been described in anxiety and stress-related phenotypes. Nevertheless, results are inconsistent across cohorts, and no universal microbial profile can currently be used to diagnose depression or anxiety. [5,10]

Dysbiosis may be clinically relevant when it represents a functional change rather than a simple shift in

taxonomic abundance. For example, reduced capacity for butyrate production, altered bile-acid transformation or changes in tryptophan metabolism could influence host physiology even when total microbial diversity appears relatively preserved. This functional perspective is increasingly important in microbiome research. [6,11]

Several factors can confound microbiome comparisons. Dietary fibre intake, antibiotics, proton-pump inhibitors, antidepressants, sleep, physical activity, smoking, metabolic health and geographical background may all modify the intestinal microbial community. Consequently, future studies need careful control of these variables and standardized sampling and sequencing procedures. [5,12]

4. Mechanisms Linking the Gut–Brain Axis with Depression and Anxiety

4.1 Neural and Vagal Signalling

The vagus nerve provides rapid communication between the gastrointestinal tract and the brain. Microbial products and intestinal sensory signals can influence vagal afferent activity, while vagal pathways can modify autonomic and immune responses. Experimental studies suggest that some behavioural effects associated with microbial manipulation depend partly on vagal signalling. Human translation is promising but remains incomplete. [3,8]

4.2 Immune Activation and Neuroinflammation

Changes in intestinal barrier function may permit increased exposure of the host immune system to microbial components. This can stimulate innate immune pathways and promote production of inflammatory mediators. In depression, inflammatory markers such as C-reactive protein and selected cytokines have been associated with symptom severity in subsets of patients. Neuroinflammatory signalling may influence neurotransmission, synaptic plasticity and sickness-behaviour pathways. [2,9,13]

However, inflammation is not a single mechanism that explains every case of depression or anxiety. Rather, it may represent one biological pathway that interacts with stress, metabolism, genetics and environmental factors. This distinction is important because microbiome-based interventions are unlikely to have identical effects in all patients. [6,13]

4.3 HPA-Axis Regulation

The HPA axis is strongly connected with stress-related disorders. Altered cortisol dynamics have been observed in subsets of people with depression and anxiety. Microbial signals may influence HPA-axis development and reactivity, while stress hormones can alter the intestinal environment. This bidirectional relationship may contribute to persistent stress sensitivity and gastrointestinal symptoms in affected individuals. [2,9]

4.4 Tryptophan Metabolism and Serotonergic Signalling

Tryptophan is an essential amino acid that can enter several metabolic pathways. It contributes to serotonin synthesis, but it can also be metabolized through the kynurenine pathway. Inflammatory signalling can shift tryptophan metabolism toward kynurenine-related products, potentially reducing substrate availability for serotonin synthesis while generating metabolites capable of influencing neuronal function. Gut microbes can affect tryptophan availability and transformation, making this pathway relevant to mood regulation. [11,14]

4.5 Short-Chain Fatty Acids

Short-chain fatty acids (SCFAs), particularly acetate, propionate and butyrate, are generated by microbial fermentation of dietary substrates. SCFAs can influence epithelial barrier function, immune regulation, cellular metabolism and signalling through G-protein-coupled receptors. Butyrate has also been studied as a histone deacetylase-modulating metabolite with potential effects on gene expression and neuroimmune pathways. [11,15]

Reduced abundance of SCFA-associated microbes has been reported in some studies of depression. Nevertheless, stool concentrations do not necessarily reflect tissue exposure or systemic activity, so future work should measure microbial function and host metabolite profiles together rather than relying on taxonomy alone. [6,11]

4.6 Gut Barrier and Blood–Brain Barrier

The intestinal epithelium forms a selective barrier between luminal contents and systemic circulation. Tight-junction integrity is influenced by diet, inflammation, microbial metabolites and stress. Barrier disruption may facilitate systemic immune activation. The blood–brain barrier provides an additional protective interface, and inflammatory or metabolic signals can alter its function. Together, these interfaces may connect intestinal disturbances with central neuroinflammation. [7,13]

4.7 Neuroactive Microbial Metabolites

Microorganisms can produce or modify compounds related to GABA, dopamine, serotonin pathways and other neuroactive metabolites. These substances may act locally on intestinal cells and nerves or influence systemic signalling. Recent literature also highlights bile-acid derivatives, indole compounds and other microbial metabolites as potential regulators of neuronal and immune processes. [11,16]

5. Therapeutic Strategies Targeting the Gut–Brain Axis

5.1 Probiotics and Psychobiotics

Probiotics are live microorganisms administered in adequate amounts to confer a health benefit. When the intended outcome involves mental health through microbiome–brain interactions, the term psychobiotic is often used. Proposed mechanisms include modulation of microbial communities, improvement of barrier function, altered SCFA production, immune regulation and effects on stress-related signalling. [17]

