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Melancholy in the Microbiome: Decoding the Gut-Brain Axis in Major Depression – A Systematic Review

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Abstract

Background. Major Depressive Disorder (MDD) is a debilitating affective condition that is increasingly recognized as a systemic disease driven by the Microbiota-Gut-Brain Axis (MGBA).

Aim. This systematic review aimed to summarize and identify common ground among current findings regarding the correlation between pathological microbiome growth and the development of MDD.

Material and methods. A systematic literature search was conducted in the PubMed and Scopus electronic databases to identify clinical studies evaluating gut microbiota composition in adult patients (aged 18–65) with Major Depressive Disorder (MDD). Applying strict PICOS eligibility criteria, a three-person independent screening process was performed following PRISMA guidelines. From the initial 915 identified records, a final cohort of 66 unique publications was selected for multi-omics synthesis. Extracted data parameters included clinical psychometric scores (BDI, HAM-D), microbial metabolite profiles, and specific alpha- and beta-diversity metrics.

Results. The synthesis of the 66 studies highlighted a clear pathobiological cascade, where the depletion of protective strains (*Faecalibacterium* and *Roseburia*) and overgrowth of pathobionts (*Klebsiella* and *Ruminococcus*) compromised intestinal barrier integrity. This "leaky gut" triggers a systemic influx of LPS and cytokines (IL-1β, IL-6, TNF-α), which cross the blood-brain barrier and enter the brain. This molecular synergy exacerbates both depressive severity and gastrointestinal comorbidities (IBS/IBD).

Conclusions. MDD-associated dysbiosis drives neuroinflammation via the gut–brain axis, as conceptualized in the NIMETOX framework. Translating these findings into personalized microbiome-targeted therapies requires standardization of methodologies, accounting for antidepressant confounders, and integration of multi-omic research.

Key words: Major Depressive Disorder, Microbiota-Gut-Brain Axis, Dysbiosis, Neuroinflammation, Tryptophan-Kynurenine Pathway.

1. Introduction

Major Depressive Disorder (MDD) is an affective disorder diagnosed based on a persistent depressed mood or clinical anhedonia lasting at least two weeks, accompanied by significant somatic and cognitive symptoms—such as sleep rhythm disturbances, changes in appetite and body weight, extreme psychophysical exhaustion, and impairment of concentration and executive functions, which lead to a significant decline in a patient's daily functioning. The scale of this phenomenon makes MDD one of the key challenges of modern medicine. According to epidemiological analyses [1], the global number of people suffering from depression is nearly 279.6 million. Moreover, long-term projections forecast a drastic increase in incidence, indicating that in the coming decades, depressive disorders will solidify their position as one of the leading causes of the global disease burden [2].

For years, the primary cause of depression was sought in neurotransmitter deficiencies—mainly serotonin and norepinephrine—within the synaptic clefts of the central nervous system. However, the lack of linear correlation between serotonin levels and clinical affective symptoms is increasingly being emphasized. Instead, MDD is now presented as a heterogeneous disease resulting from the interaction of environmental factors, genetic predispositions, and systemic disorders—such as hormonal and inflammatory dysregulation—which, combined with neurotransmitter dysfunction, comprise the final clinical picture [3]. This theory is also supported by the fact that approximately 30% of patients suffer from treatment-resistant depression, failing to respond to standard pharmacotherapy with SSRIs or SNRIs [4]. Contemporary research increasingly indicates that MDD development is strongly influenced by lifestyle and diet, which modify the body's homeostasis at the peripheral level [5].

The mechanism integrating these peripheral signals is the Microbiota-Gut-Brain Axis (MGBA). It is not a single anatomical connection, but a dynamic, bidirectional network of homeostatic integration. This communication occurs simultaneously on three complementary levels: neural, immune, and neuroendocrine. Disturbance of any of these components affects the central nervous system (CNS), modulating behavior, stress susceptibility, and the patient's affective functions.

The direct, bidirectional neuroanatomical connection within this axis is based on the interaction of the enteric nervous system (ENS) with the vagus nerve (CN X), whose afferent (sensory) fibers constitute 80% of the entire structure and terminate in the lamina propria of the intestinal mucosa. These receptors, although lacking direct contact with the intestinal lumen,

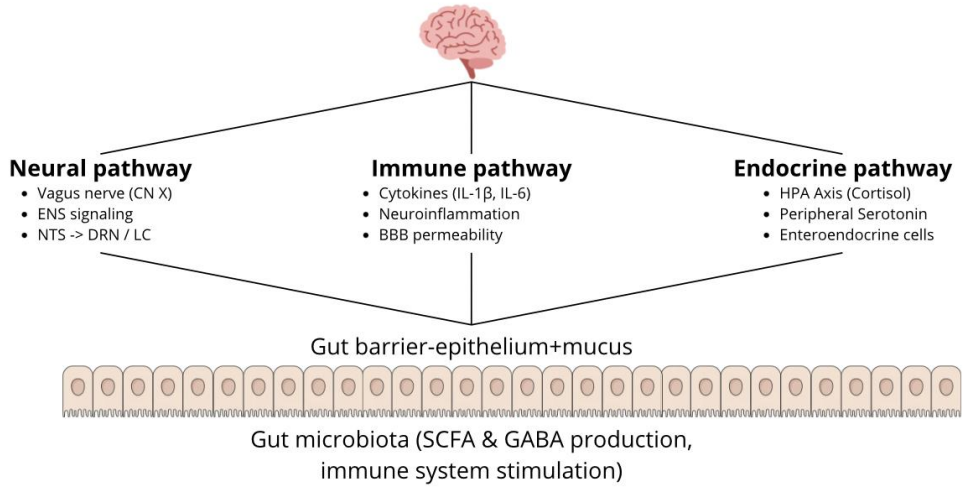
respond to chemical stimuli, including gamma-aminobutyric acid (GABA) and short-chain fatty acids (SCFAs) produced by bacteria of the Lactobacillus and Bifidobacterium genera. These impulses are transmitted to the nucleus tractus solitarius (NTS) in the brainstem, and subsequently to limbic system structures (hippocampus, amygdala), where they directly modulate neurogenesis and the expression of brain-derived neurotrophic factor (BDNF), influencing anxiety and the patient's mood.

At the neuroendocrine level, serotonin produced in the enterochromaffin cells of the gut plays a crucial role, stimulating the afferent fibers of the vagus nerve (CN X) to transmit signals to the NTS. This nucleus, in turn, influences the activity of serotonergic neurons located in the dorsal raphe nucleus (DRN) and noradrenergic cells in the locus coeruleus (LC) [6]. These key brain areas are responsible for stress response, emotional regulation, and immune response mechanisms. Recent findings suggest that microbial metabolites, particularly SCFAs, influence serotonin production in the gut, thus forming the foundation of gut-brain communication. In addition to serotonin, the gut microbiota also influences the synthesis of other neurotransmitters, such as GABA, dopamine, and acetylcholine, which play a critical role in emotion regulation.

