

Mechanisms and Intervention Strategies of the Gut-Brain Axis in the Development and Progression of Depression

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Abstract. Major depressive disorder is a heterogeneous psychiatric syndrome in which affective, cognitive, somatic, endocrine, and immune phenotypes arise from interacting biological networks rather than from a single neurotransmitter deficit. The gut-brain axis provides a biological model for explaining how intestinal microorganisms, epithelial barrier integrity, mucosal immunity, microbial metabolites, vagal afferents, and hypothalamic-pituitary-adrenal signaling shape brain function under conditions of stress and disease. Clinical studies have reported altered fecal microbial composition, reduced microbial richness in selected patient groups, changes in tryptophan and short-chain fatty acid metabolism, and associations between neuroactive microbial potential and depressive symptoms. Experimental transfer studies further indicate that depression-associated microbiota can reproduce behavioral, metabolic, and inflammatory features in recipient animals, supporting a causal contribution in susceptible contexts. This review summarizes the structural basis and research evidence for gut-brain axis involvement in depression, analyzes mechanisms involving microbial metabolites, neuroactive substances, intestinal barrier disruption, immune inflammation, neuroendocrine imbalance, and impaired neuroplasticity, and discusses intervention strategies based on dietary modulation, probiotics, prebiotics, fecal microbiota transplantation, live biotherapeutic products, and pathway-oriented precision approaches. Current data support the gut-brain axis as a biologically plausible and clinically tractable target, while indicating that patient stratification, mechanistic biomarkers, and rigorous longitudinal trials are required before microbiome-centered interventions can be integrated into standardized depression care.

Keywords: Gut-brain axis, Depression, Gut microbiota, Neuroinflammation, Microbial metabolites

1. Introduction

Major depressive disorder is defined clinically by persistent low mood, anhedonia, cognitive impairment, sleep and appetite disturbances, psychomotor changes, and recurrent somatic symptoms, but its biological substrate is distributed across neural, immune, endocrine, and metabolic systems. The incomplete efficacy of monoaminergic antidepressants in a substantial proportion of patients has promoted broader models that incorporate stress biology, neuroinflammation, impaired neuroplasticity, circadian disturbance, and peripheral metabolic

dysregulation. Within this framework, the gut-brain axis describes bidirectional signaling between the gastrointestinal tract and the central nervous system through neural, endocrine, immune, barrier, and microbial routes. Its relevance to depression is supported by the frequent co-occurrence of gastrointestinal symptoms and mood disorders, by the sensitivity of intestinal microbial ecology to chronic stress, and by experimental evidence showing that microbial communities can alter emotional behavior, neurochemistry, and inflammatory tone [1].

The gut microbiota is not a passive correlate of host physiology. It participates in nutrient conversion, bile acid transformation, short-chain fatty acid production, tryptophan metabolism, mucosal immune education, and epithelial barrier maintenance. These functions are positioned to influence depression-relevant pathways because immune activation, altered kynurenine pathway flux, hypothalamic-pituitary-adrenal axis dysregulation, and changes in brain-derived neurotrophic factor signaling have all been implicated in depressive phenotypes. Human studies have described shifts in bacterial taxa and functional gene profiles in major depressive disorder, while animal studies have shown that stress-induced microbial changes can modify behavior and that microbiota transfer from depressed donors can induce depressive-like phenotypes in recipient animals [2, 3]. These observations do not establish a uniform microbial signature for all patients, yet they support a model in which intestinal ecological states participate in disease expression through host-context-dependent mechanisms.

This review focuses on the mechanisms by which the gut-brain axis participates in the development and progression of depression and on intervention strategies designed to modify this axis. The discussion integrates clinical association studies, metabolomic and functional microbiome analyses, stress and transfer models, and interventional trials involving diet, probiotics, prebiotics, fecal microbiota transplantation, and live biotherapeutic products. Emphasis is placed on biologically verified pathways rather than on taxonomic cataloguing alone, because microbial taxa vary across geography, diet, medication exposure, sequencing platform, and disease subtype. A mechanistic review of this field needs to connect microbial ecology with epithelial barrier biology, immune inflammation, vagal and endocrine signaling, and neural plasticity in a manner that can inform translational study design.

