Review

Gut Feelings: Linking Dysbiosis to Depression – A Literature Review

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Abstract

The balance between physiological, psychological, and environmental factors often shapes human experience. In recent years, research has drawn attention to the gut microbiota as a significant contributor to brain function and emotional regulation. This review examines how changes in gut microbiota may relate to depression. We selected studies that explore the link between intestinal dysbiosis and mood, focusing on mechanisms such as inflammation, vagus nerve signaling, HPA axis activation, gut permeability, and neurotransmitter balance. Most of the available data come from animal models, but findings from human studies suggest similar patterns. Findings are somewhat difficult to compare due to differences in measurement procedures and patient groups. However, several microbial shifts have been observed in people with depressive symptoms and trials with probiotics or fecal microbiota transplant show potential. These results still remain limited. We argue that these interventions deserve more attention, especially in cases of treatment-resistant or inflammation-driven depression. Understanding how the gut and brain interact could help define clearer subtypes of depression and guide new treatment approaches.

Keywords: gut-brain axis; intestinal dysbiosis; depression; microbiota-targeted therapy; neuroinflammation

1. Introduction

Depression is a complex mental disorder affecting individuals across all demographics. Marked by persistent feelings of sadness, it combines psychological suffering with physiological dysregulation [1]. Between the years 2018-2020, 6.54% European adults were suffering from clinically relevant depressive symptoms [2]. More than 75% of individuals in low- and middle-income countries remain untreated and roughly half of patients show poor response to current antidepressants [3,4]. With treatment resistance still a major challenge, identifying underlying vulnerabilities for depression is crucial for the development of more efficient treatments. Experimental and genetic research have identified multiple contributing mechanisms, such as hypothalamic-pituitary-adrenal (HPA) axis disruption, neuroinflammation, alterations in neuroplasticity, dysfunction in pathways linked to the monoaminergic and endocannabinoid systems and genetic predisposition. These understandings, with the help of recent technological advancements, have led to novel therapies: Transcranial Magnetic Stimulation (TMS), Ketamine and Esketamine administration, Psychedelic therapy, as well as AI-based Interventions. Increasing attention is given to gut-brain interactions, with probiotics and fecal microbiota transplantation (FMT) showing promising results as potential interventions. An integrated approach to depression is essential. This holistic perspective contrasts with the traditional concept that views psychiatric conditions as solely disorders of the mind. As emerging studies on the immune system also suggest

a biological basis for mental illness, alterations in the development or composition of the gut microbiota (GM) can also be seen as a potential key element.

The gut-brain axis (GBA) is a bidirectional communication pathway between the Central nervous system (CNS) and the gastrointestinal tract (GT). Advances in neuroscience and microbiology highlighted its impact on brain function, making it a key focus in mental health, alongside systemic disorders. The GBA comprises neural, immune, endocrine, and metabolic pathways [5]. The neural pathway includes the enteric nervous system (ENS) and involves neuroimmune and neuroendocrine mechanisms related in particular to the vagus nerve (VN)[6]. Gut-associated lymphoid tissue (GALT), which comprises more than 70% of the body's total immune system, plays a key role in modulating immune responses and maintaining mucosal homeostasis. There are also multiple microbial and gut-derived neurotransmitters and metabolites (e.g., tryptophan, 5-HT, melatonin, GABA) that impact brain function to a varying degree. Moreover, the GM composition is closely linked to the HPA axis, the stress-response system within the GBA. Additionally, the GT secretes hormones (e.g., peptide YY, neuropeptide Y, cholecystokinin, glucagon-like peptide-1), which, after being modulated by the GM, interact with the ENS and CNS and regulate metabolism and mood [7,8]. The GBA components work interdependently, shaping brain function and overall mental health.

The GM, a key component of the GBA, comprises a vast network of microorganisms colonizing the intestine. Gut dysbiosis refers to an alteration or imbalance in their composition or diversity. Mutualistic symbiosis occurs as the host provides nutrients and habitat, while microbes perform essential roles. Functionally, a dysbiotic microbiota could be characterized as one not fully supplying the host with its complete range of beneficial functions [9]. GM is involved in vital processes such as digestion, fat storage, supporting immune system development and function and, as part of the GBA, in modulating neural activity with impact on brain function [10–12]. The digestive system undergoes a significant shift, transitioning from a sterile state in utero to being densely colonized within the first few weeks after birth [13]. Afterwards, the microbial composition remains relatively stable over short periods and it is host-specific [14]. It contains all three domains of life: bacteria, archaea, and eukarya, with bacteria as its predominant component [15]. Bacteria communicate through quorum sensing, which enables them to assess their population size [16]. They maintain an estimated population number of 3.8×10^{13} within and on the human body, with the bacterial biomass estimated to weigh around 0.2 kg [17]. This is comparable to the number of human cells by more recent findings, although older and widely-referenced studies previously proposed a 10:1 ratio between bacteria and human cells. By 2021, the number of bacterial species identified in humans had risen to 3.253, with an increase of 477 species, compared to the 2018 data [18]. The small intestine and colon harbor distinct bacteria through the lower GT, due to strong physiological variation along these anatomical sites [19]. The dominant intestinal bacterial phyla are *Firmicutes* and *Bacteroidetes*, while *Actinobacteria*, *Proteobacteria*, and *Verrucomicrobia* also represent major groups [20]. Experimental manipulation of the GM was shown to influence stress responses and anxious, as well as depressive behavior. Connections with stress have been illustrated for over 50 years. Rodent experiments conducted by Tannock and Savage in 1974 revealed changes in the intestinal flora of stressed mice, with a decrease in *Lactobacillus* populations [21]. The mentioned study prompted further investigation into this field. Species-specific microbial changes are identified between animals and humans, such as increased *Eggerthella* in human subjects and decreased *Acetatifactor* in rodent models of depression [22]. In a systematic review conducted on humans in 2019, fifty bacterial taxa were found significantly different between patients suffering from MDD and controls. Bacterial genera positively associated with MDD included the potentially harmful *Clostridium*, *Klebsiella*, and *Streptococcus*. *Bifidobacterium* and *Faecalibacterium* were negatively associated with MDD, while *Bacteroides* and *Roseburia* displayed mixed correlations [23]. The relative abundance of bacteria in mental health disorders shifts the balance in favor of potentially detrimental bacterial taxa and a decreased abundance of beneficial bacteria. However, these findings remain inconsistent across studies. Discrepancies highlight the need for standardized methodologies and control for factors such as antibiotic or probiotic use and

medication exposure**. The objective of this narrative review is to explore how gut dysbiosis may contribute to the development of depression, by examining the main biological pathways linking the GM to brain function and emotional regulation.

2. Materials and Methods

We conducted a comprehensive search of the PubMed, Embase and PsychINFO, including new studies, as well as studies older than 10 years. The later provided important theoretical foundations and helped shape current hypotheses. Both human and relevant preclinical studies were considered. The search strategy targeted studies exploring GM composition, gut-brain axis communication, intestinal permeability, and their association with depression. We focused on microbiota alterations, pathways involving neuroimmune, neuroendocrine, and neurotransmitter regulation, and microbiota-targeted therapeutic strategies. The synthesis prioritised mechanistic understanding, aiming to develop a clearer understanding of gut-brain interactions in depression. The key pathways investigated are illustrated in Figure 1 and will be discussed in the following sections.
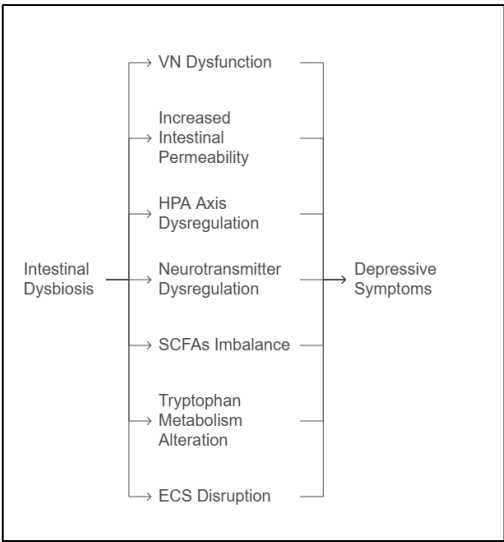

Figure 1. Mechanisms Linking Gut Dysbiosis to Depression. Abbreviations: VN = Vagus Nerve; HPA Axis = Hypothalamic–Pituitary–Adrenal Axis; SCFAs = Short-Chain Fatty Acids; ECS = Endocannabinoid System.