Furthermore, the hypothalamic-pituitary-adrenal (HPA) axis, crucial for stress adaptation, remains in an inseparable relationship with the gut-brain axis. In depression, its hyperactivity is observed (excessive CRH, ACTH, and cortisol), which damages the intestinal barrier, promotes inflammation, and triggers dysbiosis [7]. This process acts as a vicious cycle—pathological gut flora facilitates the translocation of peripheral inflammatory cytokines (e.g., IL-1β, IL-6, TNF-α) into the bloodstream and the brain, which secondary stimulates the HPA axis and intensifies the stress response. The main mechanism inhibiting this cascade is GABAergic signaling, which effectively silences the excessive reactivity of the hypothalamus and adrenal glands.

Latest preclinical models also suggest that simultaneous disruption of the intestinal barrier and the blood-brain barrier (BBB) may allow for direct translocation of microbiota into the brain parenchyma, inducing neuroinflammation and neurodegenerative processes [8]. This phenomenon has so far been proven only in animals under highly invasive, non-physiological experimental conditions. Confirmation of this pathomechanism in depression patients—and the potential implementation of future "barrier-sealing" therapies—requires further, rigorous clinical studies.

The primary aim of this systematic review is to evaluate the complex relationship and functional correlation between gut microbiota alterations and major depressive disorder in adults. We hypothesize that intestinal dysbiosis plays a critical role in the pathophysiology of depression rather than being only a consequence of the disease. We suggest that disruptions in the microbial ecosystem compromise intestinal barrier integrity, triggering a systemic inflammatory cascade and metabolic shifts that drive neuroinflammation and neurochemical imbalances, ultimately triggering both depressive symptoms and comorbid gastrointestinal disorders.



Source: Authors' own compilation based on the studies included in the literature review (References [1-8]).

Figure 1. Bidirectional communication pathways within the microbiota-gut-brain axis (MGBA)

2.Research materials and methods

2.1.Participants.

Research inclusion criteria were structured based on the PICOS framework (Population, Intervention, Comparison, Outcome, Study design). The selected articles aimed to answer the following research question: "Do adult patients with clinical depression exhibit specific gut microbiota dysbiosis compared to healthy individuals, and how do these changes correlate with the severity of clinical symptoms?"

The main inclusion criteria were: (1) clinical, cohort, and case-control studies; (2) a population of adult patients aged 18 to 65 years with a confirmed diagnosis of Major Depressive Disorder (MDD), including both individuals without additional somatic conditions and patients with comorbid inflammatory bowel disease (IBD) or irritable bowel syndrome (IBS); (3) presence of documented gut dysbiosis or significant changes in the quantitative and qualitative composition of the microbiota; (4) inclusion of a control group consisting of healthy volunteers.

Exclusion criteria included: (1) literature reviews, meta-analyses, and case reports; (2) preclinical studies conducted on animal models, as well as works covering pediatric or geriatric populations, or patients diagnosed with bipolar disorder (BD); (3) studies focused on assessing the microbiome of other anatomical areas (such as skin, oral cavity, or vagina) instead of gut microbiota; (4) studies in which the participants' gut microbiota was modified through the administration of probiotics, prebiotics, or synbiotics.

2.2.Procedure / Test protocol / Skill test trial / Measure / Instrument

To investigate the impact of gut microbiota on the occurrence and progression of Major Depressive Disorder (MDD), a systematic literature search was conducted on May 24, 2026, in the PubMed and Scopus electronic databases.

For the PubMed database, the following search query was applied:

- *("Gastrointestinal Microbiome"[Mesh] OR "Dysbiosis"[Mesh] OR "gut microbiota"[Title/Abstract] OR "gut microbiome"[Title/Abstract] OR "intestinal microbiota"[Title/Abstract] OR "gut dysbiosis"[Title/Abstract]) AND ("Depressive Disorder"[Mesh] OR "Depression"[Mesh] OR "clinical depression"[Title/Abstract] OR "depressive disorder"[Title/Abstract] OR "major depressive disorder"[Title/Abstract])*.

For the Scopus database, the search strategy was as follows:

- *(TITLE-ABS-KEY ("Gastrointestinal Microbiome" OR "Dysbiosis" OR "gut microbiota" OR "gut microbiome" OR "intestinal microbiota" OR "gut dysbiosis") AND TITLE ("Depressive Disorder" OR "Depression" OR "clinical depression" OR "depressive disorder" OR "major depressive disorder")) AND NOT (TITLE-ABS-KEY (child OR pediatric* OR adolescent* OR youth OR mice OR rat OR murine OR "animal model" OR elderly* OR geriatric* OR aged OR "older adults" OR senior*) OR TITLE*

(review OR "case report" OR "case study" OR "systematic review" OR metaanalysis)).*

As a result of applying the above strategies, a total of 915 records were identified, 274 of which came from PubMed and 641 from Scopus. The results were exported to the Rayyan platform, dedicated to literature review management. Using this platform, 44 duplicates were identified and removed after manual verification by the research team. This process allowed for the identification of 871 unique articles, which were qualified for the next selection stage.

The literature selection process was carried out in multiple stages, strictly following PRISMA guidelines. Initially, a three-person team of independent reviewers assessed the titles and abstracts of 871 articles, examining their compliance with the main objective of the study. Works failing to meet the basic assumptions of the PICOS protocol were excluded. The next step involved an independent, full-text assessment of the remaining publications by all three authors, based on detailed inclusion and exclusion criteria. Potential disagreements and conflicting assessments were subjected to joint analysis and discussed until a final consensus was reached.

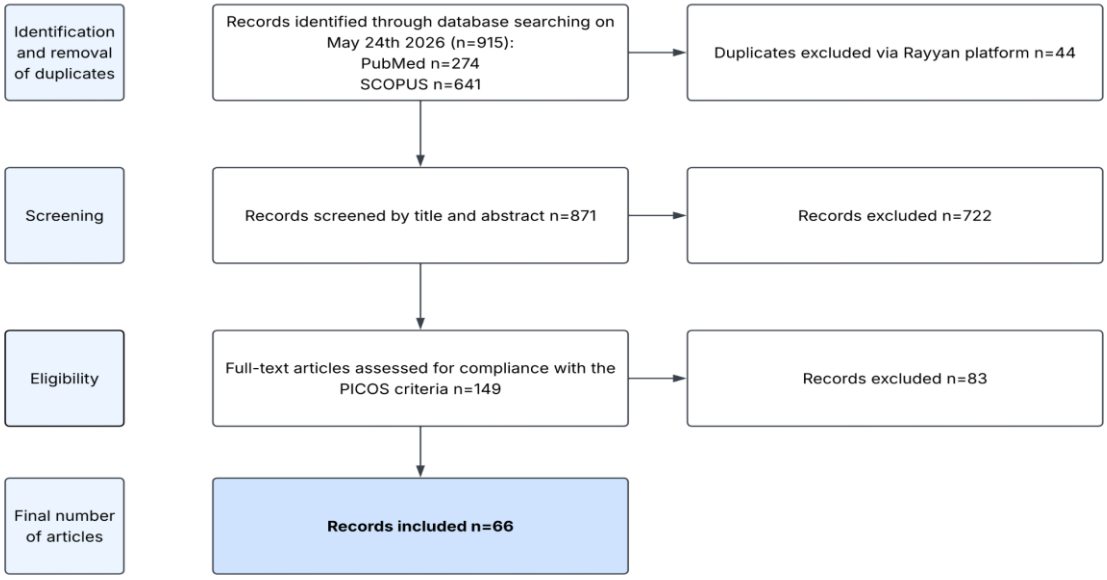
Measurement of depressive symptom severity using validated psychometric tools (e.g., Beck Depression Inventory [BDI] or Hamilton Depression Rating Scale [HAM-D]) and assessment of their direct correlation with gut microbiome parameters.

