Review

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Unlocking the Secrets of Probiotics – A Therapeutic Breakthrough for Major Depressive Disorders

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The human gut has 12 distinct phyla, among which Proteobacteria, Firmicutes, Actinobacteria, and Bacteroidetes make up >90%. Depressed individuals are a significant phylum and are differentiated from healthy individuals by their firmicutes. The microbiome is a key component of the pathological basis of major depressive illness as a result of disruption of the microbiota-gut-brain (MGB) axis. The fact is that there is bidirectional communication inside the brain, stomach, and brain-gut, wherein the brain highlights a systemic disease characterized by both brain and peripheral dysfunction. According to the microbiota hypothesis, MGB axis dysfunction is a significant contributor to the pathogenic underpinnings of major depressive disorder (MDD). The etiology of MDD is complicated and includes an imbalance of neurotransmitters, an impaired hypothalamic-pituitary-adrenal (HPA) axis, inflammation, and the MGB axis. According to research, having an aberrant microbiome or a disjointed MGB axis may directly cause psychiatric diseases such as MDD. Hence, resolving these issues may help with depression symptoms. Probiotics may therefore have therapeutic benefits for psychiatric symptoms by fostering healthy and balanced gut flora. The probiotic *Bifidobacterium longum* NCC3001 has been shown to reduce depression scores. In this review, the unknown mysteries and myths of probiotics are unlocked with special attention given to MDD or depression.

Keywords: probiotics; depression; MGB axis; gut dysbiosis; microbiota; clinical research

Introduction

Anxiety, depressed mood, altered appetite, fatigue, anhedonia, irritability, insomnia, and suicidal ideation are all symptoms of major depressive disorder (MDD). According to a recent report, MDD affects approximately 280 million individuals globally. According to a global burden of disease study, depression is among the top ten disabling diseases in terms of years lost to disability, revealing that MDD adversely affects the quality of life of individuals [1,2]. Many hypotheses have been presented to clarify the fundamental pathogenic mechanisms of this disease, even though its causes and pathology remain unknown. Researchers have suggested that malfunction of brain-derived neurotrophic factor (BDNF) and abnormalities of the hypothalamus-pituitary-adrenal axis are involved in the stress response and emerging theories for the etiology of depression. The "gut-brain axis" represents a two-way

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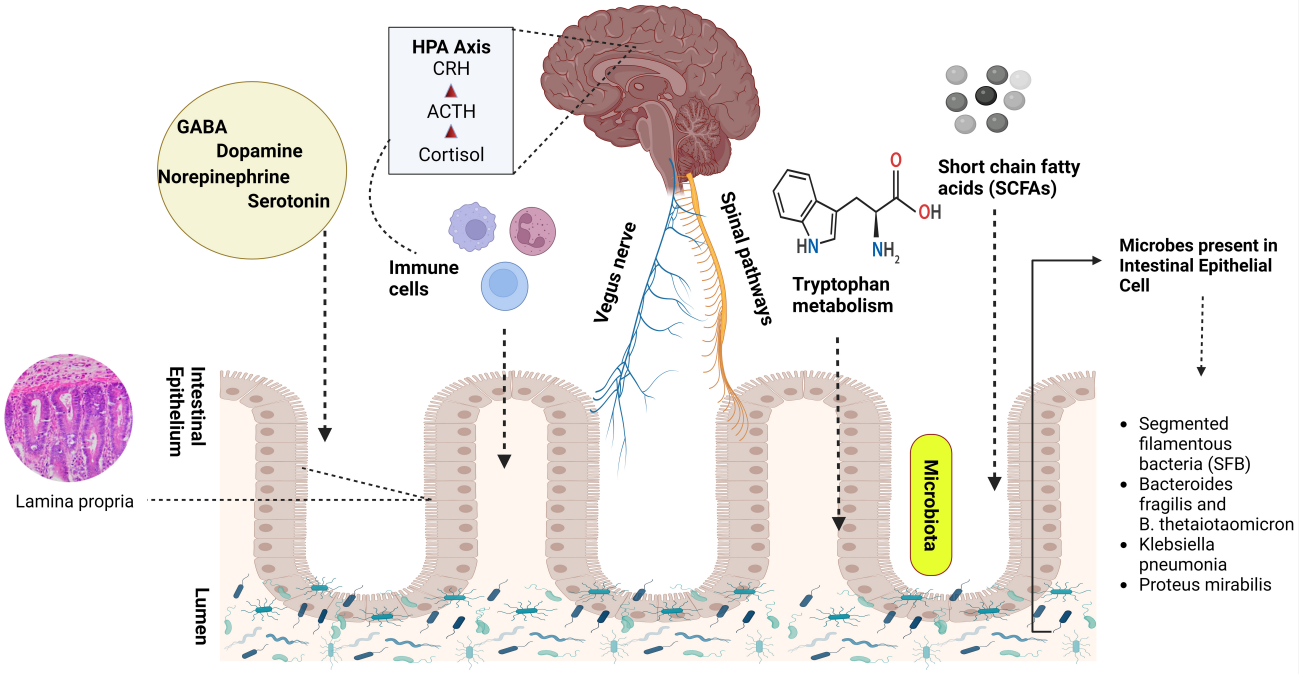

Fig. 1. Overview of the multiple bidirectional routes of communication between the brain and the gut microbiota. These routes include the vagus nerve, the hypothalamic-pituitary-adrenal (HPA) axis, cytokines produced by the immune system, tryptophan metabolism, and the production of short-chain fatty acids), as conceptualized in Reference [3], [Dinan TG, Stilling RM, Stanton C, Cryan JF.], [Journal of Psychiatric Research]; published by [Elsevier], [2015], modified with Biorender (https://www.biorender.com/). GABA, gamma-aminobutyric acid; CRH, corticotropin-releasing hormone; ACTH, adrenocorticotropic hormone.

connection between the gut and brain composed of neuronal and humoral channels and is considered the mechanism by which the gut microbiota affects brain functions.

The "microbiota-gut-brain-axis" concept has evolved in psychiatry due to the elucidation of the influence of the gut microflora on homeostasis via the gut-brain axis, which can be accomplished through the gut-brain axis (summarized in Fig. 1, Ref. [3]) [3,4]. Through the autonomic nervous system, the brain influences the functioning of the gut and the composition of the gut microbial community by regulating intestinal secretion, permeability, and motility. Stress leads to depression, which is inherited within families. People with anxiety and depression ancestry are more likely to suffer from emotional, physical, and sexual complications [5,6]. It is not possible to explain the onset and progression of depression through a single mechanism. Nonetheless, MDD and its comorbid psychiatric conditions are linked to neural signaling impairment, hippocampal volume loss, elevated inflammatory markers, decreased monoamine neurotransmitters (dopamine, epinephrine, and serotonin), growth factors (glia-derived neurotrophic factors such as GDNF and BDNF), and decreased cognitive function and synaptic plasticity [7,8]. Furthermore, two-way communication between the gut and the brain microbiome has been well documented in various studies, yet only limited research has demonstrated the crucial function of gut microbes in rejuvenating brain development [9,10].

Several metabolites generated by the gut microbiota have also been shown to act as signaling molecules that affect brain function and host immunological responses [11,12]. Moreover, the function of infection-mediated cytokines in nervous system alterations throughout fetal development and later stages of life was also investigated. Another study demonstrated that consuming a probiotic supplement formulation, including *Bifidobacterium longum* and *Lactobacillus helveticus*, had a positive psychological impact on anxiety, depression, and related mechanisms in healthy human volunteers and anxiolytic rats [13]. This research showed the significance of immune chemicals and gut microbiome-generated metabolites in brain growth and behavioral modulation. Furthermore, the microbial species in the gut directly correlate with the type of immunological component, and microbial metabolites affect nervous system function. This research showed the significance of immune chemicals and gut microbiome metabolites in brain growth and behavioral modulation. Additionally, the immunological substances and microbial byproducts that affect nervous system functions intimately correlate with microbes in the gut [14].