3. Mechanisms Linking Dysbiosis to Depression

Extensive research in animal and human studies supports the role of the GM in mental health. However, the precise mechanisms through which microorganisms influence the human brain remain incompletely understood. Chronic stress, anxiety and depression, are all linked to gut dysbiosis, intestinal inflammation and gut barrier dysfunction. However, current knowledge is largely derived from animal models, germ-free mice, and studies investigating the effects of specific microbial species, probiotics, antibiotics, and particular infections. To clarify these associations, it is important to examine the main biological pathways through which the GM may influence brain function.

3.1. The Vagus Nerve

The VN links the GM to the brain, transmitting signals via direct or indirect mechanisms. Neuroactive gut compounds act locally or reach the CNS through the bloodstream or vagal pathways. Vagal afferent fibers do not contact the intestinal lumen but can be indirectly influenced through epithelial intermediaries, such as enteroendocrine cells (EECs). These specialized cells detect luminal nutrients and microbial products, releasing serotonin and gut hormones (e.g., CCK, GLP-1, PYY) that activate vagal afferents. EECs also express receptors for bacterial components such as

lipopolysaccharides (LPS), or for microbial products such as short-chain fatty acids (SCFAs), which serve as central mediators. Additionally, LPS and SCFAs can act as direct activators of the VN [vi]. Transferring GM from chronic stress mice to healthy mice activated the VN and altered neurotransmitter (e.g., serotonin, dopamine) signaling in the brainstem and hippocampus. This led to impaired neurogenesis and neuroinflammation. These effects are prevented by vagotomy, highlighting the essential role of vagal afferents in gut-brain communication and their potential influence on depressive symptoms [24]. VN is also thought to have an important anti-inflammatory effect. Stimulation of the VN reduced proinflammatory cytokine levels in endotoxemic rodents and acetylcholine inhibited cytokine release from LPS-stimulated macrophages [25]. Later findings also established a cholinergic anti-inflammatory mechanism, as the VN's efferent pathway in immune regulation [26]. VN stimulation (VNS) has therapeutic potential and is one of the methods approved for depression treatment. VNS is thought to have antidepressant effects by enhancing monoaminergic signaling and by reducing inflammation [27]. Over the past decade, VNS has experienced a renewed scientific interest, amid the emergence of noninvasive, transcutaneous auricular vagus nerve stimulation (taVNS) [28]. However, the procedure's clinical potential is still unclear. A recent meta-analysis failed to show a consistent anti-inflammatory effect of VNS across several studies [29].

3.2. HPA Axis Dysregulation

The stress response involves complex interactions between the nervous, endocrine, and immune systems. When stressors are intense, recurrent, or prolonged, it becomes maladaptive [30]. The HPA axis regulates the stress response and basal homeostasis by producing glucocorticoids (GS), mainly cortisol. Beyond their central involvement in preserving physiological balance, GS have well-established anti-inflammatory effects. However, chronic stress leads to persistent systemic inflammation and neuroinflammation by inducing glucocorticoid resistance [31]. HPA axis hyperactivation, as seen in certain types of depression, leads to high cortisol levels and loss of normal regulatory control over the stress response. Stress, primarily through cortisol, corticotrophin releasing factor (CRH) and other signaling molecules, can impact microbial composition and diversity. This process can, in turn, alter the stress response, creating a bidirectional loop [32]. CRH has potent effects via contribution to visceral hypersensitivity, modulation of intestinal inflammation and of gut motility, altering gut transit time and nutrient availability [33]. Exposure to stressors exacerbated the intestinal inflammatory response in mice. Gene analysis identified elevated immune activation in the colon, including B cell receptor signaling, NK cell-mediated cytotoxicity pathways, leukocyte transendothelial migration and Th1 (T helper 1), Th2, Th17 cell differentiation. Stressors led to lower bacterial diversity and a fragile ecological network in rodent GM and downregulated metabolites of the dopamine-related pathway, increasing depressive behavior [34]. A landmark study illustrated that germ-free (GF) mice exhibit heightened stress-reactivity, revealed by increased plasma corticosterone and adrenocorticotrophic hormone (ACTH) levels and reduced BDNF expression in the cortex and hippocampus. The amplified HPA stress response in GF mice was normalized by administering *Bifidobacterium infantis*. Monoassociation with enteropathogenic *Escherichia coli* enhanced the stress response [35]. Both animal and human studies have shown that psychological stress may elevate intestinal permeability through CRH-driven activation of mast cells [36]. This results in bacterial translocation, triggering an immune response that further disrupts gut-brain communication. Therefore, stress and dysbiosis can mutually reinforce each other, aggravating symptoms. An elevation in serum zonulin, a protein which reversibly regulates intestinal permeability by altering tight junctions, was noted as early as 10 minutes after exposure to an acute stressor. It was followed by a decrease 60 minutes post-exposure. Highly stressed individuals also reported more abdominal symptoms, such as watery stool [37]. Gastrointestinal symptoms are commonly observed in individuals experiencing psychological stress. This is one of the most evident manifestations of the bidirectional communication between the CNS and the gut, reflecting its importance in generating anxious or depressive symptoms.

3.3. Short-Chain Fatty Acids

The GM and its primary metabolites are key elements of the GBA whose alteration may contribute to the development of depression. The metabolites include short-chain fatty acids (SCFAs) such as acetic acid, propionic acid, butyric and isobutyric acid, capnoic and isocapnoic acid, along with the synthesis or stimulation of neurotransmitters [38,39]. SCFAs are the main metabolites generated in the colon through bacterial fermentation of dietary fibers and resistant starch [40]. SCFAs are thought to play a key role in immunoendocrine modulation, with a relevant impact on both innate and adaptive immunity. They enhance the expression of anti-inflammatory cytokines, reduce the neutrophilic production of reactive oxygen species (ROS), reduce gut inflammation and promote the integrity and permeability of the gut barrier [41]. Butyrate reduces microglial activation and promotes a homeostatic phenotype [42]. Similarly, acetate lowers IL-6 and TNF-α expression and decreases p38 MAPK, JNK, and NF-κB phosphorylation in primary microglial cultures, reducing inflammatory signaling [43]. Propionic acid stimulates the expression of tryptophan 5-hydroxylase 1 (TPH1), a key enzyme in serotonin synthesis [44]. SCFA dysregulation has been strongly linked to depression. SCFA levels were altered in depressed patients, while supplementation with SCFAs had antidepressant and anxiolytic-like effects and ameliorated intestinal permeability in mice [39,45]. Observational studies have suggested that depression is linked to an increased relative abundance of potentially harmful microbial strains, as well as a decreased occurrence of SCFA-producing bacteria [46]. A systematic review carried out in 2021 identified differences in bacterial taxa indicating a higher abundance of proinflammatory species in anxiety and depression (e.g., *Enterobacteriaceae* and *Desulfovibrio*), and lower SCFA producing-bacteria (e.g., *Faecalibacterium*) [47]. Depleted levels of *Faecalibacterium*, *Butyricicoccus* and *Coprococcus*, which are butyrate producers belonging to the Clostridium cluster, and higher levels of *Eggerthella*, *Flavonifractor*, *Holdemania*, *Enterococcus*, *Streptococcus*, were consistently observed in depressive disorder, as reinforced by the most recent data [xlvi]. SCFAs cross the BBB and enhance its integrity by upregulating tight junction proteins. The lack of a normal GM in GF mice was associated with increased permeability of the BBB and the administration of sodium butyrate increased the expression of occludin in brain regions of GF mice and decreased BBB permeability [48]. Moreover, SCFAs contribute to the up-regulation of brain-derived neurotrophic factor (BDNF). Gut dysbiosis leads to reduced BDNF levels, affecting neuronal development and synaptic plasticity and potentially contributing to the genesis of mental health disorders [49]. SCFAs derived from GM represent a key pathway through which the gut can impact brain function. Their involvement in multiple regulatory pathways supports their potential role in the pathophysiology of depression.

