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THE ROLE OF THE GUT–BRAIN AXIS IN THE PATHOGENESIS OF DEPRESSION AND ANXIETY DISORDERS: THE SIGNIFICANCE OF MICROBIOTA, BACTERIAL METABOLITES, AND VAGUS NERVE SIGNALLING — A SYSTEMATIC REVIEW

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Abstract

Introduction and aim: Depression and anxiety disorders are leading causes of disability worldwide, and many patients respond inadequately to conventional treatment. The microbiota–gut–brain axis has emerged as a candidate contributor to their pathogenesis. This review aimed to synthesise mechanistic and clinical evidence linking gut microbiota, bacterial metabolites, and vagal signalling to depression and anxiety. Material and methods: A systematic search of PubMed, Embase, and Scopus (2011–2025) was performed following PRISMA principles, using terms for the gut–brain axis, microbiota, short-chain fatty acids, tryptophan, vagus nerve, depression, and anxiety. Studies were synthesised narratively across three mechanistic pillars. Results: Patients with depression and anxiety show reduced short-chain-fatty-acid-producing taxa and enrichment of pro-inflammatory bacteria. Bacterial metabolites—short-chain fatty acids, tryptophan catabolites, and gamma-aminobutyric acid—modulate neuroinflammation, blood–brain-barrier integrity, and neurotransmission. Several anxiolytic and antidepressant-like microbial effects are abolished by vagotomy, confirming a vagal route. Randomised trials of psychobiotics show small but significant reductions in depressive symptoms. Conclusions: The gut–brain axis is a biologically plausible, therapeutically tractable contributor to mood and anxiety disorders, though heterogeneity and causal uncertainty remain.

Keywords: gut–brain axis; gut microbiota; short-chain fatty acids; vagus nerve; depression; anxiety disorders

1. Introduction

Depression and anxiety disorders rank among the most prevalent and disabling mental health conditions, together affecting hundreds of millions of people and imposing an enormous personal and socioeconomic burden (Asad et al. 2024). According to the World Health Organization, clinical depression affects roughly 5% of adults, and existing therapies remain suboptimal for a substantial subgroup of patients (Lukić et al. 2022). This therapeutic gap has motivated a search for pathophysiological mechanisms beyond the classical monoamine hypothesis.

Over the past two decades, the bidirectional communication network linking the gastrointestinal tract and the central nervous system—the microbiota–gut–brain axis (MGBA)—has emerged as a critical determinant of brain function and behaviour (Ma 2024). The genesis of anxiety and depression is increasingly understood to involve not only neurochemical alterations in the brain but also changes in the composition and function of the gut microbiota (Zhou et al. 2024). Patients with mood and anxiety disorders frequently present with gastrointestinal comorbidity, and a bidirectional relationship between the gut and the brain is now well documented (Xiong et al. 2025).

The MGBA integrates neural, endocrine, immune, and metabolic signalling pathways. Three mechanistic pillars are of particular translational interest and form the focus of this review: (i) the composition of the gut microbiota itself; (ii) bacterial metabolites, notably short-chain fatty acids (SCFAs), tryptophan catabolites, and gamma-aminobutyric acid (GABA); and (iii) signalling along the vagus nerve, the principal neural conduit between the gut and the brainstem (Bonaz et al. 2018; Dalile et al. 2019). Understanding how these pillars interact is essential for evaluating the microbiota as a therapeutic target.

The gut harbours a microbial community of extraordinary scale and metabolic capacity, comprising trillions of organisms whose collective genome vastly exceeds that of the host and whose enzymatic repertoire enables biochemical transformations the host cannot perform unaided. This community synthesises neurotransmitters and neurotransmitter precursors, ferments dietary components into bioactive metabolites, and continuously interacts with the intestinal immune system. It is this metabolic and immunological reach, operating across a mucosal surface richly innervated by vagal afferents, that endows the microbiota with the capacity to influence distant organs, including the brain. Framed this way, the gut–brain axis is less a single pathway than a densely interconnected communication system, and its relevance to psychiatry follows naturally from the observation that the systems it engages—stress, immunity, and neurotransmission—are the same systems implicated in mood and anxiety disorders.

The aim of this systematic review was to synthesise current preclinical and clinical evidence on the role of the gut–brain axis in the pathogenesis of depression and anxiety disorders, with specific emphasis on the microbiota, bacterial metabolites, and vagal signalling, and to appraise the therapeutic potential of interventions targeting this axis.

The conceptual origins of this field can be traced to observations that germ-free animals—raised entirely without a microbiota—display marked abnormalities in stress reactivity and social behaviour, and that these abnormalities can be normalised by microbial colonisation within defined developmental windows (Clarke et al. 2016). Such findings established that the microbiota is not a passive commensal population but an active regulator of neurodevelopment and behaviour. Subsequent work extended these insights from gnotobiotic models to conventionally raised animals and, ultimately, to human clinical cohorts, giving rise to the integrated framework examined here. The clinical stakes are considerable: with conventional antidepressants producing remission in only a minority of patients at first-line treatment, even a modestly effective, mechanistically distinct adjunctive strategy could yield meaningful population-level benefit.

2. Material and Methods

2.1 Search strategy

A systematic literature search was conducted in the PubMed/MEDLINE, Embase, and Scopus databases for records published between January 2011 and September 2025. The search combined controlled vocabulary and free-text terms across three concept blocks joined by the Boolean operator AND, with synonyms within each block joined by OR: (a) exposure/mechanism—“gut–brain axis” OR “microbiota-gut-brain axis” OR “gut microbiota” OR “short-chain fatty acids” OR “butyrate” OR “tryptophan” OR “kynurenine” OR “vagus nerve” OR “vagal”; (b) outcome—“depression” OR “depressive disorder” OR “anxiety” OR “anxiety disorder”; (c) design filters for reviews, randomised controlled trials, and experimental studies. Reference lists of retrieved reviews were hand-searched for additional records.