Several investigations have also shown that pathogenic bacteria produce inflammatory immunomodulating metabolites and compounds that communicate with the brain, modifying its function and stimulating the hypothalamic-pituitary-adrenal (HPA) axis [15,16]. Bene-

ficial bacteria are accountable for generating short-chain fatty acids, antioxidants, serotonin, gamma-aminobutyric acid (GABA), and other anti-inflammatory substances and metabolites. These compounds and metabolites positively affect the functioning of the central nervous system (CNS) by enhancing the functioning of the brain, memory, and human behavior [17,18]. This suggests that probiotics may be advantageous in the treatment of psychological illnesses, including anxiety and depression. Furthermore, recovery from sadness and anxiety associated with mood disorders is exceedingly sluggish, and medicine must be continued for a long time [19]. Prolonged use of synthetic antidepressants and antianxiety medicines has negative health consequences and causes further health difficulties [20]. As a natural and risk-free option for synthetic antidepressant drugs, probiotics may be beneficial for both the prevention and treatment of this disorder. It has been shown that stress alters the intestinal microbiome by decreasing the population of useful *bifidobacteria* and *lactobacilli*, increasing the population of harmful microbes, and increasing the concentrations of immunological chemicals [21,22]. Probiotics are now the key focus of enteric neuroscience investigations as a new area that integrates neuropsychiatry with gastroenterology. Various rodent and early human studies have shown that probiotics alter neural growth, brain biochemistry, and a series of behavioral phenomena [23].

Thus, this article primarily delves into the fundamental acquaintance of the correlation between depression or MDD and the gut microbiota axis, stressing factor correlations such as abnormal stress response, neuroinflammation, and dysregulation mechanisms of monoamines and GABA, which leads to neuroinflammation. The later stage of this article constructively verifies the crosstalk between depression and the gut microbiota by exemplifying clinical investigations. Probiotics offer a variety of health advantages to their hosts, including the synthesis of vitamins, the downregulation of inflammatory responses, the induction of IgA secretion, the development of regulatory T cells, the generation of cytokines, and immune function modification. Therefore, a unique emphasis has been placed on the utilization of probiotics as a successful alternative treatment strategy for MDD based on their antioxidant and anti-inflammatory capabilities. To provide more evidence of the efficacy of probiotics or psychobiotics, precise attention has been given to several clinical trials involving patients with depression or major depressive disorder (MDD) who are receiving probiotic supplements. This discussion also addresses the potential difficulties encountered and proposes future tactics to address these limitations. Thus, this study thoroughly described a “single-platted” analysis of the relationships between probiotics and the gut microbiota and the yield of successful treatment techniques or probiotic-based delivery approaches for major depressive disorder (MDD) or depression.

Depression Pathogenesis of the Microbiota-Gut-Brain (MGB) Axis

Depression research is currently concentrating on the brain, the gut, the brain-gut and gut-brain axis, the microbiota-gut-brain axis, and other systems in addition to the mind. According to the gut microbiota hypothesis, dysbiota-gut-brain axis dysfunction is the fundamental etiology of depression. Abnormalities in the gut microbiota can also directly cause depression. Finally, the gut microbiota can affect behavior and mental health through the microbiota-gut-brain axis. The theory states that treating depression will includes regulating the gut microbiota and improving the microbiota-gut-brain axis [24]. In order to clarify the pathophysiology of depression along the microbiota-gut-brain (MGB) axis, consider the following mechanisms of interaction between the gut microbiome and nervous system: immune system, gut hormonal response, metabolism of serotonin and tryptophan, and short-chain fatty acids [25]. Moreover, the depression pathogenesis of the microbiota-gut-brain (MGB) axis is discussed in detail as follows:

Abnormal Stress Response

It is well established that life conditions with consistent stress might increase one’s risk of developing MDD. The HPA axis is well recognized as an essential mammalian stress response mechanism. Stress triggers the hypothalamus to release corticotropin-releasing hormone (CRH), which in turn causes the adrenal glands to release adrenocorticotropic hormone (ACTH) (ACH). Then, ACTH is secreted into the circulation to stimulate the adrenal cortex to release glucocorticoids (such as cortisol in humans and corticosterone in rats), which regulate the body’s stress response. In addition to affecting metabolism and the immune system, glucocorticoids can regulate glucocorticoid production by inhibiting negative feedback processes to stimulate the HPA axis and the secretion of CRH. Patients with melancholic MDD exhibited greater plasma cortisol levels when tested with dexamethasone (DEX, a glucocorticoid), and a subsequent approach (the DEX/CRH test) showed that these individuals had deficient negative feedback [26]. Therefore, MDD patients have consistently high blood cortisol levels, which causes inflammation and a significant reduction in BDNF levels in the brain. These effects are assumed to be responsible for the pathophysiology of MDD [27]. A recent study showed that cumulative HPA axis activity based on hair cortisol levels correlated increased cortisol levels with stress and associated signs of depression [28,29].

Furthermore, in a study on mice with stress-induced depression, the BDNF level in the brain decreased with increasing blood corticosterone to trigger inflammation in the prefrontal cortex and hippocampus [30,31]. Prolonged corticosterone treatment has been shown to have a comparable

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effect on rodents [32,33]. These results showed that deregulation of the stress response by the HPA axis influences the development and progression of depressive symptoms (hyperactivation of the HPA axis). Accumulating data suggest that the MGB axis is involved in modulation. It has been demonstrated that administering *Lactobacillus paracasei* and *Lactobacillus casei* strains to rats exposed to water activated a CRH-positive group of neurons involving the paraventricular nucleus in the brain, especially the hypothalamus, to reduce stress and stimulate the action of vagal afferents to block the stress-induced rise in blood corticosterone [34]. The study further suggested that sensory signals from the gastrointestinal environment (including probiotic therapy) be transmitted to the brain through vagal afferents, regulating the stress response [34].

Correlation between BDNF and Neurogenesis

Neurogenesis is sustained throughout life in the hippocampus, and BDNF contributes to changes in hippocampal volume associated with reduced neurogenesis [35,36]. Astrocytes, microglia, and nerve cells generate BDNF in different areas of the brain, which is required for nerve cell differentiation, survival, maintenance, and synaptic plasticity. Patients with MDD have been found to have lower serum, blood, and plasma levels of BDNF [37–39]. Structural imaging revealed that the serum levels of BDNF and hippocampal volume were lower in patients with major depressive disorder than in healthy controls [40,41]. Furthermore, selective serotonin reuptake inhibitor (SSRI) dosing increases BDNF levels in the hippocampus and neurogenesis while decreasing depressive behavior [42]. Human studies have shown that the restoration of reduced blood BDNF levels in MDD patients and improvements in related symptoms support this conclusion [43,44]. A variety of factors, including age, inflammation, and extreme stress, influence the amount of BDNF. Additionally, it has been suggested that the gut microbial flora is critical for regulating the BDNF level in the host. One of the bacteria-derived substances, butyrate, may link the control of BDNF in the brain to the gut microbiota. Short-chain fatty acids, in particular, play a vital role as biochemical mediators in the MGB axis. In addition, butyrate was shown to increase the level of BDNF in the hippocampus in mice and stimulate the production of BDNF in the hippocampus through the inhibition of histone deacetylases [45,46].

Neuroinflammation

Several inflammatory markers are present at higher levels in MDD patients, and attention has recently been given to the role of inflammation—both neuroinflammation and systemic inflammation—in depressive symptoms. Peripheral blood C-reactive protein (CRP) levels are greater in patients with MDD, particularly in treatment-resistant patients [47]. Plasma CRP is a peripheral biomarker that detects both peripheral and central inflammation. The plasma CRP concentration is strongly correlated with the Cerebrospinal fluid (CSF)-CRP concentration and indicates the severity of depression symptoms [48]. Microglia are essential for generating inflammatory cytokines in neuroinflammation. Further stimulation of microglia via Toll-like receptor 2 (TLR-2) and TLR-4 increases social aversion and anxiety in response to repeated social defeat stress [49].