2.3. Data collection and analysis / Statistical analysis.

The following data were extracted from the qualified publications: DOI number, first author's name, year of publication, study region, study type, number of participants in the study and control groups, mean age and gender of the study group, depression diagnosis method, microbiota analysis method, bacterial taxa with observed quantitative changes relative to the control group, alpha diversity indices, beta diversity indices, microbial metabolite profiles, and systemic inflammatory marker designations.

2.3.1. Statistical Software.

The results were exported to the Rayyan platform, dedicated to literature review management. Using this platform, 44 duplicates were identified and removed after manual verification by the research team. To ensure maximum objectivity and minimize systematic error, this stage [title and abstract screening] was conducted independently on the Rayyan platform.



Source: Authors' own compilation based on the studies included in the literature review (References [9-74])

Figure 2. PRISMA flow diagram of the literature search and study selection process

3.Research results

3.1.Major bacterial genera associated with clinical depression and their potential role in the gut–brain axis

Table 1. Summary of the major bacterial genera reported to be associated with major depressive disorder (MDD), including the direction of abundance changes, proposed biological mechanisms, involvement in gut–brain axis signaling, and potential clinical relevance based on the current literature. Downward arrows (↓) indicate decreased abundance, upward arrows (↑) indicate increased abundance, and ↑/↓ indicates inconsistent findings across studies. **Abbreviations:** SCFA -short-chain fatty acid; LPS -lipopolysaccharide.

Bacterial genus	Direction of change	Main mechanism	Gut–brain axis pathway	Clinical relevance
Faecalibacterium	↓	Reduced butyrate production; impaired intestinal barrier integrity	SCFA production → gut barrier maintenance → reduced neuroinflammation	Potential psychobiotic target; candidate biomarker of depression
Roseburia	↓	Reduced SCFA synthesis and anti-inflammatory activity	SCFA signaling → immune regulation → brain function	Potential therapeutic target
Coprococcus	↓	Decreased butyrate production	SCFA-mediated modulation of inflammation and neurotransmission	Candidate biomarker
Lachnospiraceae	↓	Reduced production of beneficial microbial metabolites	SCFA pathway → gut–brain communication	Potential therapeutic target
Dialister	↓	Impaired microbial homeostasis	Microbial metabolism and immune regulation	Requires further validation
Akkermansia	↓	Reduced mucus layer maintenance and barrier protection	Mucosal integrity → reduced endotoxin translocation	Potential biomarker of gut barrier dysfunction

Alistipes	↑	Altered tryptophan metabolism and kynurenine pathway activation	Tryptophan metabolism → serotonin and kynurenine signaling	Candidate biomarker of depressive symptoms
Eggerthella	↑	Pro-inflammatory metabolism and bile acid transformation	Immune activation → neuroinflammation	Biomarker of inflammatory dysbiosis
Streptococcus	↑	Promotion of inflammatory responses	Cytokine production → neuroimmune activation	Potential marker of disease severity
Parabacteroides	↑	Altered bile acid metabolism	Bile acid signaling → gut–brain communication	Requires further investigation
Proteobacteria	↑	Increased endotoxin production and dysbiosis	LPS translocation → systemic inflammation	Marker of severe gut dysbiosis
Bacteroides	↑/↓	Context-dependent effects on carbohydrat	Immune and metabolic regulation	Inconsistent findings

		e and bile acid metabolism		
Blautia	↑/↓	SCFA production; findings remain inconsistent	SCFA signaling and immune modulation	Conflicting evidence
Ruminococcus	↑/↓	Fiber degradation and SCFA production	Gut barrier and metabolic regulation	Conflicting evidence
Bifidobacterium	↑/↓	Immune regulation and cross-feeding interactions	Neurotransmitter and immune modulation	Conflicting evidence

Source: Authors' own compilation based on the studies included in the literature review (References [10, 13, 14, 16-48])

3.1.1 Results

Analysis of the included studies revealed a relatively consistent pattern of gut microbial dysbiosis in patients with major depressive disorder (MDD). Despite considerable methodological heterogeneity among studies, several bacterial taxa demonstrated reproducible alterations, suggesting that gut microbial imbalance represents a characteristic feature of depressive disorders.

The most consistent finding across the analyzed literature was a reduction in beneficial short-chain fatty acid (SCFA)-producing bacteria, particularly members of the genera *Faecalibacterium*, *Roseburia*, *Coprococcus*, and the family *Lachnospiraceae*. Among these, *Faecalibacterium* was the most consistently depleted genus, being reported as significantly

reduced in approximately 24 of the included studies [13, 16–38]. Similar findings have been consistently reported across numerous clinical studies conducted in diverse populations, including both Asian and European cohorts, further supporting the association between reduced *Faecalibacterium* abundance and depressive disorders [13, 16–38]. Since *Faecalibacterium* is one of the major butyrate-producing bacteria within the human gut microbiome, its depletion has been proposed as one of the most robust microbial signatures associated with depression.

A comparable reduction was observed for other SCFA-producing genera, including *Roseburia* and *Coprococcus*, as well as members of the *Lachnospiraceae* family. Although these taxa were reported less consistently than *Faecalibacterium*, the overall trend strongly suggests impaired SCFA production as a hallmark of gut dysbiosis in depression. Reduced abundance of these bacteria may compromise intestinal epithelial integrity, promote immune dysregulation, and alter bidirectional communication along the gut–brain axis.

Conversely, several bacterial genera were repeatedly reported to be enriched in patients with depression. Increased abundances of *Eggerthella*, *Alistipes*, *Streptococcus*, *Parabacteroides*, and members of the phylum *Proteobacteria* were observed across multiple independent cohorts [10, 14, 17, 19–21, 23, 24, 29–32, 34–37, 39–48]. Among these taxa, *Eggerthella* and *Alistipes* demonstrated the most reproducible increases. These findings have been consistently confirmed across independent clinical studies conducted in diverse populations, suggesting that these taxa may represent reproducible microbial signatures associated with depressive symptomatology [10, 14, 17, 19–21, 23, 24, 29–32, 34–37, 39–48]. Unlike SCFA-producing bacteria, these taxa are frequently linked to pro-inflammatory activity, altered bile acid metabolism, and disturbances in microbial-host metabolic interactions.

Several bacterial genera exhibited inconsistent alterations across the included studies. *Bacteroides*, *Blautia*, *Ruminococcus*, and *Bifidobacterium* were reported as either increased or decreased depending on the investigated cohort. Such discrepancies most likely reflect differences in dietary habits, ethnicity, geographical location, antidepressant treatment, disease severity, body mass index, sequencing methodology, and bioinformatic analysis rather than genuine biological contradictions.

Overall, the microbial profile observed across the included studies was characterized by depletion of beneficial SCFA-producing bacteria accompanied by enrichment of potentially pro-inflammatory taxa. These findings support the concept that gut microbial dysbiosis is a

common feature of major depressive disorder and may contribute to disease pathophysiology through alterations in microbial metabolism, immune regulation, and gut–brain communication.