2.2 Eligibility criteria

Studies were eligible if they were peer-reviewed, published in English, and reported original or synthesised data on the relationship between the gut microbiota, bacterial metabolites, or vagal signalling and depressive or anxiety phenotypes in humans or validated animal models. Excluded were conference abstracts without full text, opinion pieces without primary data, and studies addressing exclusively unrelated neuropsychiatric conditions. The review followed the reporting principles of the PRISMA 2020 statement; a formal meta-analysis was not undertaken given the heterogeneity of designs and outcome measures.

2.3 Study selection and synthesis

Titles and abstracts were screened against the eligibility criteria, and potentially relevant full texts were assessed. Given the mechanistic scope, data were synthesised narratively and organised according to the three predefined pillars—microbiota composition, bacterial metabolites, and vagal signalling—followed by an integrative section on clinical and therapeutic evidence. Because the evidence base spans heterogeneous preclinical and clinical designs, findings are reported qualitatively, with quantitative effect estimates cited where randomised trials or meta-analyses were available.

The screening process followed the four PRISMA phases of identification, screening, eligibility, and inclusion. Records identified across the three databases were first de-duplicated; remaining records were screened at the title and abstract level, and those clearly outside the scope—unrelated disorders, non-original commentary, and studies without a microbiota, metabolite, or vagal component—were removed. Full texts of the residual records were then assessed against the eligibility criteria, and studies meeting all criteria were carried forward into the qualitative synthesis. Priority was given to systematic reviews, meta-analyses, and randomised controlled trials for the clinical sections, and to mechanistically rigorous experimental studies—particularly those employing vagotomy, germ-free, or faecal-transplantation designs—for the pathophysiological sections, as these designs permit stronger causal inference than observational cross-sectional data.

The evidence carried into the synthesis spanned the full range of relevant designs. Human observational studies—principally case-control comparisons of the faecal microbiota between patients and healthy controls—established the compositional associations, while randomised controlled trials and their meta-analyses supplied the interventional evidence for psychobiotics. Mechanistic understanding rested largely on controlled animal experiments, including gnotobiotic (germ-free) models that isolate the contribution of the microbiota, faecal-transplantation studies that test sufficiency, and vagotomy studies that test the necessity of neural signalling. Foundational and integrative reviews were used to situate primary findings within the wider framework of the axis. This deliberate weighting toward designs capable of supporting causal inference, rather than toward the more numerous but weaker cross-sectional reports, shaped the emphases of the synthesis that follows and is reflected in the confidence attached to each of the three pillars.

3. Gut Microbiota Composition in Depression and Anxiety

A recurring observation across clinical microbiome studies is that depression and anxiety are associated with characteristic shifts in the composition of the gut microbiota. A systematic review of human studies concluded that these conditions may be characterised by an enrichment of pro-inflammatory bacteria and a depletion of anti-inflammatory, SCFA-producing bacteria (Xiong et al. 2025). Reduced microbial diversity is commonly reported in depressed individuals relative to healthy controls, although the direction and magnitude of taxon-level changes vary between cohorts.

At the taxon level, butyrate-producing genera such as Faecalibacterium and Coprococcus have been positively associated with higher self-reported quality of life and are frequently depleted in depression (Valles-Colomer et al. 2019). Conversely, several studies have reported relative increases in genera such as Alistipes—an indole-positive organism that can reduce serotonin availability—and alterations in Prevotella and Bifidobacterium in patients with major depressive disorder (Petakh et al. 2024; Lin et al. 2017). Importantly, causality has been probed through faecal microbiota transplantation (FMT): transfer of microbiota from depressed patients to microbiota-depleted rodents can induce depression-like behavioural and physiological changes, supporting a contributory rather than merely correlational role (Zheng et al. 2016).

The pattern that recurs most consistently across these studies is not the presence of any single organism but a broad ecological signature: reduced overall diversity, depletion of anti-inflammatory SCFA producers, and relative expansion of taxa associated with inflammation or with unfavourable tryptophan handling (Xiong et al. 2025). This ecological framing is more robust than genus-by-genus comparison and dovetails with the functional perspective developed below. It also mirrors observations in other inflammation-associated conditions, suggesting that the depressive microbiota signature may partly reflect a general dysbiotic, pro-inflammatory state rather than a disorder-specific fingerprint—an interpretation consistent with the high rates of depression and anxiety observed in inflammatory bowel disease and other chronic inflammatory illnesses. Narrative and correlational reviews of the same literature reach concordant conclusions, reporting altered microbial diversity, immune activation, intestinal-barrier dysfunction, and disturbed tryptophan metabolism in depression while cautioning that human evidence remains largely associative (Wojciechowska et al. 2026; Czachor and Kotula 2025).

These compositional findings must be interpreted with caution. Confounders including diet, body mass index, and concurrent psychotropic or antibiotic medication strongly shape the microbiota and may account for part of the reported heterogeneity (Xiong et al. 2025). Antibiotic exposure provides a striking illustration: in mice, oral cefaclor induced anxiety- and depression-like behaviour together with dysbiosis, and the behavioural phenotype was attenuated by vagotomy, linking a compositional perturbation to a specific neural pathway (Wang et al. 2023). Reviews of the clinical literature similarly highlight early-life antibiotic exposure and dietary pattern as major modifiers of the depression-associated microbiota, and note the bidirectional influence of antidepressants on microbial diversity (Kosyra et al. 2024).