Additionally, microglia have been linked to the etiology of MDD through peripheral lipopolysaccharide (LPS)-related inflammation. It has been demonstrated that astrocytes play a role in the pathophysiology of stress and depressive symptoms associated with LPS-induced inflammation [50,51]. In the context of the link between MDD and inflammation, the intestinal mucosa plays a substantial role in MDD onset. Intestinal luminal antigens/toxins enter the bloodstream, provoking systemic inflammation and depressive symptoms [52]. LPS and inflammatory cytokines also disrupt the blood-brain barrier [53,54]. Accordingly, they hypothesized that intestinal barrier disruption results in the inflow of intraluminal antigens and toxins, inflammatory cytokines, T cells, and macrophages into the brain and microglia and astrocyte activation.

Sleep Disorders

Sleep disturbances are recognized as a risk factor for the emergence of mental diseases (including MDD) and are related to them [55]. The microbiota-gut-brain axis may be a major factor in the etiology and pathophysiology of sleep disorders, as evidence suggests that it regulates sleep behavior both directly and indirectly. The gut microbiota become dysfunctional whenever sleep deprived, and sleep disorders are linked to changes in the makeup of the gut microbiota [56]. Studies on humans have shown that short sleepers vary from standard length sleepers in the microbial composition of their feces, for example, having more Pseudomonas in their feces [57]. Breslau *et al*. [58] evaluated the cross-sectional and prospective associations between sleep disruption and psychiatric disorders in a longitudinal epidemiological investigation on young adults. After considering the presence of other past depressive symptoms (such as psychomotor retardation or agitation, suicidal ideation), a history of insomnia persisted as a highly significant predictor of recurrent severe depression. They have revealed that if sleeplessness is reported for at least two weeks almost every night, it may serve as a good indicator of the probable onset of serious depression [58].

In a pilot study, Anderson *et al*. [59] established a link between gut microbiome composition, sleep quality, and cognitive flexibility in elderly people in excellent physical condition. Zhai *et al*. [60] reported that short and extended sleep durations were significantly linked to a greater risk of MDD in selected adults [60]. Vandekerckhove *et al*. [61] showed that sleeplessness is related to a link between feelings and sadness. These findings imply that insomnia might be a separate medical problem rather than a sign of depres-

sion. The gut microbiota has been proven to have an impact on sleep quality. In addition, Ogawa *et al*. [62] demonstrated that the decrease in the gut microbiota resulting from antibiotic use alters the architecture of sleep and wakefulness and affects the intestinal balance of neurotransmitters. Research on electroencephalogram data has revealed that probiotic supplementation can improve human sleep quality [63].

Metabolic Disorders

Metabolic diseases are frequently present in MDD patients, and depressive symptoms are frequently present in metabolic disorder patients [64]. Recent studies have shown that systemic chronic inflammation contributes to the development of obesity and type 2 diabetes, both of which are linked to intestinal mucosal barrier failure [65]. Additionally, patients with MDD have been found to have greater levels of hormones in the gut (ghrelin and leptin) [66]. These hormones (secreted by adipocytes and gastric endocrine cells) control appetite. Several studies have demonstrated that hormones influence brain processes from the digestive tract, including sleep, cognition, the reward system, and the stress response (HPA axis activity) [67,68].

Dysregulation Mechanism of Monoamines and Gamma-Aminobutyric Acid (GABA)

According to Gallopin *et al*. [69] monoamines play a role in mood status, emotion, appetite, arousal, motivation, anxiety, and the reward system. Changes in monoamine function in the nervous system can result in the development of depressive symptoms such as increased anxiety, decreased motivation, and anhedonia. Gamma-aminobutyric acid (GABA) has been explored as the key inhibitory neurotransmitter in the brains of patients with MDD at lower concentrations [70]. According to Mann *et al*. [71] MDD patients had lower GABA levels in their CSF than healthy controls. GABA neurons are broadly distributed throughout the brain and are involved in various processes, such as anxiety, motivation, and the reward system [72,73], which further play a significant role in reducing the symptoms of MDD.

Linkage between the Gut-Brain Axis (GBA) and Depression

Numerous studies have demonstrated that FMT treatment reduces depression symptoms in people with irritable bowel syndrome [74,75]. FMT is believed to improve gut and neuropsychiatric symptoms by restoring or reconstructing the gut microbiota. However, it is essential to consider the confounding bidirectional correlations between Irritable Bowel Syndrome (IBS) and MDD. A therapeutic strategy concentrating on the properties of particular bacteria has been applied to psychiatric illnesses, including MDD. The ability of probiotics, which are a butyrate-producing group of bacteria, to improve the pathophysiology of MDD through the MGB axis is described in this section (depicted in Fig. 2). Two critical mucus layers, along with one layer of epithelial cells, separate the gut bacteria from the body's immune cells [76,77], enabling immune system regulation [78,79]. They help the host by enhancing gut health and supplying nutrients such as vitamins [80–82], encouraging defense against invasion by pathogenic species, and providing energy for mowing [83,84]. Thus, dysbiosis—a pathological change in the gut microbiota makeup—can harm the host's health, ranging from chronic GI conditions to neuropsychiatric illnesses [85,86].

Microbiota Dysbiosis in Critical Depression

Depression is a severe neuropsychiatric condition that significantly reduces quality of life by causing chronic sadness and loss of interest over an extended period or repeatedly [87,88]. Typical symptoms include a decrease in attentiveness or enjoyment of previously pleasurable activities, libido, altered appetite, severe weight loss or gain, sleep problems, motor slowness, and repeated thoughts of death and guilt [89]. It is more prevalent than the worldwide population growth rate and affects approximately 4.4% of the world's population [90]. Despite the high incidence of depression and continual efforts to improve the abilities of healthcare professionals, this mental illness has still not been adequately identified and treated [91]. The necessity of early intervention is shown by the association between a delayed diagnosis followed by the treatment of depression and a lower treatment result [92]. Biochemical, genetic, and environmental variables contribute to depression development [93]. There are obvious links between the gut microbiome and abnormal CNS conditions (autism, schizophrenia, and ADD) [94]. Over the past ten years, there has been a growing body of evidence supporting the involvement of the gut microbiota in depression susceptibility, persistence, treatment, and resilience [95,96]. The disruption of the gut microbiota status by antibiotics led to a 20–50% increased possibility of depression [97]. An alteration in the amount and variety of microbiota in individuals with depression matched to healthy controls provides clinical proof to support the physiological functions of microbiota in depression (Table 1, Ref [98–104]). An analysis of fecal samples from MDD patients revealed elevated bacterial counts and a reduced Lachnospiraceae load. Depression can be a result rather than a reason for depression. Notably, depression can influence the variety of gut microbiota through signals from the CNS to the gut atmosphere, altering gastric motility and secretion in the stomach and intestines. The altered microbiota composition in the colon of an olfactory bulbectomy mouse model of depression may be caused by enhanced stress reaction activation and changes in colonic motility. Additionally, one of the main pathways from depression to gut microbiota dysbiosis is diet change in depression caused by the ingestion of very appetizing foods.