2. Theoretical basis and research evidence for the gut-brain axis in depression

2.1. Structural basis and bidirectional communication network of the gut-brain axis

The structural basis of the gut-brain axis includes the intestinal microbiota, epithelial and mucus barriers, enteroendocrine cells, mucosal immune cells, the enteric nervous system, autonomic afferent and efferent fibers, circulating endocrine mediators, and central stress-responsive nuclei. Microbial communities interact with epithelial cells through metabolites and microbe-associated molecular patterns, while the host regulates microbial habitat through motility, mucus secretion, antimicrobial peptides, bile acids, diet-derived substrates, and immune pressure. Signals generated in the intestinal lumen can reach the brain through several routes. Vagal afferents detect intestinal mechanical, chemical, and immune cues directly or indirectly through enteroendocrine mediators. Circulating cytokines and microbial products can influence circumventricular organs, endothelial cells, perivascular macrophages, and microglia. Endocrine communication involves cortisol, gut peptides, and enterochromaffin cell products, whereas microbial metabolites can act locally at the barrier or systemically after absorption [4, 5].

Depression-related stress exposure can modify nearly every component of this network. Chronic psychosocial stress alters gut motility, mucus production, epithelial permeability, luminal oxygen

developmental stage, and metabolic state may influence gut-brain relationships [9]. The clinical literature remains heterogeneous because depression subtypes, dietary background, psychotropic medication, body mass index, sleep, and comorbid gastrointestinal disease can all modify the microbiome.

Experimental models provide causal support that cannot be inferred from cross-sectional clinical associations alone. Zheng and colleagues showed that microbiota transplantation from patients with depression induced depressive-like behavior and host metabolic changes in microbiota-depleted mice [10]. Kelly and colleagues reported that fecal microbiota from depressed patients transferred neurobehavioral and inflammatory features to recipient rats [11]. These transfer studies indicate that microbial communities can carry disease-relevant functional information, although they do not imply that microbiota alone is sufficient to explain the full syndrome of depression. Animal models also show that chronic stress reshapes microbial composition and intestinal barrier integrity, and that microbial metabolites such as short-chain fatty acids can modify inflammatory and neurochemical outcomes [12]. The strongest interpretation is that dysbiosis acts as a modifiable contributor within a wider network of genetic vulnerability, stress exposure, immune state, diet, and neuroendocrine adaptation.

2.3. Association between gut-brain axis abnormalities and clinical heterogeneity of depression

Depression is clinically heterogeneous, and gut-brain axis abnormalities may help explain differences in symptom profiles and treatment response. Patients with prominent fatigue, anhedonia, sleep disruption, appetite change, gastrointestinal symptoms, metabolic syndrome, or elevated inflammatory markers may have different degrees of intestinal barrier disturbance, immune activation, and microbial metabolic alteration. The concept of an inflammatory or metabolically dysregulated depression subtype is consistent with data linking peripheral cytokines, kynurenine pathway activity, and gut permeability markers to depressive symptom dimensions. Microbiome-based stratification is still exploratory, yet the field has moved from simple taxonomic comparison toward combined metagenomic, metabolomic, immune, and clinical phenotyping. This shift is necessary because a microbial community can produce divergent host effects depending on its functional genes, substrate availability, and host receptor context.

Medication exposure also contributes to clinical heterogeneity. Antidepressants, antipsychotics, proton-pump inhibitors, antibiotics, metformin, and anti-inflammatory agents can affect microbial communities or host inflammatory tone. Diet and regional lifestyle patterns are additional confounders, but they are also therapeutic entry points. The absence of a universal depression microbiome should not be interpreted as evidence against gut-brain involvement. It more likely reflects the biological diversity of depressive disorders. A clinically useful model will require identifying microbial functions and host response markers that correspond to symptom dimensions, illness stage, inflammatory burden, and treatment history rather than relying on a fixed taxonomic panel.