A further consideration is the concept of the functional, rather than merely taxonomic, microbiome. Two individuals may harbour different bacterial species yet share similar metabolic output, and it is increasingly

argued that the functional repertoire of the microbiota—its capacity to produce neuroactive metabolites—is more relevant to brain function than species-level composition per se (Valles-Colomer et al. 2019). This reframing helps reconcile apparently conflicting taxonomic reports and directs mechanistic attention toward the bacterial metabolites considered in the next section. It also has therapeutic implications, suggesting that interventions should be judged by their metabolic consequences rather than by their capacity to install any particular organism.

The strongest causal evidence in this pillar comes from transplantation experiments. When microbiota from patients with major depressive disorder is transferred to germ-free or antibiotic-treated rodents, recipients develop depression-like behaviours together with alterations in host metabolism, whereas transfer of microbiota from healthy donors does not (Zheng et al. 2016). Reciprocally, restoring a disrupted microbiota can attenuate behavioural deficits. These bidirectional manipulations move the field beyond correlation, demonstrating that the microbiota can be sufficient to transmit a behavioural phenotype across organisms. Nonetheless, the translational distance between gnotobiotic rodents and humans is considerable, and human faecal-transplantation trials for psychiatric indications remain preliminary. The compositional pillar is therefore best understood as necessary context: it establishes that the microbiota differs in affected individuals and can causally influence behaviour, while the metabolite and neural pillars specify the molecular and anatomical routes by which that influence is exerted.

4. Bacterial Metabolites as Mediators of Gut–Brain Communication

If microbiota composition sets the stage, bacterial metabolites are the principal molecular actors that translate a dysbiotic gut into altered brain function. Three metabolite classes have the strongest mechanistic support: short-chain fatty acids, tryptophan catabolites, and neuroactive amino-acid derivatives such as GABA.

These metabolites reach the brain and influence behaviour through several parallel channels: direct passage across the blood–brain barrier, receptor-mediated signalling on enteroendocrine and immune cells, modulation of the vagus nerve, and epigenetic regulation of gene expression in both peripheral and central tissues. This redundancy of routes is a defining feature of the metabolite pillar and explains why disruptions in a single metabolite class can produce broad behavioural consequences. The following subsections address each class in turn, but their effects should be understood as convergent rather than independent, ultimately shaping the same neuroinflammatory and neurotransmitter endpoints.

4.1 Short-chain fatty acids

Short-chain fatty acids—principally acetate, propionate, and butyrate—are produced by bacterial fermentation of dietary fibre and act as key transducers of gut-to-brain signalling (Dalile et al. 2019). They influence brain function through several complementary routes. Butyrate strengthens blood–brain-barrier integrity, reduces microglial activation, and lowers pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 (Fock and Parnova 2023; Silva et al. 2020). SCFAs also act epigenetically as histone deacetylase inhibitors: propionate and butyrate promote histone acetylation in the brain and, in microglia, are associated with decreased HDAC1 expression, dampening neuroinflammation and neuronal apoptosis (Liu et al. 2024).

Mechanistic studies have delineated specific molecular axes. In chronic-restraint-stress models, brain SCFAs activate the ACSS2–PPARγ–TPH2 pathway to promote serotonin synthesis and exert antidepressant-like effects; neuronal knockdown of ACSS2 abolishes these benefits (Qu et al. 2024). In high-fructose-fed mice, SCFA supplementation rescued hippocampal neurogenesis and repaired blood–brain-barrier damage, reversing depressive-like behaviour (Li et al. 2022). Complementary work shows SCFAs alleviate anxiety by reducing intestinal corticotropin-releasing-factor-receptor expression and systemic inflammation (van de Wouw et al. 2018).

The three principal SCFAs are not interchangeable. Butyrate is the preferred energy substrate of colonocytes and the most potent histone-deacetylase inhibitor of the group, giving it a privileged role in barrier maintenance and epigenetic regulation; propionate contributes to gluconeogenesis and immune modulation; and acetate, the most abundant, crosses into the brain and influences appetite and neurotransmitter systems (Silva et al. 2020). These functional distinctions matter for therapy, because interventions that shift the relative production of individual SCFAs—through specific fibres or specific strains—may have qualitatively different effects. The observation that butyrate specifically protects the blood–brain barrier and activates the vagus nerve makes butyrate-producing taxa a particularly rational target for microbiota-based approaches to mood and anxiety disorders, and helps explain why their depletion is such a consistent feature of the depressive microbiota signature.

Human data are consistent with these preclinical mechanisms. Lower plasma concentrations of SCFAs have been reported in psychiatric populations, and longitudinal work in social anxiety disorder has examined changes in circulating SCFAs following cognitive behavioural therapy, linking metabolite dynamics to treatment response

(Yang et al. 2026). Together, the evidence positions SCFA depletion as a plausible mediator connecting dysbiosis to mood and anxiety symptoms.

The blood–brain barrier occupies a central place in this account. Germ-free animals exhibit increased barrier permeability that is reversed by colonisation with SCFA-producing bacteria or by butyrate administration, implicating SCFAs in the maintenance of barrier tight-junction proteins such as occludin and claudin-5 (Fock and Parnova 2023). A compromised barrier permits the entry of inflammatory mediators into the brain parenchyma, where they activate microglia and perturb neurotransmission. By simultaneously reinforcing the barrier, suppressing microglial activation, and inhibiting histone deacetylases, SCFAs act at several nodes of the pathogenic cascade at once, which may explain the breadth of their behavioural effects across depression, anxiety, and stress-related models (Silva et al. 2020; Liu et al. 2024). This multiplicity of action also makes SCFAs an attractive—if mechanistically complex—therapeutic target, whether delivered directly, through dietary fibre, or via SCFA-producing psychobiotic strains.