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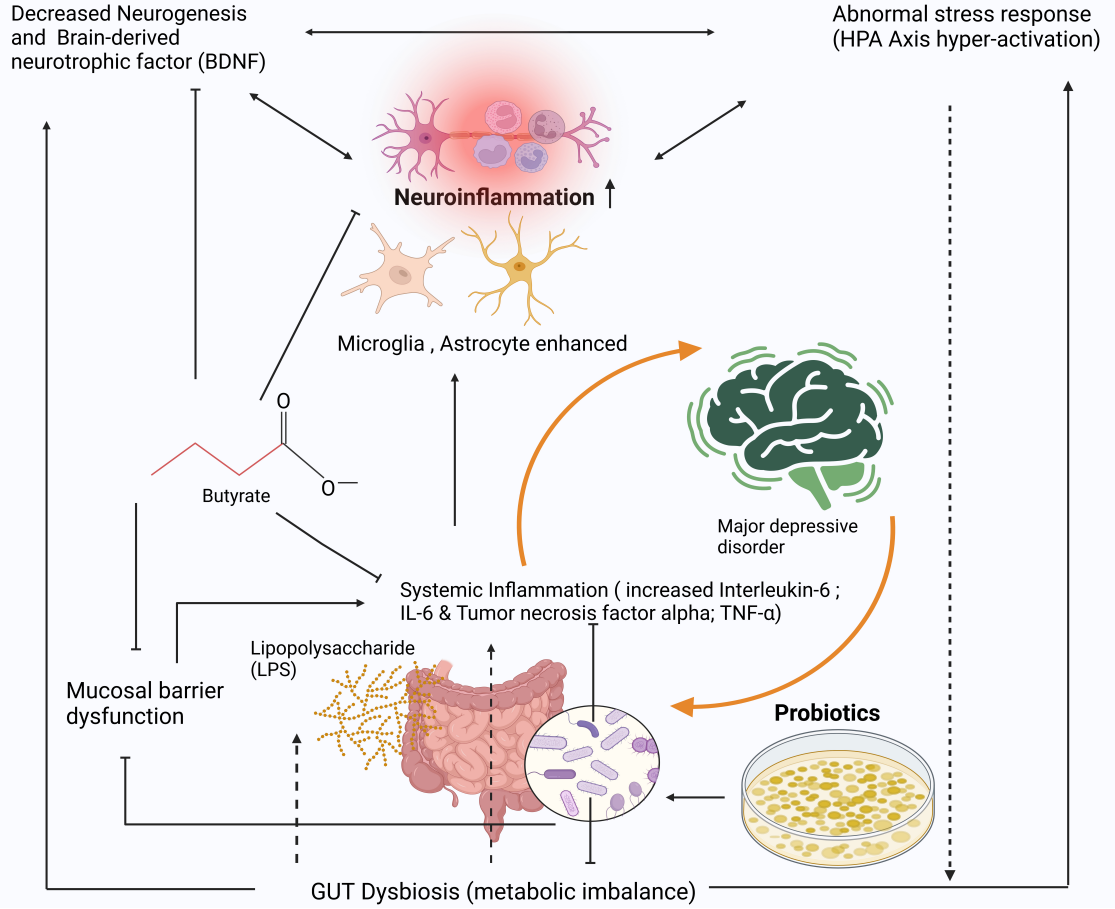

Fig. 2. Underlying mechanisms for major depressive disorder (MDD) via the gut-brain axis and the modulatory role of probiotics. Probiotics have a mechanism to overcome depressive mood disorders. Probiotics modulate the immune system, confer resistance to infections, and reduce the effects of inflammation and oxidative stress, thereby producing anti-inflammatory and antioxidant compounds. Probiotics and other gut commensal bacteria produce adequate amounts of amino acids and fatty acids essential for the synthesis of neurochemicals that are essential for the feeling of happiness and well-being in an individual. In addition, probiotics, created with Biorender (https://www.biorender.com/), produce certain bioactive molecules (peptides and hormones) that are structurally and functionally similar to those produced by hosts and thereby directly or indirectly regulate the host's behavior.

Gut-Microbiome-Brain Crosstalk in Depression

The gut bacteria can interact directly with the CNS, impacting immunological and endocrine functions and neurotransmission through vagal sensory nerve fibers [105]. Intestinal permeability (secretion and motility) is altered due to signaling molecules released from the enterochromaffin group of cells, specific neurons, and lamina propria immune cells. The CNS also indirectly or directly impacts the gut flora [106]. The digestive system is vulnerable to mental and physical stress [107]. The body is acutely threatened by stress [108]. Stress and its mediators negatively affect the physiological processes of the gastrointestinal tract and alter the release of neuroendocrine factors. This imbalance in the gut microbiome and weakened host immunity increase the susceptibility of the host to infections [109]. Low levels of inflammatory mediators, such as cytokines (interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)), and hormones, sustained neuronal configuration, synaptic modeling, memory alliance, neurogenesis, and facilitated signaling between brain cells and other associated immune cells. Additionally, infections, trauma, and stress boost systemic inflammatory cytokines, which subsequently cause microglia to become activated and produce inflammatory mediators such as prostaglandins, cytokines, and critical reactive oxygen species (ROS) inside the CNS, resulting in gradual neuronal damage [110]. Inflammatory cytokines and ROS generated due to viral contamination and lipopolysaccharide derived from gram-negative bacteria such as Neisseria meningitidis and Haemophilus influenzae cause progressive neuronal damage that eventually results in depression and other neurological diseases [111]. Furthermore, this finding is reinforced by another study showing how oxidative stress affects individuals with severe depression [112]. Reduced amounts of three polyunsaturated fatty acids in the plasma of depressive patients have also been documented. High plasma levels of antiox-

idants such as glutathione, coenzyme Q10, and critical vitamins (A, B, C and E) cause increased oxidative and nitrosative stress. The cumulative effect of all these elements creates a cycle, and the recurrent flow of this cycle causes severe psychological problems. The number of nutrients and the functional foods consumed affect not only the gut microbiome composition but also the release of gut peptides (such as leptin, cholecystokinin, gastrin, and peptide tyrosine tyrosine (PYY), which in turn alter hormone responses [113]. When piglets were given the probiotic Pediococcus acidilactici [114], the submucosal plexus ganglia in the ileum had more galanin and calcitonin genelinked peptide immune reactive neurons than did the controls. Additionally, the impact of a synbiotic mixture comprising inulin, Bifidobacterium lactis, Lactobacillus delbrueckii subsp. rhamnosus, and both the portal plasma levels of neuropeptide Y and peptide YY were evaluated.

Myths and Mysteries of Probiotics

In 1953, the term probiotic was coined for the first time from the Greek or Latin word "pro", and the Greek word "bios" indicates the "meaning of life" [115]. Several live bacteria that enhance well-being are referred to as probiotics. Probiotics offer a variety of health advantages to their hosts, including the synthesis of vitamins, the downregulation of inflammatory responses, the induction of IgA secretion, the development of regulatory T cells, the generation of cytokines, and immune function modification [116,117]. It should be emphasized that probiotics frequently have species- and strain-specific health advantages. Prebiotics are "nondigestible" food components that favorably impact the host by selectively boosting the proliferation and/or activity of one or a restricted number of bacteria already present in the colon. Synbiotics are defined as prebiotics and probiotics blended into a single product. Probiotics are commonly produced from bacteria such as *Bacillus*, *Lactobacillus*, *Bifidobacterium*, *Streptococcus*, *Enterococcus*, *Escherichia*, and fungal strains such as *Saccharomyces* [118]. Hence, a comprehensive summary of the various aspects of probiotic therapy for MDD, including its anti-inflammatory effects, antioxidant effects, lipid metabolism, microbial colonization, and epithelial penetrability, is essential to fully comprehend probiotics and their efficacy in both animal and clinical contexts. This section comprehensively summarizes the mechanisms involved in the successful treatment of MDDs with probiotics.