3.1.2.Interpretation of inconsistent findings

Although several bacterial genera demonstrated relatively consistent alterations across the included studies, others including *Bacteroides*, *Blautia*, *Bifidobacterium*, and *Ruminococcus* exhibited contradictory findings, being reported as either increased or decreased in patients with depression. Rather than representing true biological inconsistencies, these discrepancies most likely reflect the substantial heterogeneity of the available literature.

Several factors may contribute to these divergent observations. First, demographic and clinical characteristics varied considerably among study populations. Age, sex, body mass index, ethnicity, dietary habits, physical activity, smoking status, and the presence of comorbid conditions such as obesity, diabetes, or irritable bowel syndrome are all known to influence gut microbial composition independently of depression. Furthermore, patients differed with respect to disease severity, duration of illness, first episode versus recurrent depression, and treatment response, all of which may affect microbiome profiles.

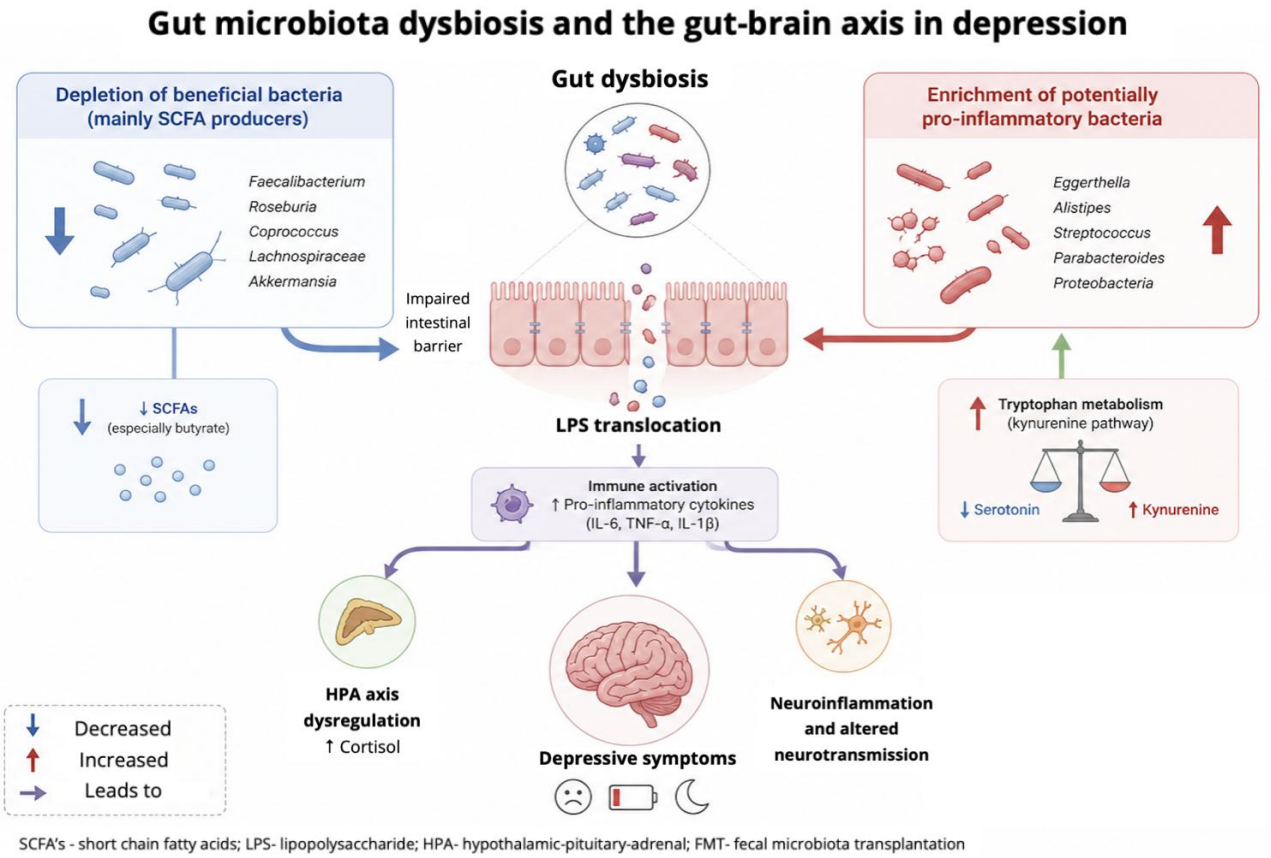
Second, geographical location represents an important determinant of gut microbial composition. Studies included in this review originated from Asia, Europe, North America, and South America, where substantial differences in dietary patterns, environmental exposures, and host genetics may contribute to distinct baseline microbiota. Consequently, identical bacterial genera may exhibit different abundance patterns across populations without necessarily reflecting contradictory biological mechanisms.

Another important source of variability is antidepressant treatment. Several studies included medicated patients, whereas others investigated drug naive individuals or patients after antidepressant washout. Since antidepressants may directly alter bacterial growth through antimicrobial activity and indirectly modify microbial composition by improving mood, appetite, sleep quality, gastrointestinal motility, and stress responses, medication status should be considered a major confounding factor in microbiome research.

Methodological heterogeneity also contributes substantially to inconsistent findings. Differences in fecal sample collection, storage conditions, DNA extraction protocols,

sequencing technologies (16S rRNA gene sequencing versus shotgun metagenomic sequencing), taxonomic databases, and bioinformatic pipelines may all influence bacterial identification and relative abundance estimates. Moreover, while some studies reported alterations at the genus level, others focused on individual species. Because species belonging to the same genus often possess distinct metabolic capabilities and immunological properties, collapsing all species into a single taxonomic category may obscure biologically meaningful differences.

Finally, the gut microbiome itself is a highly dynamic ecosystem influenced by numerous environmental and host related factors. Therefore, a single bacterial genus should not be interpreted in isolation but rather as part of a complex microbial network. Future studies should increasingly focus on microbial functions, metabolic pathways, and microbial interactions instead of taxonomic composition alone, as functional alterations may represent more robust biomarkers of depression than changes in individual bacterial taxa.



Source: Authors' own compilation based on the studies included in the literature review (References [10, 13, 14, 16-48])

Figure 3. Gut microbiota dysbiosis and the gut–brain axis in major depressive disorder. Schematic overview of the proposed mechanisms linking gut microbial dysbiosis with depression. Depletion of beneficial SCFA-producing bacteria and enrichment of bacterial genera associated with inflammation contribute to impaired intestinal barrier integrity, immune activation, altered tryptophan metabolism, neuroinflammation, and dysregulation of the HPA axis, ultimately leading to depressive symptoms. The figure also highlights the central role of the gut–brain axis in mediating these interactions. **Abbreviations:** SCFA, short-chain fatty acid; LPS, lipopolysaccharide; HPA, hypothalamic–pituitary–adrenal

3.2. Alpha and beta diversity of the microbiome in Major Depressive Disorder

Researchers have always considered two indices, alpha and beta diversity, to study the impact of the psyche on the bowel. α-diversity gives authors the data about the wealth of a single human microbiome. In patients with depression, the inner ecosystem is more indigent. In contrast, β- diversity provides an opportunity to compare different populations. It turns out that bacterial profiles of bowel microbiota in depression are different than in healthy individuals, and the microbiome composition undergoes a characteristic shift, which makes a difference in the whole body, for example neurotransmitters and level of inflammation in the organism.