3.4. Neurotransmitter Dysregulation

3.4.1. Serotonin

The enterochromaffin cells in the gut are responsible for synthesizing most of the circulating serotonin (5-HT), considered the primary neurotransmitter involved in depression pathophysiology [50]. Approximately 95% of the body's total 5-HT is located in the gut, while only around 5% is found in the brain. Certain microbial genera, including *Candida, Streptococcus* and *Escherichia*, are also capable of directly synthesizing 5-HT [38]. In GF mice, 5-HT serum levels were markedly lower than in control mice, accompanied by decreased colonic tryptophan hydroxylase-1 (TPH1) mRNA expression and increased SERT mRNA expression, underscoring the key role of the GM in regulating 5-HT synthesis. Monoassociation of GF mice with the strain *Clostridium ramosum* increased 5-HT levels and TPH1 expression in the ileum and colon [51]. Gut-derived peripheral 5-HT generally does not cross the BBB. It plays a key role in digestive processes, bone remodeling, contributes to inflammation regulation, as well as metabolic homeostasis [52]. However, peripheral serotonin can indirectly impact the CNS through the vagus nerve and by activating the HPA [27]. Gut-derived 5-HT stimulates vagal afferent fibers, relaying signals to the nucleus tractus solitarius (NTS) and influencing serotonergic activity in the dorsal raphe nucleus (DRN) and noradrenergic neurons in

the locus coeruleus (LC). This pathway plays a role in regulating emotion, stress, and immune responses. Microbial metabolites, especially SCFAs, also promote serotonin synthesis [27,44]. Researchers have investigated the link between the GM and the effectiveness of SSRIs in treating MDD. Their findings suggest that increased levels of specific microbial genera such as *Blautia*, *Coprococcus* and *Bifidobacterium*, may serve as predictive markers of treatment response [53]. These findings imply that gut microbial composition could guide personalized antidepressant strategies.

3.4.2. GABA

GABA dysfunction, which serves as the main inhibitory neurotransmitter of the CNS, has been linked to chronic diseases, including anxiety and depression. Chronic treatment with *Lactobacillus rhamnosus* alters GABA receptor expression in specific brain regions and reduces anxiety-like and depression-like behavior, along with stress-induced corticosterone levels. These behavioral and neurochemical effects were not found in vagotomized mice, identifying the VN as a major communication pathway in the GBA [54]. GABA-production has been mainly studied in the model organisms such as *Escherichia coli*, *Listeria monocytogenes*, in several *Bifidobacterium spp*. and in lactic acid bacteria (e.g., *Lactobacillus spp.*, *Streptococcus thermophilus*, *Lactococcus lactis*), mainly in the context of probiotics development [55].

3.5. Altered Tryptophan Metabolism

Tryptophan, an essential amino acid, is the main precursor for serotonin synthesis. Tryptophan follows three main metabolic pathways. A substantial proportion of dietary tryptophan, exceeding 90%, is metabolized through the kynurenine (Kyn) pathway, generating a variety of metabolites with systemic and neuroactive effects. Kynurenic acid is considered neuroprotective, while 3-hydroxykynurenine (3-HK) and quinolinic acid (Quin) are neurotoxic. Maintaining neuroimmune balance depends on the proper regulation of these metabolites. The Kyn pathway is activated by proinflammatory factors and is controlled by the enzymes indoleamine 2,3-dioxygenase (IDO) and tryptophan 2,3-dioxygenase (TDO). The gut microbiota converts approximately 5% of tryptophan through the indole pathway, generating several compounds (e.g., indole-3-acetic acid, indole-3-propionic acid) [56]. Indoles play a protective role in the gut by strengthening the epithelial barrier through enhanced tight junction expression and by limiting inflammatory cytokine release [57]. The remaining tryptophan is used for producing serotonin and, subsequently, melatonin. In MDD, research has found marked alterations in GM composition, as well as elevated IDO activity and increased Kyn pathway activation. This may result in increased neurotoxic metabolites and reduced serotonin production in the disease process [58]. LPS that cross an impaired gut barrier induce IDO expression, with deviation of tryptophan towards the Kyn pathway [59]. Investigating these phenomena in chronic restraint stress (CRS) mice, which exhibit increased intestinal permeability and depression-like behaviors, showed a significant increase in Kyn metabolism in both their brain and gut. Treatments with citalopram, IDO inhibitors, and microbiota interventions improved behavior and Kyn signaling [60]. Fecal microbiota transplantation (FMT) from healthy adolescents improved depressive behaviors in CRS mice, largely due to *Roseburia* colonization. FMT increased 5-HT and decreased Kyn pathway neurotoxins Quin and 3-HK levels in the brain and colon. Targeted *Roseburia intestinalis* administration confirmed these effects by enhancing TPH1 and tryptophan hydroxylase-2 (TPH2) expression, reducing IDO1 activity, and protecting against synaptic loss and neuroinflammation [61]. These findings suggest that dysbiosis can alter gut-brain axis function via influencing Kyn metabolism, contributing to depressive behaviors.

3.6. Increased Intestinal Permeability

GM supports mental health by preserving the intestinal barrier. When the structure is compromised ("leaky gut"), toxins can enter the bloodstream from the intestinal lumen. Factors that impair the gut barrier include stress, inflammation, dysbiosis, infections, intense exercise, heat, alcohol, pesticides, and antibiotics [36]. Increased gut permeability is a source of bacterial LPS, molecules present on the surface of most in Gram-negative bacteria. After entering the bloodstream, LPS generate a systemic inflammatory response, as well as neuroinflammation [62]. This process has strong implications on the development of depression and also involves an overactivation of the HPA axis [63]. LPS stimulate monocytes and macrophages to release inflammatory cytokines (e.g., IL-1, IL-6, and TNF-α) and other mediators, via intracellular signaling pathways [64]. Inflammatory cytokines cause stimulation of the HPA axis either alone or in synergy [32]. LPS also enhance BBB permeability, which can lead to the passage of cytokines and neurotoxins [65]. This process activates brain immune cells which mediate the inflammatory response, generating neuroinflammation, and in turn further disrupt the BBB, with effects on mental health. In HIV-infected individuals, elevated plasma LPS correlated with inflammation mediators and BBB dysfunction, despite undetectable cerebrospinal fluid (CSF) LPS. This suggests microbial translocation drives neuroinflammation without directly entering the CNS [66]. LPS also increase oxidative and nitrosative stress (O&NS), lead to peripheral and central autoimmunity and activate the kyn pathway, reducing 5-HT synthesis [59,67]. LPS are widely used for the development of animal models for various diseases linked to inflammation, including depression [62]. LPS-injected mice exhibit behavioral changes, elevated levels of TNF-α, IL-1β and IL-6 in serum, as well as in brain areas commonly related to depression (prefrontal cortex, hippocampus and striatum). An increase in IDO expression, as well as decreased 5-HT and BDNF levels, were observed [59]. Antidepressive treatment such as paroxetine, clomipramine, amitriptyline and tranylcypromine can prevent LPS-generated microglial changes and the production of inflammatory cytokines [68]. These findings suggest that certain antidepressants may exert therapeutic effects by mitigating neuroinflammation triggered by endotoxin exposure, besides neurotransmitter modulation.

3.7. The Endocannabinoid System

Evidence increasingly links MDD to dysfunction of the endocannabinoid system (ECS), with ECS deficits potentially promoting depressive behavior. Enhanced ECS signaling is thought to have therapeutic effects [69]. Interest in cannabis as a treatment has grown, though public perception often overestimates its benefits and longitudinal research offered mixed results [70]. The growing prevalence of cannabis self-medication for depressive symptoms illustrates the need to establish its efficacy and elucidate its precise effects. Changes in GM have been linked to alterations in the intestinal ECS. Researchers found that gut bacteria produce N-acyl amides, which mimic host endocannabinoids and interact with GT receptors [71]. Microbiome-targeted interventions (e.g., diet, probiotics, antibiotics) influence CB1 receptor expression and ECS activity in the colon. Deletion of the primary endocannabinoid-synthesizing enzyme in intestinal epithelial cells leads to changes in GM composition in mice [71]. Moreover, activation of CB2 receptors was shown to reduce inflammation and promote IB integrity. Treatments targeting CB2 and modulating endocannabinoid levels may help reduce inflammation and improve symptoms and quality of life in Intestinal Bowel Disease (IBD) patients, suggesting a protective role in maintaining a healthy microbiome [72]. In a mouse model of depression, GM from mice exposed to unpredictable chronic mild stress (UCMS) induced depressive-like behaviors and reduced endocannabinoid signaling in recipient mice. This was linked to lower levels of endocannabinoid (eCB) precursors. The effects were reversed by enhancing central eCB activity or administering specific *Lactobacillus* strains [73]. Research in human subjects also indicates that gut microbial diversity may influence psychological symptoms such as anhedonia and amotivation through the endocannabinoid system [74]. This highlights a potential GM–endocannabinoid axis as a novel therapeutic target for addressing these symptoms. While

interactions between ECS and GM are evident, it remains unclear whether microbiota modulates ECS tone or vice versa.

