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Review Article

Exploring The Therapeutic Potential Of Probiotics In Depression: Insights From The Microbiota-Gut-Brain Axis

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ABSTRACT

Depression is a prevalent mental health disorder with significant societal and economic burdens. Recent research has highlighted the intricate relationship between the gut microbiota and depression, emphasizing the bidirectional communication along the microbiota-gut-brain system modulation, HPA axis regulation, and brain-gut axis communication. Probiotics, particularly strains of Lactobacillus, Bifidobacterium, Faecalibacterium, and Clostridium have emerged as potential therapeutic agents for depression due to their ability to modulate the gut microbiota and influence neurochemical pathways. Studies in both animal models and clinical trials have demonstrated the antidepressant effects of probiotics, offering promising avenues for novel interventions in the management of depression and related disorders. Further research is needed to elucidate the precise mechanisms of action and optimize probiotic-based therapies for depression.

INTRODUCTION

Depression is a mental health condition marked by slowed thinking, persistent feelings of sadness, and a lack of motivation to engage in activities[1]. It often comes with thoughts of self-harm and physical symptoms like headaches or stomachaches. These aspects not only affect individual's well-being but also strain their relationships and impact their ability to work, leading to significant economic costs for families and society. Unfortunately, studies suggest that depression is becoming more common among the general population, highlighting the urgent need for effective interventions and support systems[2]. Depression's impact on global health is profound.It ranks as the third leading cause of global disability in healthy life years. Additionally, it is now recognized as the fourth most common illness

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worldwide, affecting nearly 4.4% of populations in both developed and developing countries[3]. These statistics underscore the widespread nature of depression and highlight the urgent need for comprehensive strategies to address its prevalence and impact on individuals and societies globally. The projected rise in depression by 2030 is indeed concerning, and the COVID-19 pandemic has certainly exacerbated mental health challenges worldwide. The increase in depression cases due to the pandemic underscores the importance of prioritizing mental health support and resources, both during and after public health crises. It highlights the need for accessible and effective mental health services to address the growing burden of depression and other mental health disorders[4]. Depression is a complex disorder with multifaceted origins, involving a combination of genetic, environmental, and psychological factors. The various hypotheses provides valuable frameworks for understanding some of the mechanisms involved in depression:

Monoamine Reduction Hypothesis:

This hypothesis suggests that depression is associated with a deficiency in certain neurotransmitters, particularly serotonin, norepinephrine, and dopamine. Medications like SSRIs (Selective Serotonin Reuptake Inhibitors) target this imbalance by increasing the availability of serotonin in the brain [5].

Hypothalamus-Pituitary-Adrenal (HPA) Axis Over activation:

Chronic stress can lead to dysregulation of the HPA axis, resulting in excessive cortisol production. This prolonged stress response is implicated in the development and persistence of depressive symptoms [6].

Brain-Derived Neurotrophic Factor (BDNF) Reduction:

BDNF is a protein that supports the survival and growth of neurons. Reduced levels of BDNF have been observed in individuals with depression, and this may contribute to structural changes in the brain associated with the disorder[7].

While these hypotheses provide valuable insights, it's important to recognize that depression is a heterogeneous condition with diverse underlying causes. Research continues to uncover new factors involved in its pathogenesis, including inflammation, neuroplasticity, and genetic predispositions. A comprehensive understanding of depression's etiology is crucial for developing more effective prevention and treatment strategies. Research exploring the microbiota-gut-brain axis has uncovered a fascinating new etiology towards understanding depression[8].

GUT MICROBIOME AND DEPRESSION

The gut microbiota plays a crucial role in maintaining human health and the immune system, with numerous neuroscientific studies indicating its significance in the development of brain systems[9]. The relationship between the gut microbiota and the brain is bidirectional, as evidenced by research on the microbiome-gut-brain axis. There is substantial evidence linking anxiety and depression disorders to the community of microbes residing in the gastrointestinal system[10] . Various approaches such as modified diet, increased intake of fish and omega-3 fatty acids, as well as macro- and micro-nutrients, prebiotics, probiotics, synbiotics, postbiotics, fecal microbiota transplantation, and regulation of 5-HTP, offer potential avenues for altering the gut microbiota as a treatment strategy[11]. However, there is a limited number of preclinical and clinical research studies assessing the effectiveness and reliability of these therapeutic approaches for depression and anxiety. This article examines relevant research on the correlation between gut microbiota and depression/anxiety, along with the diverse therapeutic possibilities for modifying the gut microbiota.

Mechanisms of gut microbiota in depression[13]

The connection between gut microbiota and depression is a burgeoning area of research within the field of neuroscience and psychiatry. Here's an overview of the mechanisms involved (Figure 1).