4.2 Tryptophan metabolism and the kynurenine pathway

Tryptophan metabolism is a second major metabolite pathway through which the microbiota shapes mood. Dietary tryptophan is partitioned between three routes: the serotonin pathway in enterochromaffin cells, the kynurenine pathway in immune and epithelial cells, and direct bacterial conversion to indole derivatives (Kaur et al. 2019). Approximately 95% of the body's serotonin is synthesised in the gastrointestinal tract, and indigenous spore-forming bacteria directly regulate host serotonin biosynthesis (Yano et al. 2015).

Crucially, inflammation diverts tryptophan away from serotonin. Pro-inflammatory cytokines activate indoleamine-2,3-dioxygenase (IDO), the rate-limiting enzyme of the kynurenine pathway, shifting metabolism towards kynurenine and its neurotoxic downstream catabolite quinolinic acid while depleting the serotonin precursor pool (Maes et al. 2011; Kaur et al. 2019). This “inflammatory” model of tryptophan diversion provides a mechanistic bridge between gut dysbiosis, systemic inflammation, and depressed mood. In a chronic-restraint-stress model, kynurenine signalling was activated in both the brain and the colon, with IDO up-regulated at both sites, underscoring the gut as an active participant rather than a passive bystander (Deng et al. 2021). Probiotic Bifidobacterium infantis has been shown to modulate tryptophan metabolism and attenuate the inflammatory shift, restoring serotonergic precursor availability (Desbonnet et al., cited in Correia and Vale 2022).

Beyond the serotonin and kynurenine branches, gut bacteria convert tryptophan directly into indole derivatives—including indole-3-propionic acid, indole-3-acetic acid, and tryptamine—many of which are ligands of the aryl hydrocarbon receptor (Kaur et al. 2019). Aryl-hydrocarbon-receptor signalling regulates intestinal barrier function and mucosal immunity, offering yet another route by which microbial tryptophan handling feeds back onto the inflammatory tone that governs central kynurenine metabolism. The three tryptophan branches are therefore not independent: microbial indole production, epithelial serotonin synthesis, and immune kynurenine metabolism are competitively linked through a shared substrate pool, such that a dysbiotic, inflammatory gut can simultaneously lower serotonin availability and raise neurotoxic kynurenine flux. This competitive partitioning is arguably the single most integrative metabolite mechanism in the pathogenesis of gut-related depression.

This pillar also carries implications for existing pharmacotherapy. Because the overwhelming majority of the body's serotonin is synthesised in the gut and its production is regulated by the microbiota, the microbial environment may modulate the substrate on which serotonergic treatments act. Consistent with this, the antidepressant effects of selective serotonin reuptake inhibitors have been shown in animal models to depend in part on intact vagal signalling, and these agents alter the composition of the microbiota, suggesting a reciprocal interaction between conventional pharmacotherapy and the gut–brain axis (Wang et al. 2023). Such findings hint that the microbiota may contribute to the substantial inter-individual variability in antidepressant response, and that microbiota status could one day inform treatment selection—though this remains a hypothesis in need of prospective testing rather than an established clinical tool.

4.3 GABA and other neuroactive compounds

Commensal bacteria, particularly Bifidobacterium and Lactobacillus species, ferment glutamate to produce GABA, the principal inhibitory neurotransmitter of the central nervous system (Zhou et al. 2024). Microbially derived GABA has been implicated in emotional regulation, and bacterial modulation of GABA availability is associated with changes in stress reactivity and anxiety-like behaviour (Kim et al. 2024). GABA signalling also participates directly in vagal transmission at specialised gut–neuron synapses, providing a molecular link to the neural pillar discussed below (Wang et al. 2023).

The GABAergic mechanism is notable because it connects a specific, cultivable bacterial capacity to a defined central-nervous-system target. In the canonical demonstration, Lactobacillus rhamnosus JB-1 altered the regional expression of central GABA-B and GABA-A receptor subunits in a manner opposite to that seen in animal

models of depression—raising receptor expression in cortical regions while lowering it in the amygdala, hippocampus, and locus coeruleus—and these changes tracked reductions in anxiety- and depression-related behaviour (Bravo et al. 2011). Because the same strains that produce GABA also act through the vagus, the amino-acid and neural pillars are mechanistically inseparable in these paradigms. Beyond GABA, gut bacteria influence the availability of other neuroactive molecules, including catecholamine precursors and serotonin, so that the metabolite pillar as a whole functions as a distributed neuropharmacological system operating from within the gut lumen.

5. Vagus Nerve Signalling at the Interface of the Gut–Brain Axis

The vagus nerve is the principal neural conduit of the MGBA, providing a rapid, direct route by which microbial and metabolite signals reach the brainstem. Its afferent fibres do not contact bacteria directly; instead, enteroendocrine cells sense luminal signals—including SCFAs, lipopolysaccharide, histamine, and cytokines—and relay them through hormone release (PYY, GLP-1, cholecystokinin, and serotonin) and through direct synaptic contacts with vagal afferents known as “neuropods” (Han et al. 2022; Bonaz et al. 2018). Signals converge on the nucleus of the solitary tract, from which they influence limbic and cortical circuits governing mood and fear.

Roughly eighty per cent of vagal fibres are afferent, making the nerve overwhelmingly a sensory channel that reports the state of the viscera to the brain, with a smaller efferent component that returns regulatory signals—including the cholinergic anti-inflammatory pathway, by which vagal output restrains peripheral cytokine production. This anatomy positions the vagus as both a sensor of gut inflammation and a brake upon it, so that altered vagal tone can simultaneously reflect and perpetuate a dysbiotic, inflamed gut. The nerve's dual sensory-regulatory role is central to interpreting the vagotomy experiments discussed below: severing the nerve removes not only a reporting channel but also a homeostatic feedback loop, which helps explain why vagotomy can either alleviate or prevent behavioural phenotypes depending on the microbial and inflammatory context.