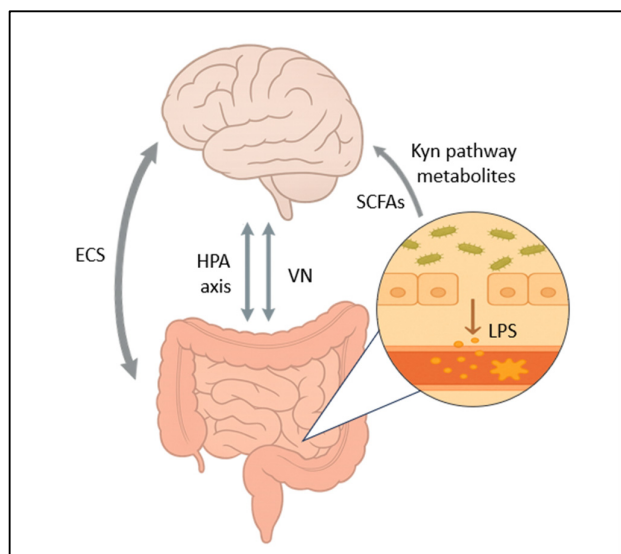The mechanisms discussed throughout this review are also illustrated in Figure 2.

Figure 2. Physiological Links Between the Gut and Brain.

The figure shows the bidirectional pathways within the GBA, involving VN, HPA axis, and ECS. Gut microbes, SCFAs and Kyn pathway metabolites may affect the brain through various mechanisms. Increased gut permeability allows LPS to enter the bloodstream, promoting inflammation and GBA dysregulation.

Abbreviations: VN = Vagus Nerve; HPA Axis = Hypothalamic–Pituitary–Adrenal Axis; SCFAs = Short-Chain Fatty Acids; ECS = Endocannabinoid System; LPS = Lipopolysaccharides; Kyn = Kynurenine

4. Potential Therapeutic Strategies Targeting Gut Dysbiosis in Depression

4.1. Probiotics and Prebiotics

Recent data highlighted the link between antibiotic use and the subsequent onset of depression, primarily due to the reduction in GM diversity caused by antibiotics [75]. Microbiome-targeted therapy (MTT), which includes probiotics and prebiotics administration beyond the classical association with antibiotic treatment, is a relatively new approach strategy for modulating the gut microbiome. Probiotics are beneficial bacteria that support host health, while prebiotics are non-digestible substrates (e.g., fiber, carbohydrates, saccharides) that nourish commensal microbes [76]. Emerging evidence suggests that MTT may reduce depressive symptoms, although findings remain partially inconclusive. Correlation with symptoms, scales or pathophysiological mechanisms of depression is not consistent across studies. Variability may stem from heterogeneous populations, comorbid conditions and medication or differences in measurement methods.

Probiotics supplementation was significantly associated with lower Beck Depression Inventory (BDI) scores. However, the formulations were not significantly effective in subjects with depression under age 40 or on depressive symptoms not associated with other somatic disorders [77]. However, there is contrasting data that determines MTT to be effective in depressed patients without comorbidities, but less effective in those with digestive disorders, such as irritable bowel syndrome, chronic diarrhea or constipation. Concerning treatment duration, up to 12 weeks of treatment, MTT was beneficial, while therapies exceeding 12 weeks were ineffective [78]. In a recent meta-analysis comparing the efficacy of probiotics with that of antidepressants, probiotics outperformed several treatments, including citalopram, duloxetine, ketamine, venlafaxine, and vortioxetine, and were

noninferior to others. In terms of efficiency, probiotics ranked second after escitalopram [79]. Despite the overall promising effects of probiotics in treating depression and their favorable safety profile, this conclusion should be interpreted cautiously due to study heterogeneity.

Bifidobacterium and *Lactobacillus*, commonly found in probiotics, are gaining attention for their ability to preserve psychological, as well as physiological homeostasis. Several species of these genera, such as *Lactobacillus helveticus* and *Bifidobacterium longum*, demonstrated anxiolytic and antidepressant effects, as well as a reduction in stress, as measured by urinary free cortisol [80]. *Lactobacillus plantarum* and *Bifidobacterium adolescentis*, exhibit antidepressant effects similar to fluoxetine in mouse models.[81] *Lactobacillus* and *Bifidobacterium* are potent GABA-producing bacteria that also impact tryptophan metabolism [56,81]. Their administration increases plasma tryptophan levels and serotonin production by reducing IDO expression and normalising the kyn-to-tryptophan ratio in mice [56,82]. Prebiotic fructo-oligosaccharides (FOS) increased the relative abundance of *Lactobacillus* and *Bifidobacterium*, as well as tryptophan levels, in the human GT. A significant change also occurred in butyrate-producing microbes, such as *Faecalibacterium*, *Ruminococcus* and *Oscillospira* [83]. Dietary fibers and probiotics of the *Lactobacillus* genus, also improved cognitive functions [84]. The positive impact on beneficial bacterial diversity reinforces the role of prebiotics, with advantages for the host. Combination of probiotics with prebiotics could further increase favorable metabolite levels beyond the effect of each individual intervention. This effect is likely due to the increased proliferation of bacteria synthesizing tryptophan, SCFAs, or GABA, among other beneficial substances.

4.2. FMT

Transplanted microbiota from one subject to another can alter exploratory, cognitive, and stereotypical behavior [85]. Exposure to chronic unpredictable mild stress (CUMS) in mice, as well as transfer of GM from the CUMS-exposed donors, led to increased behavioral signs of anxiety and depression in recipient mice. Both groups shared reduced *Lactobacillus* and elevated *Akkermansia* profiles and higher hippocampal levels of IFN-γ, TNF-α, and IDO1 expression [86]. FMT from MDD patients to rodents also induces depressive-like behavior [87,88]. Kelly et al. (2016) treated microbiota-depleted rats with fecal microbiota from depressed patients or controls. FMT from depressed patients induced anhedonia, anxiety-like behaviors, and tryptophan metabolism dysregulation [89]. These studies highlight the importance of GM in generating mental health conditions and suggest that gut dysbiosis precedes MDD onset and plays a causal role in the disorder. FMT is also a promising intervention strategy for rapidly reshaping the patient's GM by administering fecal flora from healthy donors. In preclinical studies, FMT reduced depressive-like behavior, suppressed neuroinflammation and repaired intestinal barrier damage [90]. A study published in 2022 presented the first two patients with MDD that received FMT through oral frozen capsules. Both experienced significant reductions in depressive symptoms, four weeks after receiving treatment. Effects persisted at the eight-week follow-up and no serious adverse events were reported [91]. FMT delivered through enema is also a feasible option, described as well-tolerated and safe in patients with MDD [92]. Patients suffering from depression as a neuropsychiatric-related symptom of COVID-19 also benefited from FMT [93]. Studies investigating the use of FMT in depression remain limited and largely exploratory. Well-designed clinical trials, particularly randomized controlled studies, are essential for assessing the feasibility, safety, and potential efficacy of FMT as an innovative therapeutic approach in mood disorders.

5. Conclusion and Future Directions

The pathophysiological role of intestinal dysbiosis in mental health disorders has become an increasingly recognized phenomenon in the past few years. As part of the interactions within the GBA, GM communicates with the CNS through neural, endocrine, immune and metabolic pathways, modulating brain function. The complexity of this system is reflected by key disruptions, including IB permeability, microbial metabolite and neurotransmitter imbalance and HPA axis activation.

These mediating processes have been repeatedly linked to mood-related disorders, including depression, although findings are not uniformly replicated. MTT represents a promising option for adjunctive treatment in depression, with encouraging preliminary results. However, the therapeutic efficacy and safety of these strategies require confirmation through large clinical trials. Future research should also focus on validating microbial and gut permeability biomarkers, thus paving the way for precision psychiatry and personalized interventions.