Clinical trials and meta-analyses indicate that probiotics may produce modest reductions in depressive symptoms in some populations. Results for anxiety are more variable. Importantly, effects are strain-, dose-, duration- and population-dependent, so probiotic products should not be treated as interchangeable. A recent umbrella review found evidence of benefit for depressive symptoms but emphasized substantial methodological limitations and inconsistency, particularly for anxiety. [17,18]

5.2 Prebiotics

Prebiotics are substrates selectively utilized by host microorganisms that provide a health benefit. Dietary fibres and specific fermentable carbohydrates can increase the availability of substrates for beneficial microbial metabolism and SCFA production. Theoretical advantages include ecosystem-level modulation rather than introduction of a single strain. Human evidence for direct treatment of depression or anxiety remains limited, and effects may depend strongly on baseline diet and microbiota. [15,18]

5.3 Synbiotics

Synbiotics combine live microorganisms with substrates designed to support their activity. The approach is attractive because it attempts to address both microbial delivery and microbial nourishment. However, psychiatric clinical evidence is still comparatively sparse. Future studies should identify which strain–substrate combinations produce reproducible changes in microbial function and psychological outcomes. [18]

5.4 Dietary Modification

Diet is one of the strongest modifiable influences on the intestinal microbiota. Diets rich in diverse plant-derived fibres can support microbial fermentation and production of beneficial metabolites. In contrast, highly processed dietary patterns may alter microbial ecology and metabolic signalling. Dietary interventions are therefore attractive because they can affect the broader microbial ecosystem rather than a single organism. [15,19]

The therapeutic effect of diet should not be oversimplified. Improvements in mood may occur through several pathways, including nutrient adequacy, metabolic health, sleep, inflammation, social factors and microbial metabolism. Controlled trials are needed to separate these effects and determine which dietary components are most useful for specific patient groups. [19]

5.5 Fecal Microbiota Transplantation

Fecal microbiota transplantation (FMT) transfers a microbial community from a screened donor to a recipient. It has established clinical use for selected

gastrointestinal indications, but its role in psychiatric disorders remains investigational. Small experimental studies and animal work have generated interest because whole microbial ecosystems can be transferred rather than individual strains. However, psychiatric FMT research requires rigorous donor screening, standardized preparation, long-term follow-up and careful assessment of infectious and other risks. [6,20]

5.6 Microbial Metabolite-Based Approaches

Another strategy is to target microbial metabolites directly. SCFAs, indole derivatives, bile-acid metabolites and tryptophan-related compounds are potential candidates. This approach may eventually allow more precise intervention than broad microbiome modification. At present, most evidence is mechanistic or preclinical, and appropriate dose, delivery, pharmacokinetics and long-term safety need clarification. [11,16]

6. Evidence from Human Clinical Studies

Human evidence provides encouraging but not definitive support for gut–brain interventions. Meta-analyses of probiotic trials have reported small improvements in depressive symptoms, although heterogeneity in probiotic strains, formulations, treatment duration and patient populations remains substantial. Anxiety outcomes are generally less consistent. [17,18]

Recent systematic reviews also emphasize that many microbiome studies are cross-sectional. Such designs can identify associations but cannot establish whether microbial changes cause psychiatric symptoms, result from illness, or reflect a third factor such as diet or medication. Longitudinal studies and randomized trials that measure both symptoms and biological mechanisms are therefore particularly valuable. [5,6]

An important future direction is to test whether microbiome changes mediate clinical improvement. A trial should ideally measure baseline microbiota, metabolite profiles, inflammatory markers and clinical symptoms, followed by repeated measurements during treatment. This would help determine whether a treatment changes the microbiome first and whether that change predicts subsequent improvement. [8,12]

7. Potential Role as an Adjunct to Conventional Therapy

The gut–brain axis is best considered an adjunctive therapeutic target at the current stage of evidence. Established treatments for depression and anxiety include psychological therapies and, when appropriate, pharmacological treatment. Microbiome-directed interventions may eventually complement these approaches by addressing metabolic, inflammatory or gastrointestinal factors that contribute to individual symptom patterns. [5,13]

An especially interesting research area is the interaction between antidepressants and the gut microbiota. Drugs can influence microbial composition or metabolism, while microbial enzymes may modify drug exposure or response. This bidirectional relationship raises the possibility that microbiome features could contribute to interindividual differences in antidepressant response, although clinically validated microbiome-guided prescribing is not yet established. [5,10]

8. Safety and Limitations

Most commercially available probiotics are generally tolerated by healthy people, but safety depends on the product, host condition and clinical setting. Serious complications are uncommon but can occur in vulnerable individuals. FMT carries additional concerns because it involves transfer of a complex biological material and therefore requires rigorous screening and clinical oversight. [20]