Neurotransmitter Production:

The gut microbiota plays a crucial role in the production and regulation of neurotransmitters such as serotonin, dopamine, and gamma-aminobutyric acid (GABA). Serotonin, in particular, is heavily involved in mood regulation, and its production in the gut is influenced by the composition of gut bacteria.

Immune System Modulation:

The gut microbiota interacts with the immune system, influencing its activity and response. Dysbiosis, an imbalance in gut bacteria composition, can lead to chronic low-grade inflammation, which has been linked to the development of depression. Inflammation can disrupt neurotransmitter metabolism and neuronal function, contributing to depressive symptoms.

Hypothalamic-Pituitary-Adrenal (HPA) Axis:

The HPA axis is a complex system involved in the body's response to stress. Dysregulation of the HPA axis is commonly observed in depression. The gut microbiota can communicate with the HPA axis through various pathways, including the release of signaling molecules and metabolites. Dysbiosis may disrupt HPA axis function, leading to an exaggerated stress response and increased susceptibility to depression.

Brain-Gut Axis Communication:

There is bidirectional communication between the gut and the brain, known as the brain-gut axis. The gut microbiota communicates with the central nervous system through neural, endocrine, and immune pathways. Changes in gut microbiota composition can alter this communication, influencing mood and behavior.

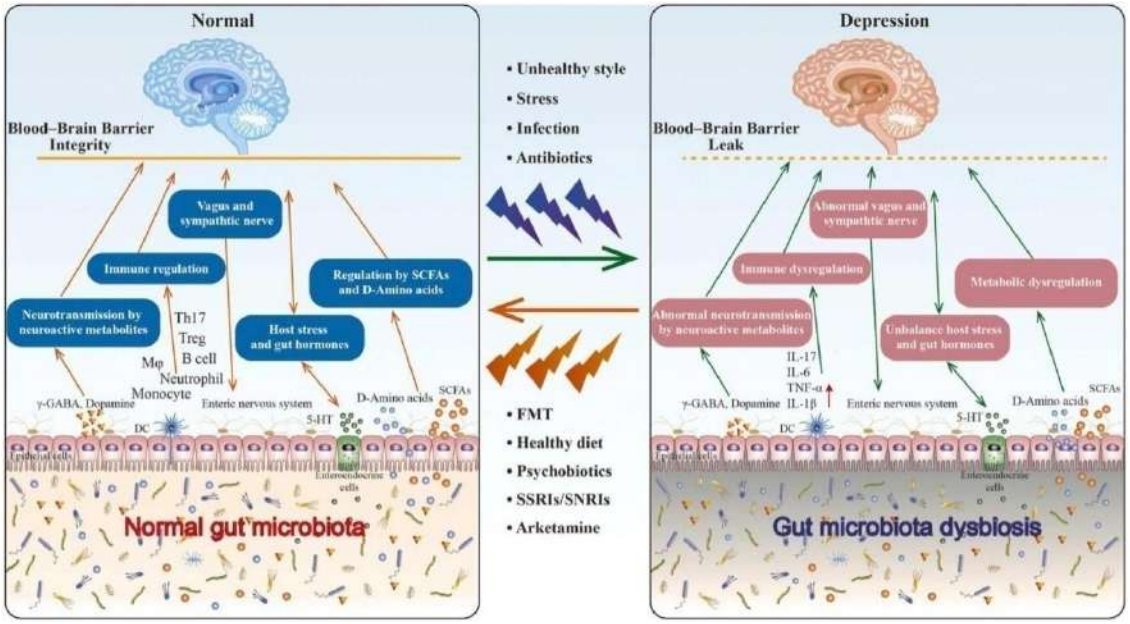

Figure.1 : The connection between gut microbiota and depression is mediated by the brain-gut-microbiota axis. Unhealthy lifestyles, stress, and infections can disrupt gut microbiota balance, contributing to depression. Various interventions like fecal microbiota transplantation, diet changes, psychobiotics, and antidepressants can restore balance, alleviating depressive symptoms. These approaches promote beneficial bacteria growth, produce neurotransmitters benefiting brain function, and modify neurotransmitter levels, offering promising avenues for improving mental health[12].