References

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington, VA: American Psychiatric Association; 2013.
2. Arias-de la Torre J, Vilagut G, Ronaldson A, Bakolis I, Dregan A, Martín V, Martinez-Alés G, Molina AJ, Serrano-Blanco A, Valderas JM, Viana MC, Alonso J. Prevalence and variability of depressive symptoms in Europe: update using representative data from the second and third waves of the European Health Interview Survey (EHIS-2 and EHIS-3). Lancet Public Health. 2023 Nov;8(11):e889-e898. doi: 10.1016/S2468-2667(23)00220-7. PMID: 37898521.
3. Akil H, Gordon J, Hen R, Javitch J, Mayberg H, McEwen B, Meaney MJ, Nestler EJ. Treatment resistant depression: A multi-scale, systems biology approach. Neurosci Biobehav Rev. 2018 Jan;84:272-288. doi: 10.1016/j.neubiorev.2017.08.019. Epub 2017 Aug 30. PMID: 28859997; PMCID: PMC5729118.
4. Evans-Lacko S, Aguilar-Gaxiola S, Al-Hamzawi A, et al. Socio-economic variations in the mental health treatment gap for people with anxiety, mood, and substance use disorders: results from the WHO World Mental Health (WMH) surveys. Psychol Med. 2018;48(9):1560-1571.
5. Dinan TG, Cryan JF. The Microbiome-Gut-Brain Axis in Health and Disease. Gastroenterol Clin North Am. 2017 Mar;46(1):77-89. doi: 10.1016/j.gtc.2016.09.007. Epub 2017 Jan 4. PMID: 28164854.
6. Bonaz B, Bazin T, Pellissier S. The Vagus Nerve at the Interface of the Microbiota-Gut-Brain Axis. Front Neurosci. 2018 Feb 7;12:49. doi: 10.3389/fnins.2018.00049. PMID: 29467611; PMCID: PMC5808284.
7. Foster JA, Rinaman L, Cryan JF. Stress & the gut-brain axis: Regulation by the microbiome. Neurobiol Stress. 2017 Mar 19;7:124-136. doi: 10.1016/j.ynstr.2017.03.001. PMID: 29276734; PMCID: PMC5736941.
8. Sonali S, Ray B, Ahmed Tousif H, Rathipriya AG, Sunanda T, Mahalakshmi AM, Rungratanawanich W, Essa MM, Qoronfleh MW, Chidambaram SB, Song BJ. Mechanistic Insights into the Link between Gut Dysbiosis and Major Depression: An Extensive Review. Cells. 2022 Apr 16;11(8):1362. doi: 10.3390/cells11081362. PMID: 35456041; PMCID: PMC9030021.

9.   Thursby E, Juge N. Introduction to the human gut microbiota. Biochem J. 2017 May 16;474(11):1823-1836. doi: 10.1042/BCJ20160510. PMID: 28512250; PMCID: PMC5433529.

10.   Backhed, F., Ding, H., Wang, T., Scott, J., S. E., & et al. (2004). The gut microbiota as an environmental factor that regulates fat storage. Proceedings of the National Academy of Sciences, 101(44), 15718-15723. doi:10.1073/pnas.0407076101

11.   SPRINZ H, KUNDEL DW, DAMMIN GJ, HOROWITZ RE, SCHNEIDER H, FORMAL SB. The response of the germfree guinea pig to oral bacterial challenge with Escherichia coli and Shigella flexneri. Am J Pathol. 1961 Dec;39(6):681-95. PMID: 13915950; PMCID: PMC1942415.

12.   Hsiao, E. Y., McBride, S. W., Hsien, S., Sharon, G., Hyde, E. R., McCue, T., … Mazmanian, S. K. (2013). Microbiota Modulate Behavioral and Physiological Abnormalities Associated with Neurodevelopmental Disorders. Cell, 155(7), 1451–1463. doi:10.1016/j.cell.2013.11.024

13.   Perez-Muñoz ME, Arrieta MC, Ramer-Tait AE, Walter J. A critical assessment of the "sterile womb" and "in utero colonization" hypotheses: implications for research on the pioneer infant microbiome. Microbiome. 2017 Apr 28;5(1):48. doi: 10.1186/s40168-017-0268-4. PMID: 28454555; PMCID: PMC5410102.

14.   Almeida C, Oliveira R, Soares R, Barata P. Influence of gut microbiota dysbiosis on brain function: a systematic review. Porto Biomed J. 2020 Mar 17;5(2):1-8. doi: 10.1097/j.pbj.0000000000000059. PMID: 33299942; PMCID: PMC7722401.

15.   Lloyd-Price, J., Mahurkar, A., Rahnavard, G., Crabtree, J., Orvis, J., Hall, A. B., … Huttenhower, C. (2017). Strains, functions and dynamics in the expanded Human Microbiome Project. Nature. doi:10.1038/nature23889

16.   Frederix M, Downie AJ. Quorum sensing: regulating the regulators. Adv Microb Physiol. 2011;58:23–80.

17.   Sender R, Fuchs S, Milo R. Revised Estimates for the Number of Human and Bacteria Cells in the Body. PLoS Biol. 2016 Aug 19;14(8):e1002533. doi: 10.1371/journal.pbio.1002533. PMID: 27541692; PMCID: PMC4991899.

18.   Diakite, A., Dubourg, G., & Raoult, D. (2021). Updating the repertoire of cultured bacteria from the human being. Microbial Pathogenesis, 150, 104698. doi:10.1016/j.micpath.2020.104698

19.   Donaldson GP, Lee SM, Mazmanian SK. Gut biogeography of the bacterial microbiota. Nat Rev Microbiol. 2016 Jan;14(1):20-32. doi: 10.1038/nrmicro3552. Epub 2015 Oct 26. PMID: 26499895; PMCID: PMC4837114.

20.   Ley, R. E., Hamady, M., Lozupone, C., Turnbaugh, P. J., Ramey, R. R., Bircher, J. S., … Gordon, J. I. (2008). Evolution of Mammals and Their Gut Microbes. Science, 320(5883), 1647–1651. doi:10.1126/science.1155725

21.   Tannock GW, Savage DC. Influences of dietary and environmental stress on microbial populations in the murine gastrointestinal tract. Infect Immun 1974;9(3):591-8. doi: 10.1128/iai.9.3.591-598.1974.

22.   Liu L, Wang H, Zhang H, Chen X, Zhang Y, Wu J, Zhao L, Wang D, Pu J, Ji P, Xie P. Toward a Deeper Understanding of Gut Microbiome in Depression: The Promise of Clinical Applicability. Adv Sci (Weinh). 2022 Dec;9(35):e2203707. doi: 10.1002/advs.202203707. Epub 2022 Oct 26. PMID: 36285702; PMCID: PMC9762301.

23.   Cheung SG, Goldenthal AR, Uhlemann AC, Mann JJ, Miller JM, Sublette ME. Systematic Review of Gut Microbiota and Major Depression. Front Psychiatry. 2019 Feb 11;10:34. doi: 10.3389/fpsyt.2019.00034. PMID: 30804820; PMCID: PMC6378305.

24.   Siopi E, Galerne M, Rivagorda M, Saha S, Moigneu C, Moriceau S, Bigot M, Oury F, Lledo PM. Gut microbiota changes require vagus nerve integrity to promote depressive-like behaviors in mice. Mol Psychiatry. 2023 Jul;28(7):3002-3012. doi: 10.1038/s41380-023-02071-6. Epub 2023 May 2. PMID: 37131071; PMCID: PMC10615761.

25.   Borovikova LV, Ivanova S, Zhang M, Yang H, Botchkina GI, Watkins LR, Wang H, Abumrad N, Eaton JW, Tracey KJ. Vagus nerve stimulation attenuates the systemic inflammatory response to endotoxin. Nature. 2000 May 25;405(6785):458-62. doi: 10.1038/35013070. PMID: 10839541.

26.   Pavlov VA, Tracey KJ. The vagus nerve and the inflammatory reflex--linking immunity and metabolism. Nat Rev Endocrinol. 2012 Dec;8(12):743-54. doi: 10.1038/nrendo.2012.189. PMID: 23169440; PMCID: PMC4082307.

27.   Hwang YK, Oh JS. Interaction of the Vagus Nerve and Serotonin in the Gut-Brain Axis. Int J Mol Sci. 2025 Jan 29;26(3):1160. doi: 10.3390/ijms26031160. PMID: 39940928; PMCID: PMC11818468.