Probiotics and Depression

A study including 47 volunteers revealed bacterial load-producing lactic acid alterations due to probiotic supplementation. Four weeks later, a follow-up revealed that these levels had decreased. This study suggested that probiotics can boost the effects of antidepressants and aid in alleviating depression. However, this brain activity returned to normal in the probiotic group following a four-week treatment but not in the placebo group [119,120]. Compared to those without depression, patients with depression have significant variations in the composition of their gut flora [121]. The rats were colonized with depressive-like symptoms. Depression lacks a particular "dysbiosis" characteristic. Numerous studies have investigated the impact of probiotics on mood. The majority of them involved subjects without properly diagnosed depressive disorders or healthy people. The use of probiotics for improving mood is currently supported by several meta-analyses [122,123]. In 2016, 40 people with major depressive disorder (MDD) were treated with probiotics [124]. The 20 patients in the active interpolation group had significantly lower Beck Depression Inventory (BDI) scores at the end of 8 weeks than did those in the placebo group. A total of 110 participants were enrolled in a different randomized controlled trials (RCT) by Kazemi *et al*. [5] of whom 36 received a probiotic, 38 a placebo, and 35 a prebiotic [125]. Compared with the placebo and probiotic supplementation groups, the probiotic group demonstrated a significantly lower BDI score after 8 weeks of supplementation. An RCT revealed a substantial decrease in depression scores but not in anxiety scores [126]. The present study revealed that 22 patients who received Bifidobacterium longum underwent a 6-week treatment, whereas 22 individuals who received a placebo did. In the most recent trial by Chahwan *et al*. [17] an 8-week probiotic intervention with many strains had no discernible impact on depression symptoms [127]. However, none of these investigations profiled the patients' gut flora before and after probiotic administration. These investigations also revealed variations in strains and treatment lengths (ranging from 6 to 13 weeks). Two of the five studies utilized single strains, such as *Bifidobacterium longum* and *Bacillus coagulans*, whereas three of the five investigations combined *Lactobacillus* and *Bifidobacterium* species.

Utilizing Probiotics for the Treatment, Management, and Prevention of Depressive Mood Disorders

Several psychological and pharmaceutical therapeutic approaches have addressed the exhaustive prevention and cure of depressive mood disorders. Therapeutic drugs are superior, with an elevated risk of side effects and a low success rate [128]. Combination therapy has become a common practice to fill the gaps in current therapies and obtain better results [129]. To combat depressive mood disorders, the scientific community is searching for practical, affordable, and safe therapeutic options. Probiotics may be helpful in this situation as a secure and all-natural adjuvant therapy technique in conjunction with current medicines to lessen the burden on depressed individuals. Additionally, commensal and probiotic bacteria may help modify the communication between the host's gut microbes and the brain [105].

Table 1. Clinical Investigations Examining the Relationship between Fecal Microbiota and Depression in Human.

Samples Types	Total (patients/controls)	Mean of Age (years ± SD)	Limitations/notes	References
Fecal	Total: 55 Controls: 18 Patients: 37	Controls: 46.1 ± 13.9 Patients: 49.2 ± 13.9	The paucity of information regarding the individuals' eating habits A small cohort that could have unintended consequences	[98,99]
Fecal	Total: 76 Controls: 30 Responded-MDD: 17 Active-MDD: 29	Controls: 26.8 ± 5.4 Responded- MDD: 27.1 ± 5.4 Patients: Active-MDD: 25.3 ± 5.4	Insufficient information concerning the food habits of participants Probable effects of atypical antipsychotic drugs. To determine the microbiome's usefulness as a biomarker, more research is necessary	[100]
Fecal	Total: 121 Controls: 63 Treated-MDD: 19 Drug-naïve MDD: 39	Controls: 41.8 ± 12.3 Patients: 40.6 ± 11.7	There has been no investigation into additional mental conditions with MDD-like clinical manifestations Possibility of biases in microbial phenotypes due to ethnic and site-specific factors	[101]
Fecal	Total: 100 Controls: 57 Patients: 43	Controls: 42.8 ± 12.7 Patients: 39.4 ± 10.0	Investigated only Lactobacillus and Bifidobacterium Antidepressant medications' additional effects	[102]
Fecal	Total: 20 Controls: 10 Patients: 10	Controls: 39.6 ± 9.0 Patients: 43.9 ± 13.8	A small size sample, no detailed information on diet and alcohol intake, Antidepressant medication side effects	[103]
Fecal	Total: 73 Controls: 37 Patients: 36	Controls: 41.19 ± 12.73 Patients: 45.83 ± 14.08	A cross-sectional study design without a connection between changes in the microbiome and depression. A modest sample size that did not generate reliable cluster analysis findings was utilized to examine the impact of eating habits on microbiota compositions	[104]

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Pathogen Exclusion and Probiotics Have Anti-Inflammatory Effects on Reducing Depression

By preventing and displacing pathogen adherence, competing with pathogens for receptors present on epithelial cells through colonization, creating antibacterial metabolites, and fortifying the intestinal barrier, probiotics are known to control gut health [130]. Additionally, probiotics prevent enteric infections by lowering the luminal pH and encouraging epithelial cells to produce defensins [131]. To support this, an *in vitro* study employing the C2Bbe1 epithelial cell model examined the effects of the Lactobacillus and Bifidobacterium classes on *L. monocytogenes* septicity and mucosal immune reactions. In the present study, *Listeria monocytogenes* were inhibited by an unidentified secretory protein and an acid generated by Lactobacillus sp., as opposed to Bifidobacterium. Additionally, probiotic therapy of epithelial cells before *Listeria monocytogenes* infection dramatically inhibited IL-8 secretion while increasing IL-10 secretion [132]. Another study employing Caco-2 cell lines revealed that *Lactobacillus acidophilus* strains and *Streptococcus thermophilus* species dramatically reduced invasive adhesion and physiological disturbance caused by *Escherichia coli* [133]. These results demonstrate the impact of probiotic bacteria on host mucosal immunity and pathogen exclusion. Probiotics have also been shown to interfere with the transduction pathway of signals in pathogens, which inhibits the expression of pathogenic genes and proteins. Probiotics have been shown to influence host immunity through Toll-like receptors on eukaryotic lymphoid, endothelial, and epithelial cells [134]. Probiotics also create cytokine antagonists that maintain an essential balance in the pro- and anti-inflammatory cascades [135].

Importance of Early Microbial Colonization and Metabolites

Microbes have evolved organizations for sensing signals associated with the host, including hormones, as they have coexisted with their eukaryotic hosts for a very long time. Bacteria and their vertebrate hosts can communicate by sending signals or producing metabolites. In addition, host signals enable bacteria to start expressing the genes necessary for their endurance in the host environment. The proliferation of advantageous bacteria in the intestine depends upon the production of various neurochemicals that are organizationally and functionally related to those generated by the host, such as serotonin, catecholamines, GABA, and acetylcholine [136]. Some peptides and neuroactive mediators produced by bacteria indirectly affect host behavior by promoting the production and release of neuroactive molecules by gut epithelial cells. Knowledge of microbial endocrinology has aided in advancing probiotic treatments for depression and other composite CNS diseases. Probiotics and some helpful commensal bacteria colonizing the gut and the beginning of signaling pathways acting on neural pathways engaged in motor control and anxious behavior may aid in the initial postnatal growth of the enteric nervous system [137]. Early development of the gut-microbiome-brain axis protects serotonin levels and provides adult tolerance to depression [138].

Role of Probiotics in Lipid Metabolism to Control Depression

The gut microbiota improved the metabolism of essential lipids and proteins, decreased the production of immunogenic peptides, increased the accessibility of amino acids and fatty acids, and improved the absorption and feeding of the pathways that produce neurochemicals [139]. Probiotic bacteria alter the fatty acid profile of the brain to change metabolic rates and the membrane lipid composition to alter the host's neuronal sensitivity and neurotransmission. These effects are strain-specific and affect the lipids and fatty acid conformation of the brain [140]. Furthermore, bacteria such as Lactobacillus strains and Bifidobacterium species are known to produce conjugated linoleic and linolenic polyunsaturated fatty acids (PUFAs) and short-chain fatty acids (acetic, butyric, and propionic acids). These fatty acids are crucial for brain development and cognitive function. They are also believed to lessen the impact of inflammation [141,142]. Butyrate and propionate are more effective anti-inflammatory compounds than acetate, whereas acetate is the primary substrate for cholesterol synthesis [143]. Omega-3 polyunsaturated fatty acids, in particular, are crucial for neurogenesis and cognitive function [144]. A sufficient intake of PUFAs increases learning behavior and provides resistance to potential neurotoxins such as triethyl lead [145].