AMELIORATIVE EFFECT OF PROBIOTICS IN DEPRESSION

The term "probiotic" emerges from a linguistic fusion, drawing from Latin ("pro") and Greek

("bios"), signifying "for life." The historical utilization of fermented dairy items underscores the enduring presence and application of probiotics throughout human history. Subsequently, there has been a notable proliferation of probiotic-infused food items and probiotic supplements, available in various forms such as capsules, tablets, liquids, and powders[14].The exploration of probiotic's potential in addressing mental disorders has delved into various hypothetical mechanisms, primarily drawing from research conducted in vitro and in vivo using animal models[15]. Subsequent sections will delve deeper into the potential mechanistic role of probiotics in depression. This includes their anti-inflammatory properties, ability to restore gut permeability, modulation of neurotransmitters, attenuation of the HPA axis, and involvement in epigenetic mechanisms[16](Fig 2).

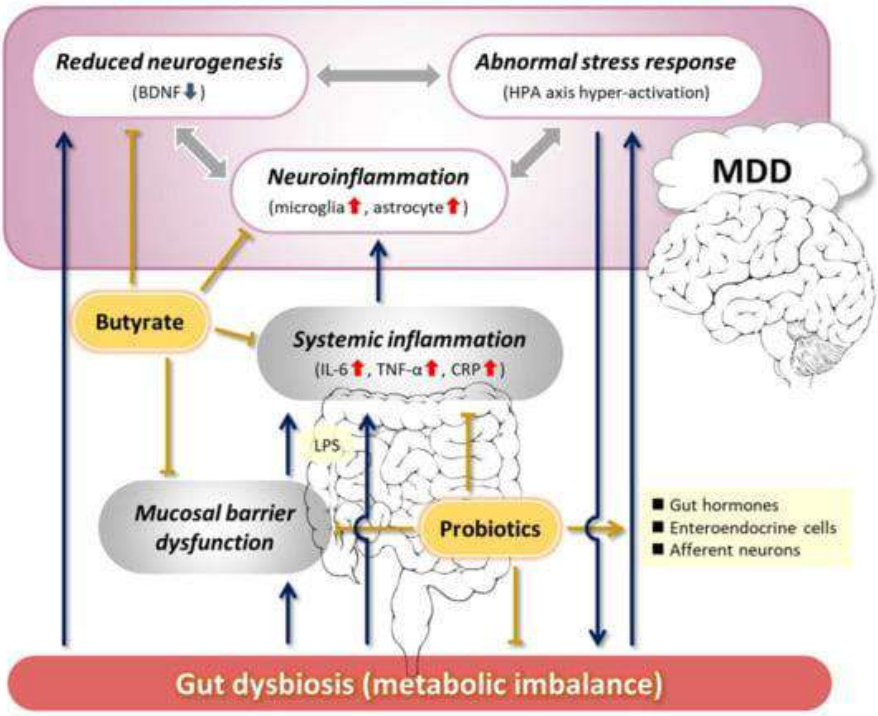

Figure 2 : The modulating role of probiotics in the underlying mechanisms of Major Depressive Disorder (MDD) via the gut-brain axis[17].

Lactobacillus

Lactobacillus is among the most extensively utilized and researched probiotic bacteria within the gut microbiota. These bacteria, identified as Lactobacillus spp., are anaerobic, gram-positive, peroxidase-negative, non-spore-forming rods that thrive under microaerobic conditions. Being a natural component of the healthy microbiota in the human gut, vagina, and oral cavity, Lactobacilli are generally regarded as safe microorganisms, posing low pathogenic risks and lacking the capability to transfer antibiotic resistance traits to pathogens[18].Therefore, Lactobacilli strains derived from natural sources have emerged as promising candidates for probiotic use. Numerous strains of Lactobacilli, such as L. plantarum, L. fermentum, L. rhamnosus, and L. casei, isolated from the gut, have been employed as probiotics. These strains offer various advantages to the host, including the alleviation of anxiety and cognitive of these Lactobacilli strains on mood, anxiety, and cognition, positioning them as potential psychobiotics[19]. One of the notable Lactobacilli strains is L. rhamnosus, known for its resilience to acidity and bile, as well as its significant adherence to human intestinal mucosal cells. Numerous