28. Austelle CW, O'Leary GH, Thompson S, Gruber E, Kahn A, Manett AJ, Short B, Badran BW. A Comprehensive Review of Vagus Nerve Stimulation for Depression. Neuromodulation. 2022 Apr;25(3):309-315. doi: 10.1111/ner.13528. Epub 2021 Sep 6. PMID: 35396067; PMCID: PMC8898319.

29. Schiweck C, Sausmekat S, Zhao T, Jacobsen L, Reif A, Edwin Thanarajah S. No consistent evidence for the anti-inflammatory effect of vagus nerve stimulation in humans: A systematic review and meta-analysis. Brain Behav Immun. 2024 Feb;116:237-258. doi: 10.1016/j.bbi.2023.12.008. Epub 2023 Dec 7. PMID: 38070618.

30. Chu B, Marwaha K, Sanvictores T, Awosika AO, Ayers D. Physiology, Stress Reaction. 2024 May 7. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan–. PMID: 31082164.

31. Knezevic E, Nenic K, Milanovic V, Knezevic NN. The Role of Cortisol in Chronic Stress, Neurodegenerative Diseases, and Psychological Disorders. Cells. 2023 Nov 29;12(23):2726. doi: 10.3390/cells12232726. PMID: 38067154; PMCID: PMC10706127.

32. MAYER, E. A. (2000). The neurobiology of stress and gastrointestinal disease. Gut, 47(6), 861–869. doi:10.1136/gut.47.6.861

33. Konturek PC, Brzozowski T, Konturek SJ. Stress and the gut: pathophysiology, clinical consequences, diagnostic approach and treatment options. J Physiol Pharmacol. 2011 Dec;62(6):591-9. PMID: 22314561.

34. Sun L, Wang X, Zou Y, He Y, Liang C, Li J, Li P, Zhang J. Cold stress induces colitis-like phenotypes in mice by altering gut microbiota and metabolites. Front Microbiol. 2023 Apr 11;14:1134246. doi: 10.3389/fmicb.2023.1134246. PMID: 37113236; PMCID: PMC10126409.

35. Sudo N, Chida Y, Aiba Y, Sonoda J, Oyama N, Yu XN, Kubo C, Koga Y. (2004) Postnatal microbial colonization programs the hypothalamic-pituitary-adrenal system for stress response in mice. J Physiol 558:263–275

36. Rudzki L, Maes M. The Microbiota-Gut-Immune-Glia (MGIG) Axis in Major Depression. Mol Neurobiol. 2020 Oct;57(10):4269-4295. doi: 10.1007/s12035-020-01961-y. Epub 2020 Jul 22. PMID: 32700250.

37. Linninge, C., Jönsson, P., Bolinsson, H., Önning, G., Eriksson, J., Johansson, G., & Ahrné, S. (2018). Effects of acute stress provocation on cortisol levels, zonulin and inflammatory markers in low- and high-stressed men. Biological Psychology. doi:10.1016/j.biopsycho.2018.08.0

38. Han W, Wang N, Han M, Ban M, Sun T, Xu J. Reviewing the role of gut microbiota in the pathogenesis of depression and exploring new therapeutic options. Front Neurosci. 2022 Dec 8;16:1029495. doi: 10.3389/fnins.2022.1029495. PMID: 36570854; PMCID: PMC9772619.

39. Skonieczna-Żydecka K, Grochans E, Maciejewska D, Szkup M, Schneider-Matyka D, Jurczak A, Łoniewski I, Kaczmarczyk M, Marlicz W, Czerwińska-Rogowska M, Pełka-Wysiecka J, Dec K, Stachowska E. Faecal Short Chain Fatty Acids Profile is Changed in Polish Depressive Women. Nutrients. 2018 Dec 7;10(12):1939. doi: 10.3390/nu10121939. PMID: 30544489; PMCID: PMC6316414.

40. Silva YP, Bernardi A, Frozza RL. The Role of Short-Chain Fatty Acids From Gut Microbiota in Gut-Brain Communication. Front Endocrinol (Lausanne). 2020 Jan 31;11:25. doi: 10.3389/fendo.2020.00025. PMID: 32082260; PMCID: PMC7005631.

41. Fusco W, Lorenzo MB, Cintoni M, Porcari S, Rinninella E, Kaitsas F, Lener E, Mele MC, Gasbarrini A, Collado MC, Cammarota G, Ianiro G. Short-Chain Fatty-Acid-Producing Bacteria: Key Components of the Human Gut Microbiota. Nutrients. 2023 May 6;15(9):2211. doi: 10.3390/nu15092211. PMID: 37432351; PMCID: PMC10180739.

42. Wang P, Zhang Y, Gong Y, Yang R, Chen Z, Hu W, Wu Y, Gao M, Xu X, Qin Y, Huang C. Sodium butyrate triggers a functional elongation of microglial process via Akt-small RhoGTPase activation and HDACs inhibition. Neurobiol Dis. 2018 Mar;111:12-25. doi: 10.1016/j.nbd.2017.12.006. Epub 2017 Dec 14. PMID: 29248540.

43. Soliman ML, Puig KL, Combs CK, Rosenberger TA. Acetate reduces microglia inflammatory signaling in vitro. J Neurochem. 2012 Nov;123(4):555-67. doi: 10.1111/j.1471-4159.2012.07955.x. Epub 2012 Sep 28. PMID: 22924711; PMCID: PMC3472042.

44. Nankova B.B., Agarwal R., MacFabe D.F., La Gamma E.F. Enteric bacterial metabolites propionic and butyric acid modulate gene expression, including CREB-dependent catecholaminergic neurotransmission, in PC12 cells—Possible relevance to autism spectrum disorders. PLoS ONE. 2014;9:e103740. doi: 10.1371/journal.pone.0103740.

45. van de Wouw M, Boehme M, Lyte JM, Wiley N, Strain C, O'Sullivan O, Clarke G, Stanton C, Dinan TG, Cryan JF. Short-chain fatty acids: microbial metabolites that alleviate stress-induced brain-gut axis alterations. J Physiol. 2018 Oct;596(20):4923-4944. doi: 10.1113/JP276431. Epub 2018 Aug 28. PMID: 30066368; PMCID: PMC6187046.

46. Gao M, Wang J, Liu P, Tu H, Zhang R, Zhang Y, Sun N, Zhang K. Gut microbiota composition in depressive disorder: a systematic review, meta-analysis, and meta-regression. Transl Psychiatry. 2023 Dec 8;13(1):379. doi: 10.1038/s41398-023-02670-5. PMID: 38065935; PMCID: PMC10709466.

47. Simpson CA, Diaz-Arteche C, Eliby D, Schwartz OS, Simmons JG, Cowan CSM. The gut microbiota in anxiety and depression - A systematic review. Clin Psychol Rev. 2021 Feb;83:101943. doi: 10.1016/j.cpr.2020.101943. Epub 2020 Oct 29. PMID: 33271426.

48. Braniste, V., Al-Asmakh, M., Kowal, C., Anuar, F., Abbaspour, A., Toth, M., … Pettersson, S. (2014). The gut microbiota influences blood-brain barrier permeability in mice. Science Translational Medicine, 6(263), 263ra158–263ra158. doi:10.1126/scitranslmed.3009759

49. Suda K, Matsuda K. How Microbes Affect Depression: Underlying Mechanisms via the Gut-Brain Axis and the Modulating Role of Probiotics. Int J Mol Sci. 2022 Jan 21;23(3):1172. doi: 10.3390/ijms23031172. PMID: 35163104; PMCID: PMC8835211

50. Gershon, M. D., & Tack, J. (2007). The Serotonin Signaling System: From Basic Understanding To Drug Development for Functional GI Disorders. Gastroenterology, 132(1), 397–414. doi:10.1053/j.gastro.2006.11.002

51. Legan TB, Lavoie B, Mawe GM. Direct and indirect mechanisms by which the gut microbiota influence host serotonin systems. Neurogastroenterol Motil. 2022 Oct;34(10):e14346. doi: 10.1111/nmo.14346. Epub 2022 Mar 5. PMID: 35246905; PMCID: PMC9441471.

52. Banskota S, Ghia JE, Khan WI. Serotonin in the gut: Blessing or a curse. Biochimie. 2019 Jun;161:56-64. doi: 10.1016/j.biochi.2018.06.008. Epub 2018 Jun 14. PMID: 29909048.