3. Mechanisms by which the gut-brain axis mediates depression development and progression

3.1. Regulation of neural signaling by gut microbial metabolites and neuroactive substances

Microbial metabolites provide a direct biochemical route through which the gut can influence neural signaling. Short-chain fatty acids, including acetate, propionate, and butyrate, are produced by bacterial fermentation of dietary fibers and resistant starches. These metabolites regulate epithelial

energy metabolism, tight junction integrity, regulatory T cell differentiation, microglial maturation, and histone deacetylase activity. In depression-relevant contexts, reduced capacity for short-chain fatty acid production may weaken barrier function and increase inflammatory tone, whereas butyrate has been linked experimentally to anti-inflammatory and neuroplastic effects. The magnitude and direction of these effects depend on concentration, exposure duration, receptor distribution, and the metabolic state of the host. Recent mechanistic reviews and experimental studies support a role for short-chain fatty acids in linking microbial ecology with neuroinflammation and behavior, while indicating that translation requires metabolite-level measurement rather than inference from bacterial abundance alone [13].

Tryptophan metabolism is another major interface between intestinal microbiota and depression biology. Tryptophan can be used for serotonin synthesis, converted through the kynurenine pathway, or transformed by microorganisms into indole derivatives that activate aryl hydrocarbon receptor signaling. Peripheral inflammation increases indoleamine 2,3-dioxygenase activity and shifts tryptophan away from serotonin-related pathways toward kynurenine metabolites. Some kynurenine products influence glutamatergic neurotransmission, oxidative stress, and microglial activation. Microbial regulation of tryptophan availability and indole production may affect mood-related circuits through immune, endocrine, and receptor-mediated processes. Clinical metabolomic data in adolescent depression and broader depression cohorts support altered tryptophan-related metabolism, although individual metabolite patterns vary with inflammation, diet, age, and medication.

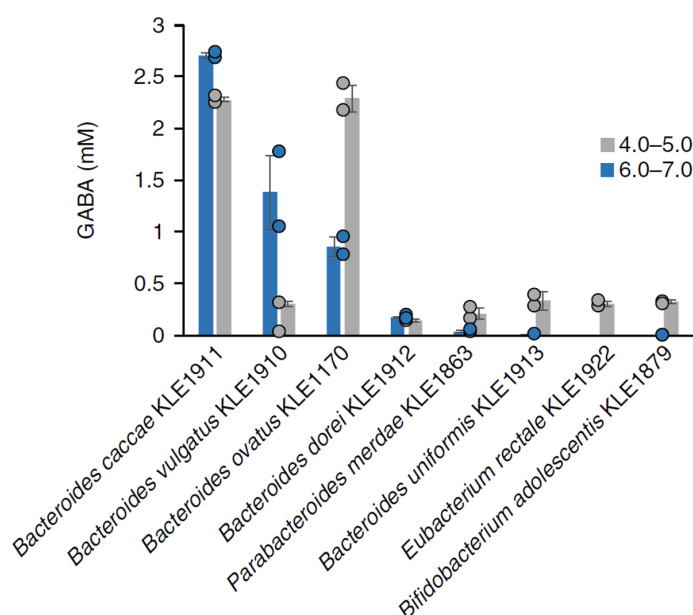


Figure 2. GABA-producing capacity of representative human gut bacterial strains [14]

Several gut bacteria can synthesize or modulate neuroactive molecules, including gamma-aminobutyric acid, glutamate, dopamine precursors, serotonin-related metabolites, and acetylcholine-related compounds. Strandwitz and colleagues identified GABA-modulating bacteria in the human gut microbiota, providing a functional example of microbial participation in inhibitory neurotransmitter metabolism [14]. Experimental evidence further showed that representative gut bacterial strains, particularly members of the genera *Bacteroides* and *Parabacteroides*, are capable of producing GABA, with production levels varying among bacterial species and environmental pH

conditions (Fig. 2). These molecules do not necessarily cross the blood-brain barrier in large amounts, but they can affect enteric neurons, enteroendocrine cells, immune cells, vagal afferents, and peripheral metabolic pathways that project onto central circuits. The neuroactive capacity of a microbial community is better understood as a distributed signaling property than as a simple source of brain neurotransmitters. Functional metagenomics and metabolomics are needed to determine whether a patient has reduced production, altered degradation, or abnormal host responsiveness to these compounds.