animal studies have revealed the psychoactive and neuroactive attributes of a specific strain, L. rhamnosus JB-1 (JB-1), following oral administration. JB-1 has demonstrated the ability to modulate neurotransmitter levels in the brains of mice, thereby mitigating anxiety and depression-related behaviors induced by stress[20]. JB-1 consistently modulates the expression of GABAA and GABAB receptors in mice in a manner dependent on the region, thereby restoring levels of metabolites like GABA and glutamate to their baseline and diminishing corticosterone levels[21]. Researcher documented that treatment with the JB-1 strain for four weeks in BALB/c mice resulted in a 25% increase in central GABA levels[22].The antidepressant effects of JB-1 rely on the presence of an intact vagus nerve connection linking the gut and the brain[23]. Several Lactobacilli strains have been used as probiotics, including L. plantarum, L.fermentum, L.rhamnosus and L. casei, which are isolated from the gut and exertvarious benefits to the host, including attenuation of anxiety and cognitive improvement. People experiencing low mood reported increased happiness following the consumption of milk containing L. casei, whereas there was no such effect observed with the placebo[24]. Consumption of probiotics containing a mix of bacterial species, including L. casei, also led to a reduction in clinical depression and symptoms resembling depression in patients diagnosed with Major Depressive Disorder (MDD)[25]. The ingestion of Lactobacillus helveticus facilitated the recovery of rodents subjected to chronic and sub chronic stress from their depressive state[26]. Probiotic sticks containing L. helveticus, in addition to Bifidobacterium longum, reduced clinical depression and depressive-like symptoms in MDD patients[27].Research indicates that L. helveticus could potentially regulate the central NE system and HPA axis to enhance cognition, and the central 5-HT system and BDNF expression to alleviate depression[28]. The introduction of heat-killed L. paracasei through dietary intervention prevented mood decline during periods of stress in healthy individuals[29]. In mice with depression induced by corticosterone, administering either live or heat-killed L. paracasei via oral gavage demonstrated antidepressant effects comparable to or surpassing fluoxetine. Furthermore, the study revealed that live and heat-killed L. paracasei exerted their effects through distinct mechanisms: live L. paracasei elevated 5-HT levels, while heat-killed L. paracaseie levated DA levels in the brain[30].

Bifidobacterium

Bifidobacterium is a common bacterium found in the intestines, belonging to the Actinobacteria phylum and the Bifidobacteriaceae family. It is characterized as a Gram-positive bacterium that is typically non-motile, forms spores, and produces gas[31]. Mounting evidence suggests that probiotics containing Bifidobacteria have the potential to prevent and treat a range of mental and psychological disorders, including depression and anxiety[32]. In a three-blind randomized placebo-controlled trial, healthy subjects were administered a daily dose of lyophilized probiotics powder containing Bifidobacteria (2.5×10^9 CFU). Before and after the intervention, participants were assessed using the revised Leiden Depression Sensitivity Scale (LEIDS-r), Becker Depression Scale II (BDI-II), and Becker Anxiety Scale (BAI). The results revealed a significant reduction in overall cognitive response to depression, particularly in aggressive and reflective thinking, following the 4-week probiotics intervention. This study provided the first confirmation that a 4-week intake of multi-species probiotics positively impacted the cognitive response to natural fluctuations in mood in healthy individuals. Additionally, other research demonstrated that after treatment with

Bifidobacterium infantis, maternally isolated rats exhibited reversed immune function, normalized norepinephrine concentration in the brain, and ultimately, reduced depressive behavior[33].Administering 1.0×10^{10} CFU of Bifidobacterium longum NC3001 to adult patients with irritable bowel syndrome (IBS) and mild to moderate depression for 6 weeks resulted in significantly lower depression scores compared to the control group. Functional magnetic resonance imaging (fMRI) results revealed that Bifidobacterium longum NC3001 reduced the response of multiple brain regions, particularly the amygdala and frontal limbic regions, to fear stimuli. The decreased activation of the amygdala frontal limbic complex was associated with the reduced depression scores. These findings indicate a positive role of Bifidobacterium in the treatment of depression[34]. Numerous studies have affirmed the potential of Bifidobacteria in alleviating depressive symptoms. However, the precise mechanisms remain incompletely understood. These mechanisms might involve reducing the abundance of pathogenic bacteria, exerting anti-inflammatory effects, enhancing the integrity of the intestinal barrier, regulating tryptophan levels, influencing serotonin (5-HT) synthesis, and modulating the hypothalamus-pituitary–adrenal (HPA) axis[35].Exposure to chronic social defeat stress (CSDS) for 10 consecutive days altered the composition of intestinal microbial communities and increased the expression of interleukin-1 beta (IL-1β) in the brain in mice. This stress paradigm also led to heightened depressive behavior. However, administration of heat-sterilized Bifidobacterium breve M-16V could effectively lower the abundance levels of specific bacteria, potentially mitigating CSDS-induced depression and reducing IL-1β expression in the brain[36].