Antioxidant Properties of Probiotics

Several researchers have recently commenced to utilize the different beneficial features of probiotics due to increasing interest in the use of probiotics as primary functional foods as well as nutraceuticals [146]. Due to its essential function in managing oxidative stress-induced aging diseases and mood disorders, its antioxidant properties have garnered increasing attention [147]. Stress produces reactive oxygen and nitrogen species, which damage cells and eventually lead to cell death. Furthermore, tissue cultures from people with significant depression were used to study oxidative stress and the associated glutathione response. This provides proof that major depressive illness is linked to elevated peripheral oxidative stress indicators [148]. Oxidative stress in cells can be reduced by using antioxidant defense mechanisms such as ROS scavenging, preventing ROS generation, eliminating oxygen, and binding to metal ions that promote the generation of ROS [149]. It has been revealed that probiotics exhibit an antioxidant defense mechanism involving vitamins, bioactive peptides, and several enzymes with antioxidant potential. Lactobacillus species, i.e., Lactococcus, Bifidobacterium, and *Streptococcus thermophilus*, possess potential antioxidant properties in both *in vitro* and *in vivo* studies.

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This is further established in an *in vitro* assay for antioxidant enzymes such as superoxide dismutase (SOD), Trolox equivalent antioxidant capacity (TEAC), and intracellular glutathione (TGSH). The study's findings revealed that *Bifidobacterium animalis subsp*. lactis and Lactobacillus (compared to the oxidation of ascorbic and linolenic acid, TGSH, and TEAC values) had significantly greater antioxidant activity than the lactic acid species. This finding suggested that the antioxidative effect of these strains is strain-specific at 108 colony forming unit (CFU)/day for 18 days of probiotic treatment, resulting in a substantial reduction in doxorubicin-induced oxidative stress in the rats [150]. Another study explained how innate cereal proteins are proteolyzed by sourdough during fermentation to produce peptides with antioxidant potential [151]. Additionally, lactic acid bacteria such as *Lactobacillus plantarum*, *Leuconostoc sp*., *Streptococcus thermophilus*, and a few yeasts have been shown to yield large amounts of carotenoids and folate, as well as enzymes such as glutathione reductase and superoxide dismutase, which make up the antioxidant defense response [152]. Therefore, fermented dairy products and vegetables are significant sources of antioxidants, and consuming them may be helpful as an adjuvant remedy for the treatment of depression and associated psychiatric disorders.

Role of Probiotics in Sustaining Intestinal Epithelial Penetrability in Depression

Generally, stress causes intestinal inflammation, increases the possibility of pathogenic infections, impairs intestinal barrier integrity, and increases epithelial permeability. It has been established that viruses, bacterial pathogens, and parasites in the body affect intestinal tight junction configuration and permeability [153]. Intestinal homeostasis is harmed by increased permeability, which enables the rearrangement of luminal antigens, inflammatory mediators, and toxins. TNF- and IFN-like inflammatory cytokines increase intestinal tight junction penetrability by decreasing Zonula occludens I protein genetic expression and increasing Nuclear factor kappa B (NF-κB) dependent myosin light chain kinase-based tight junctions (TJ) barrier opening. Therefore, maintaining gastrointestinal health and mitigating the consequences of stress-mediated pathogenesis in people with depressive mood disorders depend significantly on the management of intestinal tight junctions and membrane permeability. Additionally, probiotics enhance the integrity of the intestinal barrier by regulating TJ proteins. The cellular membranes of neighboring epithelial cells contain TJ proteins, which fuse to the TJs of transepithelial cells [154]. Additionally, it was found that probiotic bacteria increased the transcription of TJ proteins, predominantly occludin and Zonula occludens I, while decreasing the expression of the pore-forming protein claudin-2, indicating that probiotics could directly maintain intestinal permeability and TJ configuration at the transcriptional stage [155,156]. Additionally, it was discovered that probiotic bacteria increased the expression of TJ proteins, specifically occludin and Zonula occludens I, while decreasing the expression of the pore-forming protein claudin-2, indicating that probiotics could directly sustain intestinal permeability and TJ integrity at the transcriptional level [157]. In one study, the effect of living bacterial cells on intestinal permeability varied from strain to strain [158]. In contrast, in additional research, heat-killed Enterococcus hirae reduced TNF-induced TJ barrier damage via TLR-2 signaling. This finding suggested that the cell wall constituents of E. hirae contribute to improving the epithelial TJ barrier [159].

Probiotic Bacteria as Psychobiotics in Depression

The effectiveness of therapeutic approaches for treating depression needs further improvement. Only a small proportion of individuals with MDD opt for antidepressant treatment, and most of them experience no response, slow or limited progress, or persistent symptoms [160,161]. Due to a growing awareness of the cross-communication between the gut and the brain, probiotics are currently being intensively researched for their psychological modulatory qualities. Probiotics, ingested in the right amounts, provide favorable mental benefits in patients with psychopathological diseases (psychobiotics). Psychobiotics alter emotional, cognitive, and neurological factors by affecting host-brain links and acting as antidepressants [162]. Probiotics can affect behavior, brain function, and development through their action on the MGB axis. Through dynamic MGB interactions, psychobiotics can boost the host's mental health [163]. Probiotic supplements may have antidepressant effects by normalizing physiological outputs linked to depression, including corticosterone, noradrenaline, BDNF, and immunological function, according to a growing body of research. We have discussed current developments in the use of probiotics in depression-related illnesses to determine whether probiotics have this potential. Therefore, these developments will offer new therapeutic alternatives for comorbid disorders associated with depression. A solid basis for therapeutic application has been established by the encouraging advantages of probiotics in depression, as demonstrated by both *in vitro* and *in vivo* investigations [164,165]. Table 2 Ref. [166–181]) lists a few probiotic microbes that have been studied for their potential to reduce anxiety or depression. By lowering oxidative stress, modifying the cytokine milieu to mitigate the levels of proinflammatory factors such as cytokines, and/or changing brain hormones or neurotrophic factors, psychobiotics lessen anxiety, depression, and neurodegeneration in hosts. Additionally, the mode of action of psychobiotics varies depending on the strain, with different strains of the same species having different mechanisms for lowering psychological stress [166]. Table 2 describes the role of psychobiotics in relieving depression and various comorbid disorders [167–182].

Table 2. The role of probiotics in relieving depression and various comorbid disorders.