3.2. Neuroinflammatory responses mediated by intestinal barrier injury and immune-inflammatory signaling

Intestinal barrier disruption can convert local dysbiosis into systemic immune activation. Tight junction injury, mucus thinning, altered antimicrobial peptide secretion, and epithelial stress increase contact between microbial products and mucosal immune cells. Lipopolysaccharide, peptidoglycan fragments, flagellin, and bacterial DNA can activate pattern-recognition receptors such as Toll-like receptors and NOD-like receptors, promoting cytokine production and inflammasome signaling. Circulating cytokines can communicate with the brain through endothelial activation, humoral routes, vagal afferents, and immune cell trafficking. In the central nervous system, these signals may alter microglial phenotype, astrocyte function, synaptic pruning, and neurotransmitter metabolism. This intestinal barrier-inflammation pathway provides a mechanistic explanation for clinical links among gastrointestinal symptoms, immune activation, and depressive phenotypes.

Microglia and astrocytes are central effectors in inflammation-related depression mechanisms. Activated microglia can release interleukin-1 β , interleukin-6, tumor necrosis factor- α , reactive oxygen species, and prostaglandins, all of which can influence synaptic plasticity, monoamine metabolism, and glutamatergic signaling. Astrocytic dysfunction can impair glutamate uptake, metabolic support, and blood-brain barrier maintenance. Gut-derived inflammatory signals may also modify peripheral immune cell polarization, leading to altered regulatory T cell and Th17 balance. Reviews of gut dysbiosis in depression have integrated these immune pathways with alterations in microbial metabolites and stress hormones, supporting a multi-hit model in which barrier injury, cytokine signaling, and glial activation reinforce each other [15].

3.3. Gut-brain regulation of neuroendocrine imbalance and abnormal neuroplasticity

The hypothalamic-pituitary-adrenal axis is a principal route through which stress and gut biology converge. Chronic stress increases corticotropin-releasing hormone, adrenocorticotrophic hormone, and glucocorticoid exposure, which can impair hippocampal neurogenesis, increase visceral sensitivity, alter gut motility, and change epithelial permeability. Microbial communities can modulate stress reactivity, and germ-free or antibiotic-treated animals often show altered endocrine responses to stress. The direction of endocrine change depends on developmental timing, microbial recolonization, strain composition, and stress paradigm. In depression, persistent HPA-axis activation may interact with dysbiosis and inflammation to maintain sleep disturbance, appetite change, anxiety, and impaired cognitive flexibility [16].

Neuroplasticity provides another convergence point. Brain-derived neurotrophic factor and its receptor TrkB regulate neuronal survival, dendritic remodeling, synaptic strength, and antidepressant response. Gut-derived inflammation, altered tryptophan metabolism, oxidative stress, and reduced short-chain fatty acid signaling can impair neurotrophic pathways, whereas selected dietary, microbial, and natural product interventions have been associated with restoration of BDNF-related

signaling in experimental systems [17]. These effects should not be reduced to a single biomarker because BDNF expression varies across brain region, disease stage, and treatment context. A more precise model places neuroplasticity downstream of immune, endocrine, and metabolic gut-brain signals that reshape limbic and cortical circuit function over time.

4. Intervention strategies and translational progress targeting the gut-brain axis in depression

4.1. Microecological regulation through dietary patterns, probiotics, and prebiotics

Dietary intervention is a practical route for modifying the gut-brain axis because diet determines microbial substrate availability, fermentation output, bile acid pools, and systemic metabolic inflammation. The SMILES trial provided clinical evidence that structured dietary improvement can reduce depressive symptoms in adults with major depression, supporting the therapeutic relevance of nutrition within psychiatric care [18]. Diets rich in fiber, legumes, whole grains, vegetables, fruits, unsaturated fats, and fermented foods may increase microbial diversity and short-chain fatty acid production, whereas highly processed dietary patterns may promote inflammation and metabolic disturbance. Dietary effects are not microbiome-specific, because nutrient quality also influences insulin sensitivity, vascular function, oxidative stress, and sleep. For this reason, future dietary studies should combine symptom outcomes with microbial, metabolomic, inflammatory, and endocrine measurements.