Faecalibacterium

Faecalibacterium prausnitzii, standing as the solitary species within the Faecalibacterium genus[37]. In a recent extensive cohort study, there was an inverse correlation observed between fecal levels of F. prausnitzii and depressed mood, while a positive correlation was found with quality of life[38].Faecalibacterium prausnitzii is known to produce significant amounts of butyrate through the fermentation of glucose and dietary fiber[39].F. prausnitzii also releases microbial anti-inflammatory molecules, which have the ability to suppress the proinflammatory nuclear factor (NF)-κB pathway in intestinal epithelial cells (IECs)[40]. The immunomodulatory effects align with neurochemical alterations observed in depressed mice treated with F. prausnitzii. Specifically, there was an increase in cecum short-chain fatty acids (SCFAs) and plasma interleukin-10 (IL-10) levels, alongside a decrease in corticosterone and IL-6 levels[41]. Additionally, intragastric administration of F. prausnitzii resulted in reduced colonic cytokine levels and improved intestinal permeability in mice suffering from colitis[42]. The capacity of F. prausnitzii to alleviate gut inflammation is significant enough to mitigate depressive- and anxiety-like behaviors in mice [43].

Clostridium

Treating chronic-stressed mice with C. butyricum resulted in improved depressive-like behaviors. Additionally, these treated mice exhibited increased expression of central serotonin (5-HT), brain-derived neurotrophic factor (BDNF), and glucagon-like peptide-1 (GLP-1) receptors in the brain[44]. Remarkably, when combining C. butyricum with antidepressants, approximately 70% of treatment-resistant MDD patients experienced a reduction in depression symptoms, with 30% achieving full remission[45]. These studies provide evidence supporting the antidepressant effectiveness of non-pathogenic strains of C. butyricum. However, it's important to

note that certain strains of C. butyricum can be pathogenic, potentially leading to conditions such as botulism and necrotizing enterocolitis[46]. Another study found that the intake of C. butyricum increased the activity of neurogenesis-related pathways, such as BDNF, through the production of butyrate in mice[47]. While GLP-1 is recognized for its role in appetite and glucose regulation, activating central GLP-1 receptors has been demonstrated to modulate the central serotonin system and alleviate anxiety- and depressive-like behaviors in rats[48].Thus, the antidepressant mechanism of C. butyricum likely encompasses an increase in central BDNF-5-HT system and GLP-1 receptor expression facilitated by butyrate, akin to the effects observed with L. paracasei and B. infantis[49].

FUTURE PERSPECTIVE

The emerging research on the gut microbiota and its connection to depression opens up promising avenues for novel interventions in mental health. Probiotics, particularly strains like Lactobacillus, Bifidobacterium, Faecalibacterium, and Clostridium, show potential in modulating the gut microbiota and influencing neurochemical pathways associated with depression. Lactobacillus strains, such as L. rhamnosus and L. casei, have demonstrated antidepressant effects in both animal models and clinical trials. These effects are attributed to their ability to modulate neurotransmitter levels, particularly GABA and glutamate, and regulate the HPA axis, leading to reduced corticosterone levels and alleviation of depressive symptoms. Similarly, Bifidobacterium strains, like B. infantis and B. longum, have shown promise in improving depressive symptoms by influencing neurotransmitter synthesis, reducing inflammation, and modulating the HPA axis. Faecalibacterium prausnitzii, through its production of butyrate and anti-inflammatory molecules, has been linked to improvements in gut inflammation and depressive-like behaviors. Clostridium butyricum has also shown antidepressant effectiveness by increasing central serotonin and BDNF levels in the brain, potentially through the production of butyrate. However, further research is needed to fully understand the mechanisms of action of these probiotic strains and optimize their use in the treatment of depression. Future studies should focus on elucidating the precise pathways through which probiotics exert their effects, as well as exploring combination therapies and personalized approaches to treatment. Additionally, clinical trials with larger sample sizes and longer follow-up periods are necessary to establish the safety and efficacy of probiotic-based interventions for depression. Overall, the gut microbiota represents a promising target for the development of novel therapeutic strategies in mental health.

CONCLUSION

In conclusion, the emerging research on the gut microbiota and its connection to depression offers promising prospects for innovative interventions in mental health. Probiotics, including strains like Lactobacillus, Bifidobacterium, Faecalibacterium, and Clostridium, have demonstrated potential in modulating the gut microbiota and influencing neurochemical pathways associated with depression. Lactobacillus and Bifidobacterium strains have shown antidepressant effects by modulating neurotransmitter levels, reducing inflammation, and regulating the HPA axis. Faecalibacterium prausnitzii and Clostridium butyricum have also exhibited antidepressant effectiveness through their production of butyrate and modulation of central serotonin and BDNF levels. However, further research is necessary to fully understand the mechanisms of action of these probiotic strains and optimize their use in depression treatment. Future studies should explore combination therapies, personalized approaches, and larger clinical trials to establish the safety and efficacy of probiotic-based

interventions for depression. Overall, targeting the gut microbiota represents a promising avenue for developing novel therapeutic strategies in mental health.

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