To determine the global trends in the gut microbiome structure of patients with depressive disorders, 66 scientific publications were analyzed. Both alpha and beta diversity indices were reported in 55 of these studies, whereas 11 publications did not conduct assessments of β- diversity [15, 40, 49–57]. In fact the β- diversity plays a crucial role in microbiome function. The systematic categorization revealed a strong predominance of variants exhibiting statistically significant changes in the compositional structure of the microbiome (i.e., significant β-diversity).To assess these inter-sample distances, the analyzed studies predominantly relied on Bray-Curtis dissimilarity matrices, visually projected via Principal Coordinate Analysis (PCoA) and validated statistically using PERMANOVA testing ($p<0.05$).

The most prevalent configuration, identified as the benchmark model pattern for depression, was characterized by unchanged α-diversity and significant β-diversity, which was observed in 31 studies [9–11, 13, 14, 16–18, 23, 24, 26–29, 31, 33, 38, 39, 42, 45, 46, 59–67].

In these datasets, intra-sample richness and evenness were most commonly evaluated using the Shannon, Chao1, and Simpson indices, which were analyzed using Wilcoxon rank-sum tests or ANOVA ($p>0.05$). The second most frequent group demonstrated a simultaneous decrease in α-diversity and significant β-diversity in 15 studies (depleted phenotype). Together, these two models account for over 83% of all analyzed datasets, strongly confirming the presence of profound composition-driven dysbiosis in patients with Major Depressive Disorder (MDD). The 15 studies that reported a significant drop in α-diversity (the second variant) may reflect specific confounding factors within those patient cohorts, such as the severity and chronicity of depression episodes [19, 22, 30, 32, 34–37, 47, 68–73].

This prevailing pattern (unchanged α-diversity combined with significant β-diversity) highlights a crucial biological phenomenon: depression does not act as a destructive agent that drastically eradicates the overall number of bacterial species in the gut. Instead, it triggers a "compositional reshuffling." The total headcount of the microbial community remains stable, but the internal hierarchy is fundamentally altered, and beneficial and anti-inflammatory symbionts are displaced by potentially harmful opportunistic taxa.

Functionally, this profound structural shift (β-diversity) is highly clinically relevant. The literature consistently connects this specific dysbiosis to a reduction in short-chain fatty acid (SCFA) producing bacteria, such as *Faecalibacterium* and *Roseburia*, which are essential for maintaining intestinal barrier integrity. The depletion of these strains leads to increased gut permeability ("leaky gut"), allowing bacterial endotoxins (LPS) to enter the bloodstream and trigger low-grade systemic inflammation. Concurrently, this altered microbial profile disrupts the tryptophan-kynurenine pathway, directly compromising peripheral and central serotonin synthesis.

The remaining configurations represented a distinct minority. A complete absence of statistically significant differences in both intra- and inter-sample biodiversity (representing an unaltered microbiome) was reported in six studies [12, 20, 25, 41, 48, 58]. Conversely, an anomalous pattern characterized by an increase in α-diversity indices and significant β-diversity was observed in only three cases [21, 43 ,44].

Table 2. Provides an overview of the diversity pattern in MDD patients.

Diversity Pattern	α-Diversity	β-Diversity	Count (n)	References
Benchmark Model	Unchanged	Significant	31	[9–11, 13, 14, 16–18, 23, 24, 26–29, 31, 33, 38, 39, 42, 45, 46, 59–67]
Depleted Phenotype	Decreased	Significant	15	[19, 22, 30, 32, 34–37, 47, 68–73]
Anomalous Pattern	Increased	Significant	3	[21, 43, 44]
Unaltered Microbiome	—	Non-significant	6	[12, 20, 25, 41, 48, 58]
Unreported / Not Assessed	Not assessed	Unreported	11	[15, 40, 49–57]

Source: Authors' own compilation based on the studies included in the literature review (References [9-74])

3.3. Intestinal Inflammation markers

IL-6, TNF-α, and IL-1β constitute the core triad of alarm cytokines in the human immune system. In the context of the gut-brain axis, structural reshuffling of the gut microbiome and subsequent loss of mucosal barrier integrity [36] allow immunogenic bacterial components, such as lipopolysaccharides (LPS) [17, 28], to activate immune cells such as lymphocytes and monocytes within the gut wall [9, 17]. This localized irritation triggers the coordinated release of these cytokines into the peripheral circulation.

3.3.1. Interleukines, tumor necrosis factor- α, high- sensitivity C-reactive protein and imbalance of tryptophan metabolism

Elevated serum levels of IL-1β, IL-6 and TNF-α, have been consistently documented in depressed cohorts [19, 35, 49, 59]. Synthesized predominantly by the liver in response to elevated circulating cytokines (specifically Interleukine-1β and Interleukine-6), high-sensitivity C-reactive protein (hsCRP) serves as a stable and definitive marker of this ongoing low-grade chronic systemic inflammation. The presented clinical data reveal a robust correlation between elevated hsCRP levels and the severity of depressive phenotypes [34, 57, 68].

Once in the bloodstream, this cytokine network acts synergistically and is capable of crossing the blood-brain barrier, altering neuroplasticity, reducing neurogenesis, and directly disrupting neurotransmitter metabolism, particularly by activating the indoleamine 2,3-dioxygenase (IDO) enzyme. Overactivation of IDO shunts tryptophan away from its beneficial physiological pathway (peripheral and central serotonin synthesis), redirecting it toward the accelerated production of kynurenine. This metabolic shift has devastating consequences for the central nervous system. It not only causes profound depletion of serotonin (the "serotonin steal" phenomenon) but also leads to the accumulation of neuroactive kynurenine metabolites. Kynurenine readily crosses the blood-brain barrier, where it is further metabolized into neurotoxic compounds such as quinolinic acid (QUIN). QUIN acts as a potent N-methyl-D-aspartate (NMDA) receptor agonist, triggering glutamate excitotoxicity, promoting oxidative stress, and damaging hippocampal neurons—cellular changes heavily implicated in the structural and functional pathology of Major Depressive Disorder (MDD) [68].

3.3.2. Neuro-Immune-Muco-Epithelial-Tryptophan-Oxidative Stress (NIMETOX)

Currently, growing evidence highlights that MDD is intricately linked to dysregulated metabolic, autoimmune, and oxidative stress pathways, collectively conceptualized within the Neuro-Immune-Muco-Epithelial-Tryptophan-Oxidative Stress (NIMETOX) framework. Within this system, neuroinflammation drives a critical imbalance between macrophage activation and T-helper lymphocyte response. Concurrently, altered vascular endothelial growth factor (VEGF) signaling intensifies the blood-brain barrier and vascular permeability, thereby facilitating the influx of peripheral neurotoxic mediators directly into the central nervous system [25].