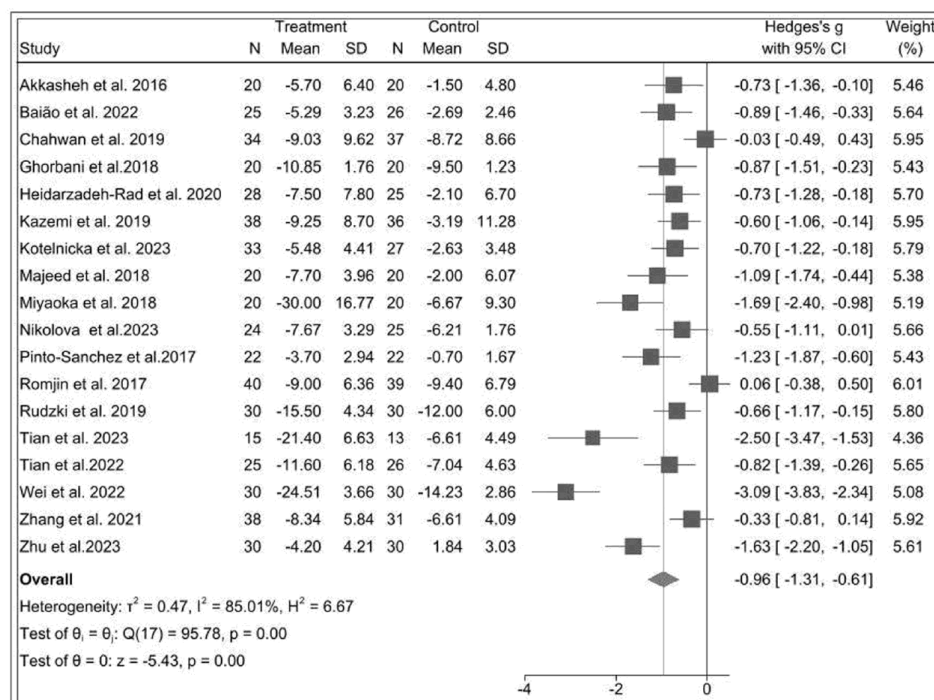


Figure 3. Meta-analytic evidence for the effects of probiotic interventions on depressive symptoms

Probiotics, prebiotics, and synbiotics have been studied as adjunctive interventions for depressive symptoms. Early human work reported psychological effects of probiotic formulations in healthy volunteers, and *Bifidobacterium longum* NCC3001 reduced depression scores and altered brain activity patterns in patients with irritable bowel syndrome [19]. More recent randomized evidence in patients with depression showed that adjunctive probiotics were acceptable and tolerable and

produced estimates of antidepressant effects that support larger trials [20]. Systematic reviews and meta-analyses further support the therapeutic potential of microbiome-targeted interventions. A recent meta-analysis of 18 probiotic RCTs involving 969 participants demonstrated a significant reduction in depressive symptoms, with a pooled standardized mean difference of -0.96 (95% CI: -1.31 to -0.61), although substantial between-study heterogeneity was observed ($I^2 = 85\%$) (Fig. 3). In contrast, the evidence for prebiotic interventions was less conclusive. These findings indicate that therapeutic response may depend on strain composition, dose, treatment duration, baseline microbiome characteristics, and clinical phenotype, supporting a targeted rather than generalized psychobiotic treatment model.

4.2. Research progress in fecal microbiota transplantation and live biotherapeutic products

Fecal microbiota transplantation represents a broader ecological intervention than single-strain or multi-strain probiotic therapy. Its psychiatric application is still exploratory because efficacy, donor selection, route of administration, durability, and safety require disease-specific evaluation. A pilot randomized controlled trial of fecal microbiota transplantation in major depressive disorder reported feasibility and clinical signals that justify further controlled studies, but sample size and early-stage design limit definitive inference. The method raises additional considerations involving pathogen screening, donor metabolic and psychiatric history, engraftment monitoring, and regulatory classification. Depression trials also need to determine whether successful engraftment corresponds to changes in microbial function, inflammatory markers, stress biology, and symptom dimensions.