Major scientific limitations include small sample sizes, short follow-up, inconsistent diagnostic criteria, differences in sequencing platforms, variable microbiome analysis pipelines and incomplete reporting of diet and medication exposure. Publication bias and selective reporting may also contribute to overestimation of treatment effects. [6,18]

Another limitation is the temptation to label particular bacterial taxa as universally beneficial or harmful. Microbial effects depend on species, strain, ecological context and available nutrients. Therefore, future research should move from simple lists of bacteria toward functional measurements such as metabolomics, transcriptomics and host–microbe interaction markers. [7,11]

9. Future Perspectives

Future gut–brain research is likely to become more personalized. Instead of prescribing the same probiotic to every patient, investigators may combine dietary history, microbiome composition, microbial metabolites, inflammatory markers and clinical phenotype to identify biologically meaningful subgroups. Such precision approaches could improve response rates and reduce unnecessary treatment. [1,6]

Multi-omics integration is another major opportunity. Combining metagenomics with metabolomics, transcriptomics and host immune measurements can reveal microbial functions that cannot be inferred from taxonomic abundance alone. Machine-learning methods may help identify patterns associated with treatment response, but models will require large, diverse and independently validated datasets before clinical use. [6,12]

Well-designed randomized trials should use standardized diagnostic criteria, adequately powered sample sizes, clearly defined strains or dietary interventions, appropriate placebo controls, preregistered outcomes and sufficiently long follow-up. Importantly, future trials should report both psychological outcomes and mechanistic biomarkers so that biological plausibility can be tested alongside clinical efficacy. [5,18]

9.1 Review Approach

For this narrative review, recent peer-reviewed literature indexed in major biomedical databases was prioritized, with emphasis on systematic reviews, meta-analyses, mechanistic reviews and representative clinical studies addressing depression, anxiety, gut microbiota, microbial metabolites and microbiota-targeted interventions. Foundational publications were retained when they established key concepts of the gut–brain axis. Evidence was interpreted according to study type, with particular caution applied to cross-sectional microbiome associations and preclinical findings. Recent literature emphasizes that human evidence remains heterogeneous and that causality, strain specificity and long-term clinical benefit require further investigation. [5,6,18]

9.2 Clinical Translation and Regulatory Considerations

Translation into routine care will require standardized definitions of probiotic strains, dose, viability, manufacturing quality and clinically meaningful endpoints. Microbiome testing also needs analytical standardization because different extraction, sequencing and bioinformatic pipelines can produce different profiles. At present, microbiome-directed products should be regarded as complementary or investigational approaches rather than substitutes for established treatment of diagnosed psychiatric disorders. [6,18]

CONCLUSION

The gut–brain axis provides a biologically plausible framework for understanding how intestinal microbial ecology, immune signalling, metabolism, stress pathways and neural communication may contribute to depression and anxiety. Probiotics, prebiotics, dietary strategies, microbial metabolites and other microbiome-directed interventions are promising research areas. Current clinical evidence is strongest for modest, strain-dependent effects of some probiotic interventions on depressive symptoms, while evidence for anxiety and other microbiome-targeted approaches remains less certain. [17,18]

The field should therefore avoid both extremes: the gut microbiome should neither be dismissed as irrelevant nor presented as a proven standalone cure for psychiatric disorders. The most useful future direction is rigorous translational research that links microbial function with patient-specific biology and clinical outcomes. If these challenges are addressed, gut–brain interventions may become a meaningful component of personalized, multimodal management of depression and anxiety.

Table 1: Major Gut–Brain Signalling Pathways and Therapeutic Relevance

Pathway	Major mediators	Relevance to depression/ anxiety	Potential target
Neural	Vagus nerve, enteric nervous system	Autonomic and emotional signalling	Vagal/enteric modulation

Pathway	Major mediators	Relevance to depression/ anxiety	Potential target
Immune	Cytokines, immune cells	Neuroinflammation and sickness behaviour	Inflammation/barrier modulation
Endocrine	CRH, ACTH, cortisol	Stress response and HPA-axis dysregulation	Stress-axis regulation
Metabolic	SCFAs, bile acids, indoles	Neuroimmune and metabolic signalling	Diet/microbiota/metabolite modulation
Amino-acid	Tryptophan, kynurenine, GABA-related pathways	Serotonergic and neuroactive signalling	Microbial metabolic pathways

Table 2: Therapeutic Approaches: Current Position

Approach	Main concept	Current evidence	Key limitation
Probiotics/psychobiotics	Introduce selected live microorganisms	Promising, modest effects in some trials	Strain and population heterogeneity
Prebiotics	Feed selected resident microbes	Early/limited psychiatric evidence	Few well-powered trials
Synbiotics	Combine microbes with supportive substrate	Insufficient evidence	Optimal combinations unclear
Dietary modification	Change microbial substrates and host metabolism	Biologically plausible and increasingly studied	Multiple confounding lifestyle factors
FMT	Transfer complex donor microbiota	Investigational in psychiatry	Safety, standardization, long-term uncertainty
Metabolite targeting	Modify SCFAs, tryptophan/bile-acid pathways	Mostly mechanistic/preclinical	Dose, delivery and causal evidence