3.3.3. Leukotrien B4

This multi-layered molecular assault on hippocampal integrity is further reinforced by the action of lipid-derived inflammatory mediators for instance elevated mucosal and systemic levels of 20-carboxy-leukotriene B4 (20-carboxy-LTB4)—produced via oxidation within the inflamed gut wall—act as potent promoters of chronic oxidative stress and microvascular inflammation. Crucially, this lipid-driven inflammatory environment directly compromises central neuroplasticity and downstream mood regulation by disrupting the glutamatergic metabolism. By altering the astrocytic glutamate-glutamine cycle, 20-carboxy-LTB4 contributes to the abnormal accumulation of extracellular glutamate, significantly reinforcing NMDA-mediated excitotoxicity initiated by the kynurenine pathway [10].

3.3.4. 2-HB and 3-HB

Furthermore, the systemic intersection of gut-derived inflammation and psychiatric pathology manifests as profound cellular energy crises that can be readily captured via metabolomic profiling. Clinical cohorts with MDD consistently demonstrate markedly elevated levels of specific organic acids, notably 3-hydroxybutyric acid (3-HB) and 2-hydroxybutyric acid (2-HB) [13]. In this biochemical context, 2-HB serves as an early, highly sensitive biomarker of mitochondrial dysfunction and glutathione depletion, reflecting a state in which cells are forced to counteract severe, ongoing oxidative stress. Concurrently, the accumulation of 3-HB, a primary ketone body, signals a fundamental disruption in systemic energy metabolism and glucose utilization. The resulting cellular starvation and oxidative burden heavily impair high-energy processes in the central nervous system, including synaptic transmission and hippocampal neuroplasticity, thereby reinforcing the core vegetative and emotional symptoms of depression.

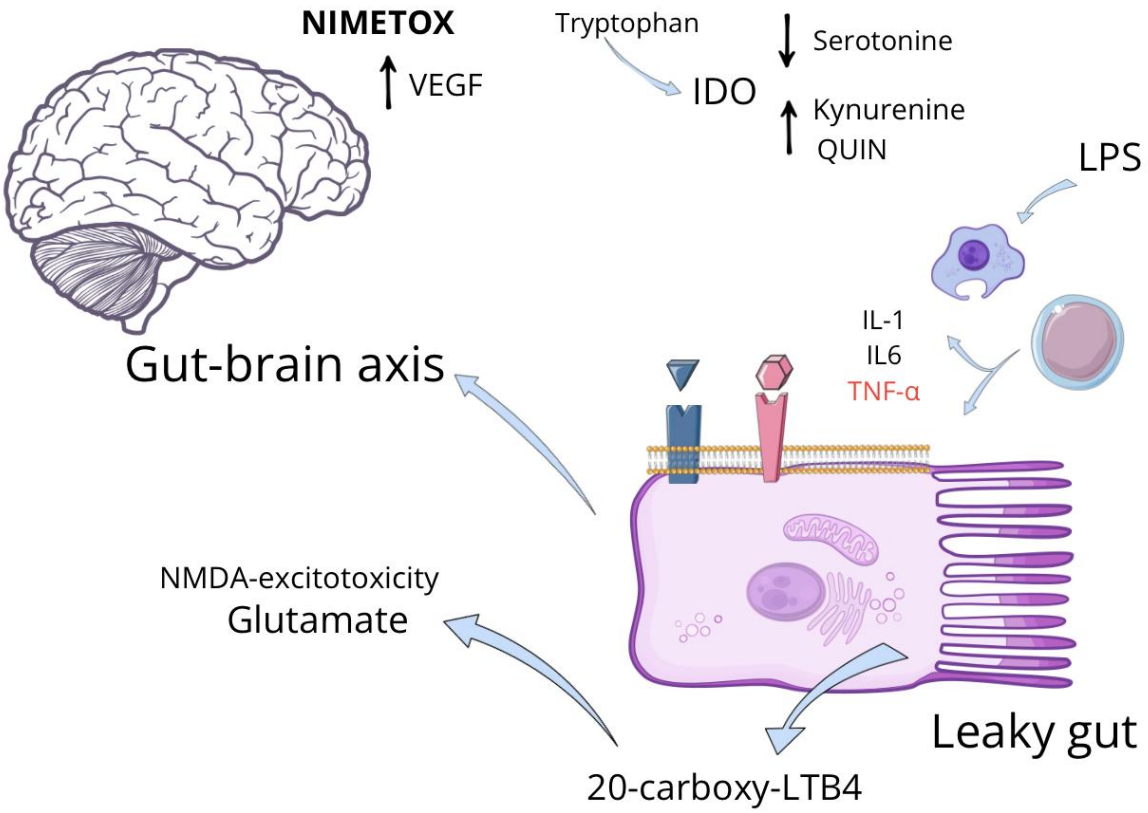


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Figure 4. The metabolic and biochemical role of the intestinal epithelium in modulating the gut-brain axis. It schematically describes the relationships between basal metabolism, its imbalance, and its impact on neurotransmitters. Lipopolysaccharide (LPS) stimulates inflammatory cells such as macrophages. Together with lymphocytes, they play a key role in initiating the inflammatory process in the intestines through the production of key interleukins—Interleukine-1 (IL-1) , Interleukine-6 (IL-6) , tumour necrosis factor -alpha (TNF-α) and C-reactive protein (CRP). This leads to the leakage of inflammatory components through the intestinal barrier. These substances enter the systemic circulation and cross the blood-brain barrier. This leads to negative regulation of the 2,3-dioxygenase (IDO) enzyme, causing tryptophan—which would normally be used in serotonin synthesis—to instead enter the kynurenine synthesis pathway and, consequently, the metabolism of quinolinic acid (QUIN), which acts as an N-methyl-D-aspartate (NMDA) agonist. 20-carboxy-leukotriene B4 (20-carboxy-LTB4), formed as a result of leukotriene B4 metabolism, exhibits a similar effect; it stimulates the astrocytic glutamate-glutamine cycle and supports the action of glutamatergic

N-methyl-D-aspartate (NMDA) receptors. Inflammatory cells trigger the Neuro-Immune-Muco-Epithelial-Tryptophan-Oxidative Stress (NIMETOX) cascade in various ways across the blood-brain barrier, contributing to vascular endothelial growth factor (VEGF) production. This, in turn, increases vascular permeability and microinflammation in the central nervous system (CNS).

3.4.Psychiatric comorbidities in Inflammatory Bowel Syndrome and Inflammatory Bowel Diseases

Patients with depression are at risk of developing many other somatic conditions. With regard to changes in the microbiome, we identified a group of diseases like inflammatory bowel syndrome (IBS) and inflammatory bowel diseases (IBD). Researchers in various studies have demonstrated that the presence of severe depressive symptoms correlates with the severity of inflammatory diseases. It is not entirely clear whether the initial symptoms are related to the somatic disease or constitute a separate cause of depression and well-being.

3.4.1. Inflammatory Bowel Syndrome

Gut dysbiosis is a primary factor contributing to the severity of symptoms. This is associated not only with the presence of pathobionts such as *Klebsiella*, *Ruminococcus*, *Barnesiella* and *Escherichia Coli* but also with a decline in the abundance of anti-inflammatory bacteria. In patients with depression, there is a drastic decrease in butyrate-producing bacteria (*Eubacterium rectale*), gut health-promoting bacteria (*Akkermansia muciniphila*), and gut-brain axis modulators (*Eubacterium eligens*). Bacteriophages are often credited with causing these changes in the gut microbiota. An increase has been observed in the population of Enterobacteria-specific phages and Escherichia phages, including Enterobacteria phage cdtI and Enterobacteria phage HK225. These changes disrupt the natural regulatory pathways of mutually antagonistic processes, leading to the dominance of negative processes. A key role in this process is played by a decrease in primary bile acids such as glycolic acid. These changes also directly affect the gut-brain axis, contributing to disturbances in tryptophan and lysine metabolism and, consequently, a decrease in serotonin, the primary neurotransmitter responsible for the onset of the first symptoms of MDD.