The most compelling evidence for a causal vagal route comes from vagotomy experiments. In the seminal study by Bravo and colleagues, chronic administration of Lactobacillus rhamnosus (JB-1) altered central GABA-receptor expression in a region-specific manner, reduced stress-induced corticosterone, and diminished anxiety- and depression-related behaviour in mice—yet every one of these effects was abolished by subdiaphragmatic vagotomy (Bravo et al. 2011). Similarly, the anxiolytic effect of Bifidobacterium longum NCC3001 was shown to depend on intact vagal pathways (Bercik et al. 2011).

The relationship is bidirectional and context-dependent. Ingestion of beneficial bacteria alleviates stress-induced behaviour via the subdiaphragmatic vagus nerve, and these antidepressant-like effects are lost after vagotomy (Zhang et al. 2020). Conversely, in a lipopolysaccharide model, the subdiaphragmatic vagus nerve was required for the emergence of the depression-like phenotype and the accompanying dysbiosis, indicating that vagal signalling can transmit both salutary and pathogenic messages depending on the microbial context (Zhang et al. 2020). Notably, gut microbiota changes require vagus-nerve integrity to promote depressive-like behaviour, further cementing the nerve's mediating role (Siopi et al. 2023). Vagus function also correlates with microbiota diversity in humans: SCFA-producing taxa such as Lactobacillales and Ruminococcaceae are more abundant in individuals with better vagal tone (Bonaz et al. 2018).

The cellular basis of this signalling has been substantially clarified by the discovery of neuropods—specialised basal protrusions of enteroendocrine cells that form direct, glutamatergic synapses with vagal afferents, transducing luminal chemical cues into rapid neural signals on a millisecond timescale (Han et al. 2018). GABA has been identified as a facilitator of transmission at these gut–neuron synapses, providing a concrete molecular junction between the metabolite and neural pillars of the axis. Vagal chemoreceptors additionally sense SCFAs and gut hormones, so that a single afferent pathway integrates microbial, metabolic, and endocrine information before relaying it to the nucleus of the solitary tract. This architecture explains how compositional and metabolite changes in the gut are converted into the fast, specific neural signals capable of shaping emotional and stress-related circuits, and it identifies the neuropod–vagus interface as a promising, if still largely preclinical, therapeutic target.

6. An Integrative Model: Neuroendocrine and Neuroimmune Convergence

The three pillars do not act in isolation but converge on two integrative systems: the hypothalamic–pituitary–adrenal (HPA) axis and the neuroimmune system. Germ-free animals display an exaggerated HPA response to stress, a phenotype partially normalised by microbial colonisation, demonstrating that the microbiota calibrates the central stress response from early life (Clarke et al. 2016). Microbial signals reaching the brain via metabolites and the vagus modulate corticotropin-releasing-factor signalling and cortisol output, closing a feedback loop in which stress alters the microbiota and the microbiota shapes stress reactivity.

The neuroimmune arm provides a second convergence point. Dysbiosis increases intestinal permeability, permitting translocation of bacterial lipopolysaccharide, which activates immune cells to release pro-inflammatory cytokines (IL-6, IL-1β, TNF-α). These cytokines disrupt blood–brain-barrier integrity, activate microglia, and—by inducing IDO—divert tryptophan toward the neurotoxic kynurenine pathway (Simpson et al. 2021; Kaur et al. 2019). This inflammatory cascade unifies the metabolite and microbiota findings into a coherent pathogenic model: dysbiosis reduces protective SCFAs, weakens the gut barrier, amplifies systemic inflammation, and thereby biases neurotransmission and neuroplasticity toward a depressive and anxious phenotype.

Neuroplasticity provides a third integrative endpoint on which the pillars converge. Brain-derived neurotrophic factor (BDNF), a central regulator of hippocampal neurogenesis and synaptic plasticity whose reduction is a hallmark of depression, is modulated by the gut microbiota through neuroendocrine routes (Zhou et al. 2024). SCFAs, GABAergic signalling, and vagal activity each influence BDNF expression, and the SCFA-driven rescue of hippocampal neurogenesis observed in dietary-stress models illustrates how a peripheral metabolite deficit can translate into a central plasticity deficit (Li et al. 2022). By situating BDNF and hippocampal neurogenesis downstream of the microbiota, this framework connects the gut–brain axis to the neurotrophic hypothesis of depression, showing that microbial and neurotrophic models are complementary descriptions of a single pathophysiological process rather than competing explanations.

The HPA axis and the neuroimmune system are themselves reciprocally coupled, and the microbiota sits at their intersection. Glucocorticoids released under HPA activation modify the microbiota and gut-barrier function, while microbial and inflammatory signals feed back to shape HPA reactivity, creating a self-reinforcing loop that can lock in a maladaptive state. Chronic stress can thus initiate a cycle in which stress alters the microbiota, the altered microbiota amplifies inflammation and HPA dysregulation, and the resulting neurochemical milieu sustains depressive and anxious symptoms. Interrupting this loop at any node—microbial, metabolic, immune, or neural—offers a conceptual rationale for the diverse intervention strategies discussed in the following section, and explains why approaches as different as dietary fibre, probiotics, and vagus-nerve stimulation can converge on similar clinical endpoints. Integrative reviews synthesising these neural, immune, and metabolite channels have likewise emphasised the bidirectional, multi-pathway character of gut–brain communication (Wójcik et al. 2025).

Table 1. Principal mediators of the microbiota–gut–brain axis implicated in depression and anxiety, and their proposed mechanisms.