Defined live biotherapeutic products may provide a more standardized alternative to conventional fecal microbiota transplantation. The MET-2 trial evaluated an orally delivered microbial ecosystem therapeutic in patients with major depression and represents a translational step toward controlled microbial consortia [22]. Such products can be manufactured, quality controlled, and mechanistically characterized more readily than donor-derived fecal preparations. Their development should be guided by functions relevant to depression, including short-chain fatty acid production, tryptophan pathway modulation, bile acid transformation, epithelial barrier support, and immune regulation. The major translational task is to identify which patient subgroup has a microbial deficit or inflammatory-metabolic state that is likely to respond to ecological replacement or supplementation.

4.3. Precision interventions targeting microbial metabolism, immune inflammation, and neuroendocrine pathways

Precision intervention targeting the gut-brain axis requires moving beyond the category of microbiome therapy as a single modality. One strategy is metabolite-oriented treatment, in which dietary fibers, prebiotics, postbiotics, or small molecules are used to increase beneficial short-chain fatty acid signaling, normalize tryptophan-kynurenine balance, or adjust bile acid receptor activation. Another strategy is barrier-oriented treatment, aimed at restoring mucus integrity, tight junction function, and epithelial immune tolerance. A third strategy is inflammation-oriented treatment, in which gut-derived inflammatory signaling is reduced through microbial, nutritional, or pharmacologic means. These approaches may be combined with conventional antidepressants, psychotherapy, exercise, sleep intervention, or anti-inflammatory agents when clinical phenotype and biomarker data indicate a relevant pathway.

Several experimental interventions illustrate the breadth of this approach. Matrine was reported to alleviate depressive-like behaviors in chronic unpredictable mild stress mice through modulation of

the microbiota-gut-brain axis, suggesting that natural products may influence microbial ecology and host inflammation simultaneously [23]. Other experimental models have connected short-chain fatty acid changes with stress-related or toxin-related depressive-like behaviors and neuroinflammation. Such experiments are mechanistically informative, but clinical translation requires rigorous characterization of active compounds, bioavailability, microbiome dependence, target engagement, and safety. A precision gut-brain strategy should combine validated clinical scales with stool metagenomics, targeted metabolomics, barrier and inflammatory markers, cortisol dynamics, and neurocognitive or neuroimaging endpoints. Such designs can determine whether an intervention changes the pathway it is intended to target and whether that pathway change mediates symptom improvement.

5. Conclusions and outlook

The gut-brain axis contributes to depression through interconnected microbial, epithelial, immune, endocrine, metabolic, neural, and plasticity pathways. Human studies have identified dysbiosis, altered microbial neuroactive potential, and metabolomic changes in depression, while experimental transfer studies support causal effects of depression-associated microbiota in susceptible hosts. Mechanistic evidence indicates that microbial metabolites, tryptophan metabolism, vagal signaling, intestinal barrier injury, cytokine release, glial activation, HPA-axis dysregulation, and impaired neurotrophic signaling can converge on emotional and cognitive circuits. The field has moved from a taxonomic association model toward a functional and pathway-oriented model of depression biology.

Interventions targeting the gut-brain axis have progressed from dietary trials and conventional probiotics to fecal microbiota transplantation, defined live biotherapeutic products, and pathway-specific metabolic or immune modulation. The available evidence supports therapeutic potential, but it also shows that response is unlikely to be uniform across all patients with depression. Future studies should define microbiome-informed depressive subtypes, standardize dietary and medication covariates, measure microbial functions rather than taxa alone, and connect biological target engagement with symptom trajectories. Integration of microbiome science with psychiatry will depend on longitudinal, adequately powered, mechanistically designed trials that identify when gut-brain modulation is an adjunctive strategy, when it is a preventive approach, and when it can become a component of individualized depression treatment.

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