In patients with depression (dIBS and adIBS), a significant decrease in ubiG gene expression was observed. The ubiG gene is responsible for the biosynthesis of ubiquinone and processes dependent on S-adenosyl-L-methionine (SAM-e). SAM-e is a key compound whose

deficiencies are directly linked to the occurrence of major depressive disorders in the psychiatric literature [3].

3.4.2. Inflammatory Bowel Diseases

Contemporary research based on multi-omics analyses has unequivocally confirmed that anxiety and depression are integral clinical manifestations of inflammatory bowel disease (IBD), and their severity depends on the level of inflammation. In the general population of patients with IBD, anxiety and depression affect 28.81% and 33.90% of patients, respectively. These rates rise sharply during the active phase of ulcerative colitis (UC), where depression affects as many as 58% of patients and anxiety affects 50% of patients. The main common factor linking neurodysbiosis in IBD/UC is a drastic decline in the taxonomic richness and alpha diversity (α-diversity) of the gut microbiome. In states of anxiety and depression, there is a sharp increase in the abundance of the genus *Sellimonas*, the order *Lactobacillales*, the class *Bacilli*, and the genera *Streptococcus*, *Enterococcus* (including *E. faecalis*), *Ruminococcus*, *Fusobacterium*, and *Prevotella* 7. These bacteria stimulate the production of polysaccharides that activate the proinflammatory NF-κB pathway. Simultaneously, protective strains responsible for epithelial homeostasis and butyrate synthesis, including *Anaerostipes*, *Lachnospira*, and *Prevotella 9*, diminish. Anxiety- and depression-related dysbiosis causes a more than threefold decrease in the expression of key serum proteins (immunoglobulins, PROS1, FETUB, and JCHAIN), which drastically weakens the intestinal barrier dysfunction. This allows for the translocation of bacterial lipopolysaccharide (LPS) into the bloodstream, which directly induces a cytokine storm (IL-1β, IL-6, and TNF-α) in the serum and brain structures. Both analyses indicated a critical deficiency of neuroprotective metabolites in the serum of patients with anxiety and depression, including alpha-ketoglutaric acid, 2′-deoxy-D-ribose, and L-pipocolic acid. Prophylactic exogenous supplementation with 2′-deoxy-D-ribose and L-pipocolic acid in in vivo models (DSS) effectively reverses depressive behaviors and inhibits the expression of inflammatory cytokines in the colon and brain, indicating new, precise therapeutic targets for the treatment of psychiatric comorbidities in IBD [12,15].

4. Discussion

This review demonstrates that microbiota alterations in major depressive disorder (MDD) follow a distinct functional pattern. Despite methodological heterogeneity among the included studies, there is a consistent depletion of beneficial short-chain fatty acid (SCFA)-producing bacteria alongside an enrichment of proinflammatory microorganisms. This specific dysbiotic shift actively contributes to the pathophysiology of depression via interconnected mechanisms along the gut–brain axis.

Among all bacterial taxa, the reduction of *Faecalibacterium* emerged as the most reproducible observation. *Faecalibacterium* is one of the major producers of butyrate, a key SCFA responsible for suppressing inflammatory responses. Its decline impairs intestinal barrier integrity, leading to increased permeability and the systemic translocation of bacterial endotoxins (such as LPS). This activates TLR4 signaling and activates a pro-inflammatory cytokine cascade (IL-6, TNF-α, IL-1β), resulting in chronic low-grade inflammation [10, 13, 14, 16-48]. Similarly, the reduced abundance of *Roseburia*, *Coprococcus*, and members of the *Lachnospiraceae* family further supports the hypothesis that impaired SCFA production is a central feature of depressive dysbiosis. Consequently, reduction of these beneficial bacteria may impair bidirectional communication between the gut and the central nervous system, facilitating neuroinflammation and alterations in neuronal function [10, 13, 14, 16-48].

In contrast, several bacterial genera were consistently enriched in patients with depression. Increased abundance of *Eggerthella*, *Alistipes*, *Streptococcus*, and *Parabacteroides* suggests a shift toward a more proinflammatory microbial ecosystem. *Eggerthella* has repeatedly been associated with inflammatory activity and altered bile acid metabolism, both of which may influence host immune responses and microbial host interactions. Several studies have also demonstrated positive correlations between *Eggerthella* abundance and the severity of depressive symptoms, suggesting that this genus may represent a promising microbial biomarker of depression.

Another reproducible finding was the increased abundance of *Alistipes*, a genus involved in tryptophan metabolism. Besides being the primary precursor for serotonin synthesis, tryptophan can also be metabolized through the kynurenine pathway during inflammatory states. Increased activity of this pathway reduces serotonin availability while simultaneously generating neuroactive kynurenine metabolites, several of which possess

neurotoxic properties. Consequently, this *Alistipes* overgrowth may contribute to disturbances in neurotransmission, neuroplasticity, and emotional regulation through the gut–brain axis.

Molecular bridge between intestinal dysbiosis and central nervous system pathology is contained within the NIMETOX framework. The cascade initiated by LPS translocation and the release of alarm cytokines (IL-1β, IL-6, TNF-α) drives a state of low-grade systemic inflammation. It is reliably captured by elevated hsCRP levels that correlate with depressive severity. However, our analysis reveals that the farther neuroinflammatory environment induces metabolic and cellular energy crises that extend far beyond simple serotonin reduction. First, neuroinflammation upregulates vascular endothelial growth factor (VEGF) signaling, which compromises blood-brain barrier integrity and enables the direct influx of peripheral neurotoxic mediators into the brain parenchyma. Second, the systemic accumulation of organic acids, specifically 2-HB and 3-HB, highlights mitochondrial dysfunction and altered systemic energy metabolism within MDD cohorts. In this context, 2-HB serves as a sensitive marker of glutathione decrease and severe oxidative stress, while 3-HB accumulation signals a fundamental disturbance in glucose utilization, leading to cellular starvation in high-energy CNS structures responsible for mood regulation. This process is further reinforced by lipid-derived inflammatory mediators, notably 20-carboxy-LTB4, produced within the inflamed gut wall. By disrupting the astrocytic glutamate-glutamine cycle, 20-carboxy-LTB4 promotes the abnormal accumulation of extracellular glutamate. This synergistically reinforces the NMDA-mediated excitotoxicity initiated by quinolinic acid (QUIN) in the kynurenine pathway, ultimately driving hippocampal neuron damage and consolidating the core vegetative and emotional symptoms of depression.