Name of Probiotic(s)	Disease Condition	Duration and Dosage of Study	Conclusion	References
L. acidophilus, *L. fermentum*, and *B. lactis* in water for drinking	Noise stress to male Wistar rats progeny exposed throughout the final pregnant trimester	One milliliter of solution per day comprising 10^{10} colony forming unit (CFU)/g	Enhancement of the behavioral responsiveness and decreased corticosterone serum levels	[167]
Faecalibacteriumprausnitzii	Mild stressors exposed to Sprague–Dawley rats	Total for four weeks, 1×10^9 CFU/mL	Showed antidepressant antianxiety-like effects and increased IL-10, IL-6, Short-chain fatty acids (SCFAs), and corticosterone concentration	[168]
Ecologic obstacle *L. acidophilus* W37, *B. lactis* W52, *B. lactis* W51, and *B. bifidum* W23.	Clinical trial study in patients with depression	Powder blend maize-starch, maltodextrins comprising 1×10^{10} CFU every day for eight weeks	Depressive symptoms did not significantly decrease from the placebo group.	[169]
Bifidobacterium breve A-1	Clinical trial study in Schizophrenic outpatients, having anxiety and associated depression	Sachet comprising B. breve A-1 dried in the freezer at 5×10^{10} CFU.	Reduced anxiety and depression symptoms in patients with schizophrenia IL-22 & tumor necrosis factor (TNF)-associated cytokine generated through activation levels rising	[170]
Lactoflorene Plus (10 milliliters of liquid combination)	Clinical study in wellness volunteers having self-reported stress in the mind	45 days at 2 billion CFU/10 mL of therapy	Enhanced integrity of the intestinal barrier through an increase in IgA and IL-10 production.	[171]
B. longum 0175, *L. rhamnosus* R0011, and *L. helveticus* R0052 in addition to prebiotics (galactooligosaccharides and galactomannan)	Healthy human volunteer with mild psychological stress	4 weeks	Mood improvement in depressed individuals; shift in the configuration of the gut's microbial community in favor of Lactobacillus and Bifidobacterium	[166]
B. lactis, *B. longum*, *B. bifidum*, and *L. acidophilus* + *sertraline*	Patients with generalized anxiety disorder (GAD) participated in a double-blind, randomized, placebo-controlled study.	18×10^8 CFU eight weeks	Fewer signs of anxiousness compared to taking sertraline alone yourself	[172]
Lactobacillus reuteri	C57BL/6 mice developed anxiety due to the drug ampicillin.	2×10^8 CFU in mice alongside 1% dextrose in a single dose for 5 days	Reduced Nuclear factor kappa B (NF-κB), anxiousness, and elevated hippocampus BDNF level and restored gut dysbiosis	[173]

Table 2. Continued.

Name of Probiotic(s)	Disease Condition	Duration and Dosage of Study	Conclusion	References
Reuptake of Serotonin inhibitors alongside *Lactobacillus plantarum* 299	Signs of clinical depression among individuals	10×10^9 CFU/capsule for four weeks, two capsules daily	Reduced Quinureenine level and enhanced in psychological functions	[174]
ERGYPHILUS plus In addition, having *L. casei* and *L. rhamnosus* GG	Randomized controlled trials (RCT) double- in 40 fibromyalgia patients	4 pills a day first, for 4 weeks (Thirty minutes before for dinner and morning) then in the gap of 3 weeks	No reduction in the feelings of depression or anxiety, despite improvements in cognition	[175]
Bifidobacterium longum NCC3001	Patients with Irritable Bowel Syndrome (IBS) and moderate depression	Patients had been directed, to solubilize 1 g of B. longum in milk (100–200 mL).	Amygdala & the frontal limbic responses to stressful or depressant stimuli were impacted physiologically by the relief of depression symptoms but not by changes in the anxiety state	[176]
Lacidofil with a 95:5 ratio made up of *L. rhamnosus* R0011 and *L. helveticus* R0052	Rats from Sprague–Dawley strained from birth by maternal separation	Lacidofil, a probiotic, was reconstituted in distilled water with 10^9 CFU/millimeter	Induction of a normal developmental trajectory and protection from early life stress in mentally stressed rat newborns	[177]
Capsule comprising *Bifidobacterium bifidum*; *Lactobacillus acidophilus*; *Lactobacillus casei*	Patients with MDD	1 capsule/day comprising 2×10^9 CFU/g in all strains for 8 weeks	Beck Depression Index scores have decreased, indicating an improvement in depression symptoms.	[178]
Lactobacillus plantarum (strain PS128)	Early-life stressed C57BL/6J mice exhibit symptoms of anxiety and sadness	5×10^9 CFU/mL for a period of four weeks in saline	Reduction of depression brought on by early life stress reduced amounts of corticosterone	[179]
Lactobacillus helveticus strain R0052 and *Bifidobacterium longum* R0175	Stress-induced groups of male Wistar rats & stressed human volunteers	3 billion CFU for 30 days (1.5 gm per stick)	Less stress on the brain and, reduced urinary free cortisol in rats and human subjects	[180,181].

Table 3. Probiotics in animal and human studies on depressive disorder models.

Animal Model	Probiotic	Dosage, Administration Method, and Treatment Duration	Outcome	References
Stress model caused by corticosterone in healthy male Sprague Dawley adolescent groups (N = 10/group)	*Lactobacillus plantarum* DP189	21-day oral gavage of 1.0×10^9 CFU/0.2 mL/day	Decreased the level of pro-inflammatory mediators like cytokines (IL-1β and TNF-α), increased expression of Bcl-2, an antiapoptotic protein, and improved memory and spatial learning	[182]
Swiss mice (male), N = 16/Group	*Lactobacillus plantarum* 286 and *Lactobacillus plantarum* 81	30 days, oral gavage of L. plantarum 286: In dose of 10^9 CFU/0.1 mL/Day	Decreased anxiety- & depression- behavior	[183]
Depression model caused by corticosterone in adolescent male C57BL/6J mice (n = 8 per group)	*Lactobacillus paracasei* PS23 live or heat-killed	40-day, oral gavage of 10^8 CFU/0.2 mL/day	Upregulated glucocorticoid and mineralocorticoid receptors and reduced symptoms of anxiety and hopelessness.	[184]
Adolescent male Wistar rats were used in groups to study prolonged random moderate stress (N = 19/Group)	*Lactobacillus rhamnosus* JB-1 (LR- JB1™)	4 weeks, oral gavage of 1.7×10^9 CFU/0.2 mL/day	Decreased stress-induced behavior and increased glutamate, total N-acetyl aspartate, and total creatine	[185]
Chronic control stress, male teenage mice ICR, with 12 mice per group	*Bifidobacterium adolescentis*	21 days, oral gavages of 0.25×10^9 CFU/kg	Decreased depression- and anxiety-like behaviors, inflammatory cytokines, and increased hippocampus BDNF expression	[186]
Human model				
Ten patients exhibiting an active MDD episode, open-label exploratory investigation	*Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175 (CEREBIOME®)	8th weeks, 3×10^9 CFU/day	Decreased depressive symptoms, anxiety, and improvement in sleep quality and overall mood	[187]
60 patients along with MDD, probiotic group (N = 30), placebo group (N = 30), followed by a double-blind, randomized study	*Lactobacillus plantarum* 299v Sanprobi IBS®	8th weeks of 10×10^9 CFU × 2/day	Improved cognitive functions and kynurenine	[115]
40 patients identified with MDD with IBS, probiotic group (N = 20), placebo group (N = 20), randomized, multicenter, pilot clinical study	*Bacillus coagulans* MTCC 5856	90 days of 2×10^9 CFU/day	Improved sleep quality and decreased myeloperoxidase, IBS, and depression clinical symptoms	[115]

Table 4. Clinical trials involving probiotic supplementation in patients with depression.