53. Gao M, Tu H, Liu P, Zhang Y, Zhang R, Jing L, Zhang K. Association analysis of gut microbiota and efficacy of SSRIs antidepressants in patients with major depressive disorder. J Affect Disord. 2023 Jun 1;330:40-47. doi: 10.1016/j.jad.2023.02.143. Epub 2023 Mar 3. PMID: 36871910.

54. Savignac HM, Dinan TG, Bienenstock J, Cryan JF. Ingestion of Lactobacillus strain regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve. Proc Natl Acad Sci U S A. 2011 Sep 20;108(38):16050-5. doi: 10.1073/pnas.1102999108. Epub 2011 Aug 29. PMID: 21876150; PMCID: PMC3179073.

55. Otaru N, Ye K, Mujezinovic D, Berchtold L, Constancias F, Cornejo FA, Krzystek A, de Wouters T, Braegger C, Lacroix C, Pugin B. GABA Production by Human Intestinal Bacteroides spp.: Prevalence, Regulation, and Role in Acid Stress Tolerance. Front Microbiol. 2021 Apr 15;12:656895. doi: 10.3389/fmicb.2021.656895. PMID: 33936013; PMCID: PMC8082179.

56. Hou Y, Li J, Ying S. Tryptophan Metabolism and Gut Microbiota: A Novel Regulatory Axis Integrating the Microbiome, Immunity, and Cancer. Metabolites. 2023 Nov 20;13(11):1166. doi: 10.3390/metabo13111166. PMID: 37999261; PMCID: PMC10673612.

57. Alexeev, E.E.; Lanis, J.M.; Kao, D.J.; Campbell, E.L.; Kelly, C.J.; Battista, K.D.; Gerich, M.E.; Jenkins, B.R.; Walk, S.T.; Kominsky, D.J.; et al. Microbiota-Derived Indole Metabolites Promote Human and Murine Intestinal Homeostasis through Regulation of Interleukin-10 Receptor. Am. J. Pathol. 2018, 188, 1183–1194.

58. Lin P, Li D, Shi Y, Li Q, Guo X, Dong K, Chen Q, Lou X, Li Z, Li P, Jin W, Chen S, Sun Y, Sun J, Cheng X. Dysbiosis of the Gut Microbiota and Kynurenine (Kyn) Pathway Activity as Potential Biomarkers in Patients with Major Depressive Disorder. Nutrients. 2023 Apr 3;15(7):1752. doi: 10.3390/nu15071752. PMID: 37049591; PMCID: PMC10096701.

59. Zhao X, Cao F, Liu Q, Li X, Xu G, Liu G, Zhang Y, Yang X, Yi S, Xu F, Fan K, Ma J. Behavioral, inflammatory and neurochemical disturbances in LPS and UCMS-induced mouse models of depression. Behav Brain Res. 2019 May 17;364:494-502. doi: 10.1016/j.bbr.2017.05.064. Epub 2017 May 29. Erratum in: Behav Brain Res. 2023 Aug 24;452:114573. doi: 10.1016/j.bbr.2023.114573. PMID: 28572058.

60. Deng Y, Zhou M, Wang J, Yao J, Yu J, Liu W, Wu L, Wang J, Gao R. Involvement of the microbiota-gut-brain axis in chronic restraint stress: disturbances of the kynurenine metabolic pathway in both the gut and

brain. Gut Microbes. 2021 Jan-Dec;13(1):1-16. doi: 10.1080/19490976.2020.1869501. PMID: 33535879; PMCID: PMC7872056.

61. Zhou M, Fan Y, Xu L, Yu Z, Wang S, Xu H, Zhang J, Zhang L, Liu W, Wu L, Yu J, Yao H, Wang J, Gao R. Microbiome and tryptophan metabolomics analysis in adolescent depression: roles of the gut microbiota in the regulation of tryptophan-derived neurotransmitters and behaviors in human and mice. Microbiome. 2023 Jun 30;11(1):145. doi: 10.1186/s40168-023-01589-9. PMID: 37386523; PMCID: PMC10311725.

62. Yin R, Zhang K, Li Y, Tang Z, Zheng R, Ma Y, Chen Z, Lei N, Xiong L, Guo P, Li G, Xie Y. Lipopolysaccharide-induced depression-like model in mice: meta-analysis and systematic evaluation. Front Immunol. 2023 Jun 8;14:1181973. doi: 10.3389/fimmu.2023.1181973. PMID: 37359525; PMCID: PMC10285697.

63. Caspani G, Kennedy S, Foster JA, Swann J. Gut microbial metabolites in depression: understanding the biochemical mechanisms. Microb Cell. 2019 Sep 27;6(10):454-481. doi: 10.15698/mic2019.10.693. PMID: 31646148; PMCID: PMC6780009.

64. Meng F, Lowell CA. Lipopolysaccharide (LPS)-induced macrophage activation and signal transduction in the absence of Src-family kinases Hck, Fgr, and Lyn. J Exp Med. 1997 May 5;185(9):1661-70. doi: 10.1084/jem.185.9.1661. PMID: 9151903; PMCID: PMC2196288.

65. Peng X, Luo Z, He S, Zhang L, Li Y. Blood-Brain Barrier Disruption by Lipopolysaccharide and Sepsis-Associated Encephalopathy. Front Cell Infect Microbiol. 2021 Nov 4;11:768108. doi: 10.3389/fcimb.2021.768108. PMID: 34804998; PMCID: PMC8599158.

66. Jiang W, Luo Z, Stephenson S, Li H, Di Germanio C, Norris PJ, Fuchs D, Zetterberg H, Gisslen M, Price RW. Cerebrospinal Fluid and Plasma Lipopolysaccharide Levels in Human Immunodeficiency Virus Type 1 Infection and Associations With Inflammation, Blood-Brain Barrier Permeability, and Neuronal Injury. J Infect Dis. 2021 May 20;223(9):1612-1620. doi: 10.1093/infdis/jiaa765. PMID: 33320240; PMCID: PMC8136977.

67. Maes, M., Kubera, M., Leunis, J.-C., Berk, M., Geffard, M., & Bosmans, E. (2012). In depression, bacterial translocation may drive inflammatory responses, oxidative and nitrosative stress (O&NS), and autoimmune responses directed against O&NS-damaged neoepitopes. Acta Psychiatrica Scandinavica, 127(5), 344–354. doi:10.1111/j.1600-0447.2012.01908.x

68. Mariani N, Everson J, Pariante CM, Borsini A. Modulation of microglial activation by antidepressants. J Psychopharmacol. 2022 Feb;36(2):131-150. doi: 10.1177/02698811211069110. Epub 2022 Jan 29. PMID: 35098788; PMCID: PMC8847767.

69. Sarris J, Sinclair J, Karamacoska D, Davidson M, Firth J. Medicinal cannabis for psychiatric disorders: a clinically-focused systematic review. BMC Psychiatry. 2020 Jan 16;20(1):24. doi: 10.1186/s12888-019-2409-8. PMID: 31948424; PMCID: PMC6966847.

70. Bright U, Akirav I. Modulation of Endocannabinoid System Components in Depression: Pre-Clinical and Clinical Evidence. Int J Mol Sci. 2022 May 15;23(10):5526. doi: 10.3390/ijms23105526. PMID: 35628337; PMCID: PMC9146799.

71. Pires, L., Gonzalez-Paramás, A. M., Heleno, S. A., & Calhelha, R. C. (2024). Gut microbiota as an endocrine organ: Unveiling its role in human physiology and health. Applied Sciences, 14(20), 9383. https://doi.org/10.3390/app14209383.

72. Rakotoarivelo V, Mayer TZ, Simard M, Flamand N, Di Marzo V. The Impact of the CB_2 Cannabinoid Receptor in Inflammatory Diseases: An Update. Molecules. 2024 Jul 18;29(14):3381. doi: 10.3390/molecules29143381. PMID: 39064959; PMCID: PMC11279428.

73. Chevalier G, Siopi E, Guenin-Macé L, Pascal M, Laval T, Rifflet A, Boneca IG, Demangel C, Colsch B, Pruvost A, Chu-Van E, Messager A, Leulier F, Lepousez G, Eberl G, Lledo PM. Effect of gut microbiota on depressive-like behaviors in mice is mediated by the endocannabinoid system. Nat Commun. 2020 Dec 11;11(1):6363. doi: 10.1038/s41467-020-19931-2. PMID: 33311466; PMCID: PMC7732982.