Mediator / pillar	Representative examples	Proposed mechanism relevant to mood/anxiety
SCFA-producing taxa	Faecalibacterium, Coprococcus, Roseburia	Depleted in depression; loss reduces butyrate, weakening the gut and blood–brain barriers and raising neuroinflammation.
Pro-inflammatory / indole-positive taxa	Alistipes, Prevotella (context-dependent)	Enriched in some cohorts; may lower serotonin availability and promote inflammatory signalling.
Short-chain fatty acids	Butyrate, propionate, acetate	HDAC inhibition, microglial suppression, barrier reinforcement, ACSS2–PPARγ–TPH2 serotonin synthesis.
Tryptophan catabolites	Serotonin, kynurenine, quinolinic acid, indoles	Inflammation-driven IDO activation diverts tryptophan from serotonin to neurotoxic kynurenine metabolites.
Neuroactive amino-acid derivatives	GABA (Lactobacillus, Bifidobacterium)	Modulates central inhibitory tone and facilitates vagal neuropod transmission.
Vagus nerve	Subdiaphragmatic vagal afferents; neuropods	Direct neural conduit; vagotomy abolishes many microbial anxiolytic/antidepressant effects.
Neuroendocrine / immune integrators	HPA axis; LPS; IL-6, IL-1β, TNF-α	Microbiota calibrates stress reactivity; barrier failure amplifies systemic and central inflammation.

Abbreviations: SCFA, short-chain fatty acid; HDAC, histone deacetylase; IDO, indoleamine-2,3-dioxygenase; GABA, gamma-aminobutyric acid; HPA, hypothalamic–pituitary–adrenal; LPS, lipopolysaccharide.

7. Clinical and Therapeutic Implications

The mechanistic plausibility of the MGBA has driven a rapidly growing body of interventional research, most prominently on psychobiotics—probiotics and prebiotics with mental-health benefits mediated through the gut–brain axis. A 2024 systematic review of 51 randomised clinical trials encompassing 3,353 participants reported notably high effectiveness specifically for depressive symptoms, with Lactobacillus and Bifidobacterium strains administered over 4–24 weeks being the most studied and most consistently effective (Sarkar et al. 2024).

The term psychobiotic was originally coined to denote live organisms that, when ingested in adequate amounts, confer mental-health benefits, but its scope has since broadened to include prebiotic fibres that nourish beneficial taxa and, more recently, defined metabolite-delivering formulations. The strains carried forward into clinical testing are typically those with the strongest preclinical vagal and metabolite credentials—Lactobacillus and Bifidobacterium species prominent among them—creating a direct line from the mechanistic pillars reviewed above to the interventions tested in patients. This mechanistic continuity is a strength of the field: unlike many empirical psychiatric treatments, psychobiotics were nominated on the basis of specified biological pathways, allowing trials to test mechanism and clinical effect together.

Quantitative synthesis tempers this optimism with realism. A meta-analysis of 13 randomised controlled trials with 786 participants found an overall small effect-size reduction in depression severity favouring treatment (standardised mean difference −0.34; 95% CI −0.45 to −0.22), with subgroup analysis indicating that probiotics—whether single- or multi-strain—drove the significant effect (Asad et al. 2024). Individual trials provide mechanistic corroboration: Bifidobacterium breve CCFM1025 attenuated major depressive disorder while measurably regulating the gut microbiome and tryptophan metabolism (Tian et al. 2022). More invasive strategies, including faecal microbiota transplantation, remain experimental but are being actively investigated, alongside emerging vagus-nerve-stimulation approaches that exploit the neural pillar directly (Zhou et al. 2024).

The comparative performance of intervention types is informative. Meta-analytic subgroup analyses have generally found that probiotics, rather than prebiotics or synbiotics, account for the reproducible signal in clinical depression, and that effects are more consistent in clinically diagnosed samples than in subclinical or general-population cohorts (Asad et al. 2024). A recent meta-analysis focused specifically on unmedicated patients—approximating monotherapy conditions and registered with PROSPERO under PRISMA 2020—was undertaken precisely to isolate the independent efficacy of probiotics from concurrent antidepressant treatment, reflecting the field's growing methodological maturity (Liu et al. 2026). Faecal microbiota transplantation, though supported by strong preclinical causal data, has been evaluated in only small psychiatric samples and cannot yet be recommended outside research settings; its principal current value is as a proof-of-concept tool confirming that microbiota manipulation can alter host physiology. Vagus-nerve stimulation, already approved for treatment-resistant depression on other grounds, is of particular mechanistic interest here because it acts directly on the neural pillar and may interact with microbial signalling, an intersection now being explored explicitly (Zhou et al. 2024). The same mechanistic logic is being extended to specific clinical populations, such as postpartum depression, where inflammatory and neuroendocrine dysregulation of the axis has been proposed as a target for probiotic and transplantation-based approaches (Komasara et al. 2025).

Several caveats constrain clinical translation. Effect sizes are modest, most trials use probiotics as an adjunct to standard care rather than as monotherapy, and substantial heterogeneity in strain selection, dosage, duration, and patient population limits direct comparison and generalisation (Sarkar et al. 2024; Liu et al. 2026). These limitations point to a need for strain-specific, mechanistically informed, and personalised interventions rather than a generic “probiotic” prescription.

A promising direction is the use of the microbiota and its metabolites as biomarkers to stratify patients and predict treatment response. Because the taxonomic signatures of depression are inconsistent but the functional signatures—particularly SCFA depletion and a pro-inflammatory kynurenine shift—are more reproducible, metabolite panels may prove more clinically useful than sequencing alone. Identifying an “inflammatory” or “metabolic” subtype of depression, in which gut-derived inflammation is a dominant driver, could allow microbiota-targeted therapies to be directed at the patients most likely to benefit, rather than applied indiscriminately. Diet represents a complementary, low-risk lever: fibre-rich dietary patterns increase SCFA-producing taxa and could plausibly augment pharmacological and psychotherapeutic treatment, though rigorous trials of dietary augmentation in clinical depression remain limited. Emerging modalities, including precision prebiotics and engineered next-generation psychobiotics designed to deliver defined metabolites, may eventually move the field beyond the current generation of broadly acting probiotic formulations.