Sample size (Intervention (INT)/Placebo (PL))	Study groups and duration	A change in the INT group	Limitations of study	References
Petrochemical workers: with 70 INT (1:25)	The study was conducted for 6 weeks. INT 1 was subjected to a 100 g/day mixture of probiotic yogurt (comprising *Lactobacillus acidophilus* LA5 and strains of *Bifidobacterium lactis*) and one placebo capsule as adjunct therapy.	Increase in GHQ in INT 1 and INT 2, and reduction of DASS scores in INT 1 & 2	There was no evaluation of the pace at which probiotics generated short-chain fatty acids in the gut, a short intervention	[188]
Sample of pregnant state of women with 14–16 weeks gestation: 423 INT: 212 PL: 211	The investigation was accomplished till 6 months postpartum in case of breastfeeding. Further, INT received *Lactobacillus rhamnosus* HN001 with a daily dose of 6×10^9 CFU.	(↓) Anxiety & depression levels in EPDS with STAI6 reduced clinically significant anxiety symptoms	The EPDS with STAI6 were screening instruments, not diagnostic, for postpartum depression and anxiety. Retrospective data collection was used, and neither the STAI6 nor the EPDS have been validated using items that were asked in the past tense	[189]
MDD: (110 INT and 1: 38 INT) with 2: 36 PL: 36	The research was completed in 8 weeks. In addition, INT 1 obtained a probiotic composition using *Bifidobacterium longum* longum and *Lactobacillus helveticus* R0052.	(↓) BDI level on INT 1 as compared to PL, Reduced Kynurenine/tryptophan ratio compared to PL, (↓) Tryptophan/BCAAs ratio in INT 2 compared to PL	The intervention was carried out throughout the year, No control over dietary modifications, lifestyle changes, vitamin D levels, etc., various types of antidepressants	[5]
MDD: (10 INT:10)	The research was completed for 8 weeks, INT 1 was subjected probiotic supplement containing *Bifidobacterium longum* R0175 & *Lactobacillus helveticus* R0052 (3×10^9 CFU dose per day).	The PSQI measures the quality of sleep, and higher values for MADRS, QIDS-SR16 and SHAPS, GAD-7, and STAI indicate higher sleep quality.	There were few participants, an open-label approach, no placebo, and less generalizability of the findings	[186]
Older adults: (249)	The study was accomplished for the duration of 12 weeks then INT received formulation of *Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175.	GSRS, depression, or anxiety ratings remain unchanged.	There is a chance that study participants with IBS were included	[104]
INT: 125 PL: 124.	*Lactobacillus reuteri* rhamnose, galactooligosaccharide and maltodextrin.	Levels remain Unchanged (PSS scores), No variation in bowel frequency, No variations in biomarker concentrations	The sensitivity may have been improved with the addition of a second, with improved sensitivity, such as the ROME III symptom assessment criteria, using a small amount of *Lactobacillus reuteri*	[104]
Subjects possessing low mood: (79 INT: 40 PL: 39)	The research was conducted for 8 weeks. (INT-subjected product comprising a mixture of *Lactobacillus helveticus* R0052 & *Bifidobacterium longum*) + xylitol, maltodextrin.	There was no significant alteration in MADRS, GAF, and DASS, also there was no difference in the levels of the biomarker.	No assessment of BMI, total body fat, daily dietary intake, and required physical activity	[16]
MDD: (60 INT: 30 PL: 30)	The research was accomplished for 8 weeks. Furthermore, INT and PL received SSRI therapy during the whole course study. INT received daily 2 capsules containing 10×10^9 CFU of stains of Lactobacillus Plantarum or whole course of study.	No significant change in levels of HAM-D 17 and SCL-90. Furthermore, work speed in APT and CVLT total recall were both enhanced, and reduction of Kynurenine concentration	Intestinal permeability measures, QUIN, and vitamin B levels were not taken, and the sample size was modest	[190]

Abbreviation: BDI, Beck Depression Inventory; APT, Attention and Perceptivity Test; DASS, Depression Anxiety Stress Scale; EPDS, Edinburgh Postnatal Depression Scale; GAF, Global Assessment of Functioning; GHQ, General Health Questionnaire; GSRS, the rating scale for gastrointestinal symptoms; HAM-D, the depression Hamilton rating scale; PSS, Perceived Stress Scale; MADRS, Montgomery–Asberg Depression Rating Scale; SCL, Symptom Checklist; QIDS, Quick Inventory of Depressive Symptomatology; STAI, State-Trait Anxiety Inventory; STAI6, State-Trait Anxiety Inventory 6 item version; SSRI, selective serotonin reuptake inhibitor.

Probiotic Studies: Animals and Humans

Research has demonstrated that adding probiotic bacteria to one's diet can help prevent and treat depression by increasing the levels of neurotransmitters in brain tissues (Table 3, Ref. [115,182–187]).

Probiotics in Clinical Trials for Depression

The role of probiotics in the management of depressive behaviors has been increasingly investigated in preclinical studies and clinical trials. There is substantial evidence in rodents that probiotics reduce depression-like behaviors. By lowering rumination and violent thoughts, multispecies probiotics were capable of lessening the cognitive response to depressive moods in healthy people. There are inadequate clinical data on the use of probiotics for the management of depression despite preclinical systematic experimental studies suggesting that the modulation of the internal gut microbiota through probiotics may offer antidepressant and anxiolytic effects. Notably, several probiotic trials did not demonstrate a reduction in depression or proinflammatory biological markers. Given our discussion of the reciprocal relationships among the microbiota, inflammation, and depression, researchers believe that the beneficial effects of probiotics may be mediated by alterations in the body's immune system response. Clinical investigations in people with depression are often necessary to thoroughly analyze their effects on numerous clinical diagnoses and related inflammatory biomarkers (further summarized in Table 4, Ref. [5,16,104,186,188–190]).

Future Cross-Talk

In regard to worldwide health issues to lessen the burden of this situation, the need for more significant management of such depression appears to always be at the top of the list. In 1910, Dr. George Porter discovered that gelatin and a mixture containing microorganisms could produce lactic acid to reduce depression-linked symptoms in the case of melancholic adults [190]. A more precise understanding of MDD and gut microbiome pathophysiology can offer better insights into other neuropsychiatric illnesses. The probiotics that comprise the gut microbiota and their byproducts, particularly Short-chain fatty acids (SCFAs) such as butyrate, are crucial for preserving host homeostasis. Some probiotic strains reduce stress-related neuronal activation and stimulate vagal afferents, which then relay the stimulus to the brain [104]. To identify bacterial components that affect host cells and determine the precise mechanisms underlying their activity, it is anticipated that the mechanisms involving host cellular sensors can be used to identify bacterial constituents and trigger signal transduction. The substantial correlation between microbiome dysbiosis and depression may open the door to improving patient phenotyping for treatment selection and diagnostic accuracy [188]. Additionally, altering the composition of the gut microbiota can improve the overall treatment and prevention of such incidences of depression and provide a crucial plan in psychiatry through nutritional therapies and prebiotic or probiotic supplements [190].

Conclusion

The modification or conversion of the gut microbiota could be a promising approach for alleviating the behavioral symptoms linked to depression and other neuropsychiatric disorders due to the significant association between the gut microbiota and the underlying mechanisms of depressive disorder or depression. Stimulation of the synthesis of inflammatory chemicals and metabolites by pathogenic bacteria alters brain function, resulting in depression, intense anxiety, and several related symptoms of mood disorders. Probiotics, which are beneficial bacteria, can indirectly help the central nervous system by generating anti-inflammatory substances and metabolites, including SCFAs, serotonin, antioxidants, and GABA. These compounds can further improve brain function, memory, and behavior. For the treatment and prevention of depression, it may be advisable to use live probiotic formulations or drugs that contain the metabolic products of probiotics. Probiotics that contain lactic acid strains of bacteria found in fermented dairy products such as yogurt, cheese, processed vegetables and fruits, cereal beverages produced through fermentation, and food made with sourdough provide adequate protection against depressive and anxious symptoms associated with mood disorders caused by both psychiatric and nonpsychiatric factors. Probiotics are beneficial for addressing metabolic disorders, pathogenic infections, nutritional deficiencies, and malabsorption. However, their usage may be limited due to the requirement for ongoing replenishment. Although several clinical trials have provided evidence for the effectiveness of these probiotics in treating mood disorders, there are currently no specific probiotic products available on the market that are specifically available for mental health. Therefore, there is an urgent demand for probiotic-based preparations to address mental health issues. Furthermore, future studies must prioritize safeguarding biologically unaltered probiotics. Consequently, it is worthwhile to investigate innovative delivery system methods that can enhance the transportation and accessibility of stable probiotics within biological systems, thereby improving their bioavailability.

Availability of Data and Materials

Not applicable.

Author Contributions

SA: Conceptualization, Writing-review & editing. MF: Conceptualization, Writing-original draft. MB, NK

and PK: Investigation, Methodology, Writing-original draft. SGh, SM and SGa: Data curation. NK: Software. PK: Writing-review & editing. SM: Writing-review & editing. BHJG, QSZ, RS and MNK: Validation, Visualization. SGh: Software. QSZ: Project administration. RS: Resources. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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