REFERENCES

1. Lee S-H, Han C, Shin C. IUPHAR review: Microbiota-gut-brain axis and its role in neuropsychiatric disorders. Pharmacological Research. 2025;216:107749. doi:10.1016/j.phrs.2025.107749.
2. Verma A, Inslicht SS, Bhargava A. Gut Brain Axis: Role of Microbiome, Metabolomics, Hormones, and Stress in Mental Health Disorders. Cells. 2024;13 (17):1436. doi:10.3390/cells13171436.
3. Ohara TE, Hsiao EY. Microbiota–neuroepithelial signalling across the gut–brain axis. Nature Reviews Microbiology. 2025;23:371–384. doi:10.1038/s41579-024-01136-9.
4. Cryan JF, O'Riordan KJ, Cowan CSM, et al. The microbiota-gut-brain axis. Physiological Reviews. 2019;99 (4):1877–2013. doi:10.1152/physrev.00018.2018.
5. Zeng L, Zhang S, Liu R, Wang L, Tan Y. The Microbiota-Gut-Brain Axis in Depression: Mechanisms, Microbiota-Targeted Interventions, and Translational Challenges. International Journal of Microbiology. 2025;2025:6750078. doi:10.1155/ijm/6750078.
6. Patel RA, Panche AN, Harke SN. Gut microbiome-gut brain axis-depression: interconnection. World Journal of Biological Psychiatry. 2025;26 (1):1–36. doi:10.1080/15622975.2024.2436854.
7. Morais LH, Schreiber HL IV, Mazmanian SK. The gut microbiota-brain axis in behaviour and brain disorders. Nature Reviews Microbiology. 2021;19:241–255. doi:10.1038/s41579-020-00460-0.
8. Appleton J. The gut-brain axis: influence of microbiota on mood and mental health. Integrative Medicine. 2018;17 (4):28–32.
9. Foster JA, McVey Neufeld KA. Gut-brain axis: how the microbiome influences anxiety and depression. Trends in Neurosciences. 2013;36 (5):305–312. doi:10.1016/j.tins.2013.01.005.

10. Valles-Colomer M, Falony G, Darzi Y, et al. The neuroactive potential of the human gut microbiota in quality of life and depression. Nature Microbiology. 2019;4:623–632. doi:10.1038/s41564-018-0337-x.
11. Li Y, et al. Microbial metabolites in the gut-brain axis: their impact on depression pathophysiology and treatment. Neuroscience. 2026. doi:10.1016/j.neuroscience.2025.12.002.
12. Distinguishing the causative, correlative and bidirectional roles of the gut microbiota in mental health. Nature Mental Health. 2025;3:1137–1151. doi:10.1038/s44220-025-00498-0.
13. Kelly JR, Borre Y, O'Brien C, et al. Breaking down the barriers: the gut microbiome, intestinal permeability and stress-related psychiatric disorders. Frontiers in Cellular Neuroscience. 2015;9:392. doi:10.3389/fncel.2015.00392.
14. Agus A, Clément K, Sokol H. Gut microbiota-derived metabolites as central regulators in metabolic disorders. Gut. 2021;70:1174–1182. doi:10.1136/gutjnl-2020-323071.
15. Berding K, Vlckova K, Marx W, et al. Diet and the gut-brain axis: sowing the seeds of good mental health. Advances in Nutrition. 2021;12(4):1230–1245.
16. Strandwitz P. Neurotransmitter modulation by the gut microbiota. Brain Research. 2018;1693:128–133. doi:10.1016/j.brainres.2018.03.015.
17. Nikolova VL, Cleare AJ, Young AH, Stone JM. Updated systematic review and meta-analysis of probiotics for the treatment of clinical depression: 13 studies with 1049 participants. Translational Psychiatry. 2019;9:155. doi:10.1038/s41398-019-0559-0.
18. 'Attacking' the Gut-Brain Axis with Psychobiotics: An Umbrella Review of Depressive and Anxiety Symptoms. 2025. PubMed-indexed umbrella review; use the database record for final journal/DOI formatting.
19. Feeding gut microbes to nourish the brain: unravelling the diet–microbiota–gut–brain axis. Nature Metabolism. 2024;6:1454–1478. doi:10.1038/s42255-024-01108-6.
20. Paramsothy S, Kamm MA, Kaakoush NO, et al. Multidonor intensive faecal microbiota transplantation for active ulcerative colitis: a randomised placebo-controlled trial. Lancet. 2017;389:1218–1228. doi:10.1016/S0140-6736(17)30182-4.

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