The favourable safety profile of most microbiota-directed interventions is an important practical consideration. Probiotic and prebiotic supplements are generally well tolerated, with adverse effects typically limited to transient gastrointestinal symptoms, and they lack the metabolic, sexual, and discontinuation effects that reduce adherence to conventional antidepressants. This tolerability, combined with mechanistic plausibility, makes them attractive as adjuncts even while their standalone efficacy remains modest. It also lowers the threshold for their use in populations where conventional pharmacotherapy is problematic, such as during pregnancy, in adolescents, or in patients with medical comorbidity—though the evidence base in these specific groups is still thin and warrants dedicated study. Against this must be weighed the current lack of regulatory standardisation of probiotic products, which vary widely in strain identity, viability, and dose, so that clinical benefit cannot be assumed to transfer across formulations. Until product standardisation and strain-specific evidence mature,

clinicians are best advised to regard microbiota-directed approaches as evidence-supported adjuncts rather than established treatments.

8. Discussion

Taken together, the evidence reviewed across the three pillars supports a coherent, multi-level model in which the gut microbiota participates in the pathogenesis of depression and anxiety through interlocking metabolic, immune, endocrine, and neural mechanisms. The consistency across independent lines of evidence—compositional shifts in patients, causal transmission of phenotypes by transplantation, mechanistic dissection of metabolite pathways, and abolition of behavioural effects by vagotomy—is more persuasive than any single finding in isolation. It is the convergence, rather than the strength of any one study, that makes the microbiota–gut–brain axis a compelling framework.

An important theme is developmental timing. The microbiota exerts its influence on the stress-response system most powerfully during early-life critical windows, when colonisation shapes the maturation of the HPA axis and of emotional circuitry (Clarke et al. 2016). This developmental dimension suggests that the axis contributes not only to the acute state of depression and anxiety but also to lifelong vulnerability, and it raises the possibility that early-life microbial interventions could have disproportionate preventive value. It also complicates cross-sectional adult studies, in which the microbiota observed at the time of illness may be as much a consequence as a cause of altered physiology and behaviour.

The field must also confront genuine inconsistencies. Taxonomic findings diverge between cohorts, the direction of change for several genera is not stable, and effect sizes in clinical trials are modest. Rather than undermining the framework, these inconsistencies are largely explained by three factors: the primacy of function over taxonomy, the powerful confounding influence of diet and medication, and methodological heterogeneity in sequencing, metabolite measurement, and psychiatric assessment. Interpreting the literature through the functional–metabolite lens, and demanding causal designs where possible, resolves much of the apparent contradiction and clarifies which findings are robust. The most reproducible signals—SCFA depletion, the inflammatory kynurenine shift, and vagal dependence of microbial effects—are precisely those grounded in mechanism rather than in taxonomy alone.

Finally, the axis should be positioned appropriately within the broader pathophysiology of mood and anxiety disorders. It is one contributor among several, interacting with genetic vulnerability, psychosocial stress, and monoaminergic and neurotrophic mechanisms, rather than a competing or exclusive explanation. Its principal value may be as a modifiable, peripherally accessible node that offers therapeutic entry points—dietary, probiotic, metabolite-based, and neuromodulatory—that are mechanistically distinct from, and potentially complementary to, existing treatments. This integrative positioning, rather than an overstated claim of primacy, best reflects the current state of the evidence.

It is instructive that gut–brain-axis aberrations are reported not only in depression and anxiety but across a range of neuropsychiatric conditions, including bipolar disorder, post-traumatic stress disorder, and autism spectrum conditions, where similar patterns of dysbiosis, altered SCFA production, and inflammatory signalling recur (Obi-Azuike et al. 2023). This trans-diagnostic footprint suggests that the axis engages mechanisms of general relevance to brain function rather than pathways unique to any one disorder. For depression and anxiety specifically, the implication is twofold: the microbiota is unlikely to be a disorder-specific cause, but it may represent a shared vulnerability substrate that, when perturbed, biases the brain toward affective dysregulation in interaction with disorder-specific genetic and environmental factors. This view accommodates both the breadth of the microbiota's influence and the specificity of clinical syndromes, and it cautions against expecting microbiota-targeted therapies to be selectively antidepressant or anxiolytic rather than broadly stabilising.

9. Limitations

This review has limitations. First, it was conducted as a narrative synthesis structured around three predefined mechanistic pillars rather than a quantitative meta-analysis, reflecting the heterogeneity of the underlying evidence. Second, much of the mechanistic data derives from rodent models, and interspecies differences in microbiota and neuroanatomy limit direct extrapolation to humans. Third, human microbiome studies are frequently cross-sectional and confounded by diet, medication, and lifestyle, precluding firm causal inference. Finally, the field suffers from methodological variability in microbiota sequencing, metabolite quantification, and psychiatric outcome measurement, which complicates cross-study comparison. These constraints should be weighed when interpreting the conclusions below.

A further limitation concerns the possibility of publication and reporting bias. Positive findings linking the microbiota to behaviour are more readily published than null results, which may inflate the apparent consistency

of the literature and the estimated effect sizes of interventions. The relatively small samples of many mechanistic and early clinical studies compound this concern, as underpowered studies are prone to exaggerated effect estimates. In addition, the reliance in this review on English-language, peer-reviewed sources indexed in major databases may have excluded relevant work published elsewhere. Readers should therefore interpret the strength of the evidence conservatively: the convergence across independent lines of investigation is genuinely persuasive at the level of biological plausibility, but the quantitative magnitude of the microbiota's contribution to human depression and anxiety, and the reliability of microbiota-targeted treatments, remain to be established by larger, pre-registered, and methodologically harmonised studies.