Although numerous bacterial alterations were consistently reported, an important question remains whether gut dysbiosis represents a cause or a consequence of major depressive disorder. Current evidence suggests that this relationship is likely bidirectional rather than unidirectional. Chronic psychological stress, altered dietary habits, reduced physical activity, sleep disturbances, and changes in gastrointestinal motility associated with depression may all contribute to alterations in gut microbial composition. Conversely, gut dysbiosis itself may promote depressive symptoms through increased intestinal permeability, chronic systemic inflammation, microbial metabolite imbalance, dysregulation of neurotransmitter synthesis, and activation of the hypothalamic–pituitary–adrenal (HPA) axis.

Evidence supporting a causal role of the gut microbiota has been strengthened by fecal microbiota transplantation (FMT) studies. Experimental transplantation of fecal microbiota obtained from patients with major depressive disorder into germ free or microbiota depleted rodents induced depression-like behaviors, increased neuroinflammation, impaired hippocampal neurogenesis, and disturbances in tryptophan metabolism. These findings suggest that alterations in gut microbial composition may actively contribute to depressive phenotypes rather than merely reflecting disease associated lifestyle changes.

Another important factor that may contribute to inconsistent findings across studies is antidepressant treatment. Increasing evidence indicates that antidepressants not only modulate neurotransmitter signaling within the central nervous system but also directly influence gut microbial composition. Experimental studies have demonstrated antimicrobial properties of several selective serotonin reuptake inhibitors (SSRIs), including fluoxetine, sertraline, escitalopram, and paroxetine. These drugs may inhibit the growth of specific bacterial taxa while simultaneously promoting expansion of others. In addition, successful antidepressant therapy frequently improves appetite, dietary habits, sleep quality, gastrointestinal motility, and stress-related activation of the HPA axis, all of which may indirectly reshape the gut microbiome. Consequently, differences in medication status including drug-naïve patients, treated individuals, treatment duration, and antidepressant class represent important confounding factors that should be carefully considered when interpreting microbiome studies.

Notably, several bacterial genera, including *Bacteroides*, *Blautia*, *Bifidobacterium*, and *Ruminococcus*, demonstrated inconsistent alterations across studies. Rather than representing genuine biological contradictions, these discrepancies most likely reflect substantial heterogeneity among the investigated populations. Factors such as geographical location, dietary habits, body mass index, age, disease severity, comorbidities, sequencing methodology, bioinformatic processing, and taxonomic resolution may substantially influence microbial composition. Moreover, several studies analyzed bacteria at the species level whereas others reported only genus level alterations. Because different species within the same genus may exert distinct metabolic and immunological functions, pooling them together may partly explain the conflicting observations reported in the literature.

Structural analysis of the gut microbiome across the 66 included studies provides critical conceptual clarity regarding biodiversity metrics. Notably, 31 studies exhibited a predominant "benchmark model," characterized by unaltered alpha diversity coupled with a significant shift

in beta diversity. This finding challenges the conventional, oversimplified idea that all pathological states are driven by a generalized eradication of bacterial species richness. Instead, this pattern highlights "compositional reshuffling". While the absolute quantitative wealth of the microbial ecosystem remains stable, the internal taxonomic hierarchy undergoes systematic disruption, resulting in the displacement of beneficial, anti-inflammatory symbionts by opportunistic pathobionts.

Conversely, the "depleted phenotype" which is defined by a simultaneous decline in absolute species richness (alpha diversity) was observed in 15 studies. This specific configuration appears closely linked to clinical confounding factors, including the severity, chronicity, and duration of depressive episodes. This divergence suggests a critical pathophysiological trajectory: while early or moderate depression induces structural rearrangements within the microbiota, prolonged and severe psychophysical stress progressively degrades the fundamental richness of the ecosystem, thereby potentially serving as an objective biomarker of disease progression.

The findings summarized in this review also have potential therapeutic implications. Restoration of beneficial SCFA-producing bacteria through dietary modification, increased dietary fiber intake, prebiotics, probiotics, psychobiotics, synbiotics, or fecal microbiota transplantation has emerged as a promising strategy for modulating gut–brain communication. Preliminary clinical trials have demonstrated modest improvements in depressive symptoms following microbiota-targeted interventions; however, current evidence remains insufficient to recommend these approaches as routine treatment for major depressive disorder. Large, well designed randomized controlled trials are required to identify the most effective therapeutic strategies and determine which patient populations are most likely to benefit from microbiota modulation.

Taken together, current evidence suggests that gut microbial dysbiosis in depression is characterized primarily by depletion of beneficial butyrate producing bacteria and enrichment of proinflammatory microorganisms. These alterations may contribute to depression through impaired intestinal barrier function, chronic systemic inflammation, altered tryptophan metabolism, immune activation, and disrupted bidirectional communication along the gut–brain axis. However, whether gut dysbiosis represents a primary pathogenic mechanism or develops as a secondary consequence of depression remains unresolved. Future longitudinal studies integrating metagenomics, metabolomics, transcriptomics, immune profiling, and controlled

microbiota-targeted interventions will be essential for establishing causality and identifying reliable microbiome-based biomarkers and therapeutic targets for major depressive disorder.

5. Conclusions

This review highlights a distinct microbial signature in major depressive disorder (MDD), defined by the depletion of beneficial SCFA-producing bacteria (e.g., *Faecalibacterium*, *Roseburia*, *Coprococcus*) and the enrichment of proinflammatory taxa (e.g., *Eggerthella*, *Alistipes*, *Proteobacteria*). Crucially, these alterations do not act in isolation; rather, they compromise intestinal barrier integrity, trigger systemic inflammation, and alter tryptophan metabolism. As proposed in our integrated NIMETOX framework, these cascading events ultimately converge to drive central neuroinflammation, excitotoxicity, and metabolic crises along the gut–brain axis.

While current evidence strongly links dysbiosis to depression, causality remains complex and bidirectional. Although human longitudinal data are limited, fecal microbiota transplantation (FMT) models provide compelling evidence that microbial alterations actively propagate depressive phenotypes rather than merely reflecting disease-associated lifestyle changes.

Importantly, substantial methodological heterogeneity continues to limit cross-study comparability. A paramount challenge for future research will be disentangling the genuine microbial signature of MDD from the confounding, microbiome-reshaping effects of antidepressant treatments, particularly SSRIs. Standardizing research protocols is therefore essential for identifying reproducible microbial biomarkers.

Beyond understanding pathophysiology, the gut microbiota represents a promising therapeutic target. Interventions such as pre/probiotics and FMT show encouraging preliminary results, though they are not yet ready for standard clinical practice. Future longitudinal research must integrate multi-omics (metagenomics, metabolomics, transcriptomics, immune profiling) to establish definitive causal links, validate reliable biomarkers, and develop personalized, microbiome-targeted therapies for MDD.

Disclosure

Author Contributions

Conceptualization, K.Ś..; methodology, K.Ś, W.Ż and J.T; validation, K.Ś and W.Ż.; formal analysis, K.Ś, W.Ż and J.T; resources, K.Ś, W.Ż and J.T.; data curation, K.Ś, W.Ż and J.T; writing—original draft preparation, K.Ś, W.Ż and J.T .; writing—review and editing, K.Ś, W.Ż and J.T; visualization, K.Ś, W.Ż and J.T.; supervision, K.Ś and W.Ż.; project administration, K.Ś and W.Ż .; funding acquisition, K.Ś, W.Ż. and J.T. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest The authors declare no conflicts of the interest.

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