74. Minichino A, Jackson MA, Francesconi M, Steves CJ, Menni C, Burnet PWJ, Lennox BR. Endocannabinoid system mediates the association between gut-microbial diversity and anhedonia/amotivation in a general population cohort. Mol Psychiatry. 2021 Nov;26(11):6269-6276. doi: 10.1038/s41380-021-01147-5. Epub 2021 May 17. PMID: 34002020; PMCID: PMC8760063.

75. Pouranayatihosseinabad M., Bezabih Y., Hawrelak J., Peterson G.M., Veal F., Mirkazemi C. Antibiotic use and the development of depression: a systematic review. J Psychosom Res. 2023;164 doi: 10.1016/j.jpsychores.2022.111113.

76. Radford-Smith DE, Anthony DC. Prebiotic and Probiotic Modulation of the Microbiota-Gut-Brain Axis in Depression. Nutrients. 2023 Apr 13;15(8):1880. doi: 10.3390/nu15081880. PMID: 37111100; PMCID: PMC10146605.

77. Lin J, Zhang Y, Wang K, Wang J, Kou S, Chen K, Zheng W, Chen R. The effect and safety of probiotics on depression: a systematic review and meta-analysis of randomized controlled trials. Eur J Nutr. 2023 Oct;62(7):2709-2721. doi: 10.1007/s00394-023-03184-y. Epub 2023 May 29. PMID: 37247076.

78. Pan B, Pan Y, Huang YS, Yi M, Hu Y, Lian X, Shi HZ, Wang M, Xiang G, Yang WY, Liu Z, Xia F. Efficacy and safety of gut microbiome-targeted treatment in patients with depression: a systematic review and meta-analysis. BMC Psychiatry. 2025 Jan 21;25(1):64. doi: 10.1186/s12888-024-06438-z. PMID: 39838303; PMCID: PMC11753086.

79. Zhao S, Liang S, Tao J, Peng Y, Chen S, Wai HKF, Chung FY, Sin ZY, Wong MKL, Haqq AM, Chang WC, Ni MY, Chan FKL, Ng SC, Tun HM. Probiotics for adults with major depressive disorder compared with antidepressants: a systematic review and network meta-analysis. Nutr Rev. 2025 Jan 1;83(1):72-82. doi: 10.1093/nutrit/nuad171. PMID: 38219239.

80. Messaoudi, M., Lalonde, R., Violle, N., Javelot, H., Desor, D., Nejdi, A., … Cazaubiel, J.-M. (2010). Assessment of psychotropic-like properties of a probiotic formulation (Lactobacillus helveticus R0052 and Bifidobacterium longum R0175) in rats and human subjects. British Journal of Nutrition, 105(05), 755–764. doi:10.1017/s0007114510004319

81. Yunes R. A., Poluektova E. U., Vasileva E. V., Odorskaya M. V., Marsova M. V., Kovalev G. I., et al. (2020). A multi-strain potential probiotic formulation of GABA-Producing Lactobacillus plantarum 90sk and Bifidobacterium adolescentis 150 with antidepressant effects. Probiot. Antimicrob. Prot. 12 973–979. 10.1007/s12602-019-09601-1

82. Desbonnet, L., Garrett, L., Clarke, G., Bienenstock, J., & Dinan, T. G. (2008). The probiotic Bifidobacteria infantis: An assessment of potential antidepressant properties in the rat. Journal of Psychiatric Research, 43(2), 164–174. doi:10.1016/j.jpsychires.2008.03.

83. Tandon D, Haque MM, Gote M, Jain M, Bhaduri A, Dubey AK, Mande SS. A prospective randomized, double-blind, placebo-controlled, dose-response relationship study to investigate efficacy of fructo-oligosaccharides (FOS) on human gut microflora. Sci Rep. 2019 Apr 2;9(1):5473. doi: 10.1038/s41598-019-41837-3. PMID: 30940833; PMCID: PMC6445088.

84. Barrio C, Arias-Sánchez S, Martín-Monzón I. The gut microbiota-brain axis, psychobiotics and its influence on brain and behaviour: A systematic review. Psychoneuroendocrinology. 2022 Mar;137:105640. doi: 10.1016/j.psyneuen.2021.105640. Epub 2021 Dec 17. PMID: 34942539.

85. Bruce-Keller AJ, Salbaum JM, Luo M, Blanchard E 4th, Taylor CM, Welsh DA, Berthoud HR. Obese-type gut microbiota induce neurobehavioral changes in the absence of obesity. Biol Psychiatry. 2015 Apr 1;77(7):607-15. doi: 10.1016/j.biopsych.2014.07.012. Epub 2014 Jul 18. PMID: 25173628; PMCID: PMC4297748.

86. Li N, Wang Q, Wang Y, Sun A, Lin Y, Jin Y, Li X. Fecal microbiota transplantation from chronic unpredictable mild stress mice donors affects anxiety-like and depression-like behavior in recipient mice via the gut microbiota-inflammation-brain axis. Stress. 2019 Sep;22(5):592-602. doi: 10.1080/10253890.2019.1617267. Epub 2019 May 24. PMID: 31124390.

87. Kelly JR, Borre Y, O' Brien C, Patterson E, El Aidy S, Deane J, Kennedy PJ, Beers S, Scott K, Moloney G, Hoban AE, Scott L, Fitzgerald P, Ross P, Stanton C, Clarke G, Cryan JF, Dinan TG. Transferring the blues: Depression-associated gut microbiota induces neurobehavioural changes in the rat. J Psychiatr Res. 2016 Nov;82:109-18. doi: 10.1016/j.jpsychires.2016.07.019. Epub 2016 Jul 25. PMID: 27491067.

88. Zheng P., Zeng B., Zhou C., et al. Gut microbiome remodeling induces depressive-like behaviors through a pathway mediated by the host's metabolism. Mol Psychiatry. 2016;21:786–796. doi: 10.1038/mp.2016.44.

89. Kelly JR, Borre Y, O' Brien C, Patterson E, El Aidy S, Deane J, Kennedy PJ, Beers S, Scott K, Moloney G, Hoban AE, Scott L, Fitzgerald P, Ross P, Stanton C, Clarke G, Cryan JF, Dinan TG. Transferring the blues:

Depression-associated gut microbiota induces neurobehavioural changes in the rat. J Psychiatr Res. 2016 Nov;82:109-18. doi: 10.1016/j.jpsychires.2016.07.019. Epub 2016 Jul 25. PMID: 27491067.

90. Rao J., Xie R., Lin L., et al. Fecal microbiota transplantation ameliorates gut microbiota imbalance and intestinal barrier damage in rats with stress-induced depressive-like behavior. Eur J Neurosci. 2021;53:3598–3611. doi: 10.1111/ejn.15192.

91. Doll JPK, Vázquez-Castellanos JF, Schaub AC, Schweinfurth N, Kettelhack C, Schneider E, Yamanbaeva G, Mählmann L, Brand S, Beglinger C, Borgwardt S, Raes J, Schmidt A, Lang UE. Fecal Microbiota Transplantation (FMT) as an Adjunctive Therapy for Depression-Case Report. Front Psychiatry. 2022 Feb 17;13:815422. doi: 10.3389/fpsyt.2022.815422. PMID: 35250668; PMCID: PMC8891755.

92. Green JE, Berk M, Mohebbi M, Loughman A, McGuinness AJ, Castle D, Chatterton ML, Perez J, Strandwitz P, Athan E, Hair C, Nierenberg AA, Cryan JF, Jacka F. Feasibility, Acceptability, and Safety of Faecal Microbiota Transplantation in the Treatment of Major Depressive Disorder: A Pilot Randomized Controlled Trial. Can J Psychiatry. 2023 May;68(5):315-326. doi: 10.1177/07067437221150508. Epub 2023 Jan 13. PMID: 36637229; PMCID: PMC10192831.

93. Jiang X, Gao X, Ding J, Pang B, Pei Y, Zhao Z, Zhao N, Wang Z, Chen C, Gao D, Yan F, Wang F, Liu C, Zhang Z, Li Z, Zhao Z. Fecal microbiota transplantation alleviates mild-moderate COVID-19 associated diarrhoea and depression symptoms: A prospective study of a randomized, double-blind clinical trial. J Med Virol. 2024 Aug;96(8):e29812. doi: 10.1002/jmv.29812. PMID: 39056206.

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