10. Future Directions

Several priorities emerge for advancing the field from association toward clinically actionable knowledge. First, longitudinal and interventional human studies are needed to establish temporal precedence and causality, moving beyond the cross-sectional designs that dominate the current literature. Cohort studies that sample the microbiota, its metabolites, and psychiatric symptoms repeatedly over time—ideally spanning the transition into and out of episodes—would clarify whether microbial changes precede, accompany, or follow mood and anxiety symptoms.

Second, methodological harmonisation is essential. The comparability of findings is currently undermined by variation in sequencing platforms and bioinformatic pipelines, in metabolite quantification methods, and in psychiatric outcome instruments. Adoption of standardised, absolute-quantification approaches to both microbiota and metabolites, together with consistent diagnostic and symptom-severity measures, would allow findings to be pooled meaningfully and would reduce the heterogeneity that presently limits meta-analysis (Xiong et al. 2025). Rigorous control for diet, body mass index, and medication—the dominant confounders—should be a standard requirement rather than an occasional refinement.

Third, mechanistic specificity should be pursued through strain-resolved and metabolite-defined interventions. Rather than testing broad probiotic mixtures, future trials should evaluate defined strains selected for specified mechanistic properties—SCFA production, tryptophan handling, or vagal engagement—and should measure the corresponding mechanistic biomarkers alongside clinical outcomes, so that mechanism and effect are tested jointly. Engineered next-generation psychobiotics and precision prebiotics, designed to deliver defined metabolic functions, represent a natural extension of this approach.

Fourth, patient stratification deserves explicit attention. If, as the evidence suggests, gut-derived inflammation drives depression in a definable subgroup, then trials enriched for such patients—identified by inflammatory and metabolite biomarkers—may reveal effects obscured in unselected samples. This stratified strategy aligns microbiota-targeted psychiatry with the broader movement toward precision medicine and may convert the currently modest average effect sizes into clinically meaningful benefits for the patients most likely to respond.

Realising these priorities will require close interdisciplinary collaboration among psychiatry, gastroenterology, microbiology, immunology, and computational biology, since no single discipline commands all the methods the field demands. The integration of multi-omics data—linking metagenomic, metabolomic, immunological, and neuroimaging measures within the same participants—offers a particularly promising route to disentangling the causal architecture of the axis, and advances in machine learning may help identify the metabolite and microbial signatures most predictive of clinical outcome. Equally important is attention to the ecological validity of interventions: because diet is the single most powerful determinant of the microbiota, dietary context must be measured and, where possible, controlled in any trial of probiotics or prebiotics, lest a genuine effect be masked or a spurious one manufactured by uncontrolled nutritional variation. With these methodological foundations in place, the coming decade should be able to determine, for the first time with confidence, how large a role the gut–brain axis plays in human depression and anxiety and how best to act upon it.

11. Conclusions

The gut–brain axis represents a biologically plausible and increasingly well-characterised contributor to the pathogenesis of depression and anxiety disorders. Convergent evidence indicates that a dysbiotic microbiota—depleted of SCFA-producing taxa and enriched in pro-inflammatory organisms—signals to the brain through three interlocking pillars: bacterial metabolites (SCFAs, tryptophan catabolites, and GABA), neuroimmune and neuroendocrine cascades, and the vagus nerve. Vagotomy experiments provide some of the strongest causal evidence, demonstrating that key anxiolytic and antidepressant-like microbial effects depend on intact vagal signalling.

Clinically, psychobiotic interventions yield small but statistically significant reductions in depressive symptoms, supporting the axis as a therapeutically tractable target while underscoring that it is one contributor among many rather than a singular cause. Future research should prioritise longitudinal, adequately powered human trials with

harmonised methodology, strain-specific mechanistic characterisation, and stratified designs that account for diet and medication. Such work will be essential to translate the compelling mechanistic promise of the microbiota–gut–brain axis into reliable clinical benefit for patients with mood and anxiety disorders.

For clinical practice, the immediate implications are cautious but real. The current evidence does not support microbiota-targeted therapies as stand-alone treatments for depression or anxiety, but it does justify their consideration as low-risk adjuncts within a broader treatment plan, and it lends mechanistic support to dietary counselling that favours fibre-rich, microbiota-supportive eating patterns. Perhaps most importantly, the framework reframes depression and anxiety as disorders with a meaningful peripheral, and potentially modifiable, dimension—an understanding that both expands the therapeutic imagination and offers patients an accessible domain of self-management. As causal human evidence accumulates and interventions become more precise, the microbiota–gut–brain axis is likely to move from a promising research frontier toward a defined component of integrative psychiatric care.

In summary, the gut microbiota, its metabolites, and the vagus nerve together constitute a biologically coherent axis through which the periphery participates in the regulation of mood and anxiety. The three pillars examined in this review are not separate mechanisms but facets of a single integrated system, converging on shared neuroinflammatory, neuroendocrine, and neuroplastic endpoints. The strength of the framework lies in this convergence and in the causal evidence provided by transplantation and vagotomy studies; its principal weakness lies in the modest and heterogeneous clinical data and the persistent gap between mechanistic promise and demonstrated therapeutic benefit. Bridging that gap—through rigorous, mechanistically informed, and adequately powered human research—represents both the central challenge and the central opportunity for this rapidly evolving field, and its resolution will determine whether the microbiota–gut–brain axis fulfils its potential to enlarge the therapeutic repertoire available to patients with depression and anxiety disorders.

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Author's contribution:

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