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Innovative way for treating depression: The potential effects and mechanism of probiotics in coping with MDD

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Abstract. Depression is a multifaceted psychiatric condition affecting more than 280 million individuals globally across diverse age brackets, constituting 12.3% of the worldwide disease burden. Among the varied manifestations, Major Depressive Disorder (MDD) stands out as a prevalent and severe form of psychopathology. The origins of depression, while not fully elucidated, are generally attributed to the intricate interplay of environmental, societal, and individual factors. Recent preclinical and clinical investigations have posited a potential association between dysbiosis, characterized by alterations in gut microbiota composition and function, and the initiation and progression of depression. Nevertheless, the precise mechanisms remain unclear, and the gut microbiota has not been a primary focal point in depression therapeutic strategies. This review outlines conceivable mechanisms linking dysbiosis in the gut microbiota to the development of depression, elucidating the intricate relationship between dysbiosis and depressive conditions. Additionally, it explores the interplay between pharmacological interventions and the gut microbiota in the context of antidepressant therapy. Simultaneously, the article investigates the potential and merits of probiotics and prebiotics as tools to modulate gut microbiota and maintain a stable gut microenvironment, positioning them as innovative agents in antidepressant therapy. This perspective introduces a novel trajectory for future research and clinical approaches in depression, underscoring the significance of preserving gut microbiota equilibrium as a promising avenue for intervention.

Keywords: Depression, Probiotics, Gut microbiota, Pathogenesis, Antidepressants

1. Introduction

The majority of microorganisms associated with humans inhabit the gastrointestinal tract, with factors like delivery method, infant feeding practices, lifestyle, medications, and host genetics influencing their composition [1,2]. The gut microbiota assumes crucial functions in educating the host immune system, digesting food, modulating endocrine functions and neural signaling within the gut [3], altering drug efficacy and metabolism, detoxifying compounds, and producing various bioactive molecules that impact the host [4].

Notably, in recent times, is a growing focus on the microbiota's effect on the human nervous system, particularly through the gut-brain axis. Studies indicate that psychological stress may promote the permeability of the gastrointestinal mucosa, disrupting the stability of the gut microenvironment [5]. Likewise, the microbiota can influence and modulate emotional behaviors, notably through neural

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pathways like HPA axis (**Figure 1**) [6,7]. The interplay between the gut-brain axis and gut microbiota, crucial for central nervous system regulation, has become a focal point of research, particularly in the realm of neurological disorders.

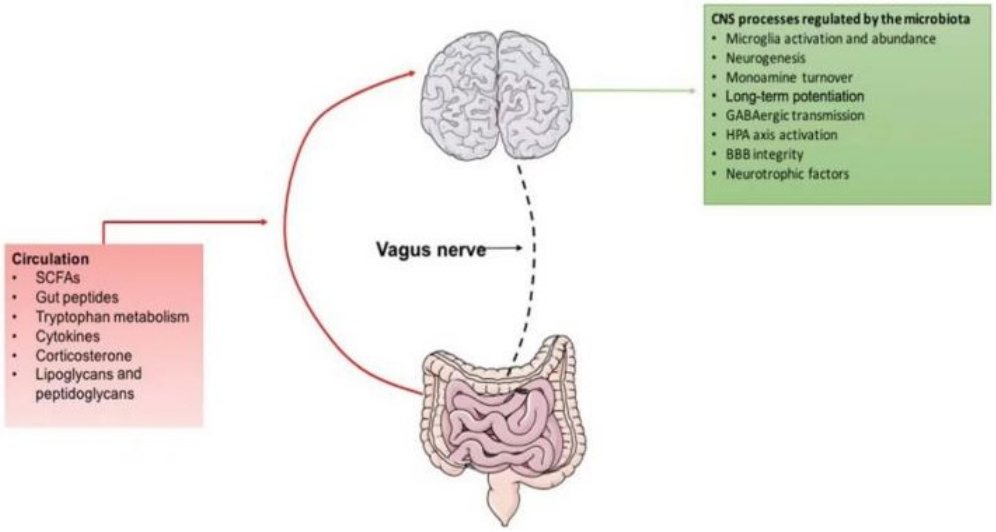

Figure 1. Vital mechanisms for interplay between human brains and the gut microbiota.

Intestinal microbes have the ability to communicate with the brain through diverse pathways. These pathways encompass the generation of SCFA metabolites, control of immune signals in human brain, and the transmission of signals through the vagus nerve. The impact of these mechanisms extends to the regulation of crucial processes within the central nervous system, including neuroinflammation, neurogenesis, and neurotransmission, all of which have implications for various neurological and psychiatric disorders. This figure is derived from Sherwin et al.'s 2017 paper [8].

Amidst the ongoing societal advancements and increasing challenges in daily life, exacerbated by a progressively stifling social environment, the prevalence of mental health disorders, particularly individual psychological conditions such as autism and depression, has risen substantially. Depression, a complex mental disorder influenced by multiple factors, poses a significant global health concern. Current statistics indicate a staggering 15% prevalence rate of depression, accounting for 12.3% of the global disease burden, with high rates of disability and mortality, posing a severe threat to human health [9]. As socioeconomic development accelerates and lifestyles become more hectic, the incidence of depression is steadily increasing, affecting over 280 million individuals across all age groups [10]. According to recent statistics released by the World Health Organization (WHO), projections indicate that by the year 2020, depression is anticipated to emerge as the second most substantial global health concern, following closely behind coronary heart disease [11].

Major Depressive Disorder (MDD) stands as one of the severe and prevalent forms of psychopathology, impacting as many as 20% of individuals and serving as a leading cause of global disability [12]. Characterized by enduring depressive symptoms lasting a minimum of two weeks, MDD typically disrupts an individual's work, sleep, learning, and eating abilities [13]. Depressive symptoms may also manifest in subclinical states, but still exert a substantial impact on daily functioning. Presently, the majority of pharmacological treatments for MDD primarily target the regulation on the activity of neurotransmitters in the brain, including the use of SSRIs, SNRIs, MAOIs, and TCAs [14]. However, these drugs often show a delayed onset of action and can lead to dependence and adverse side effects like headache, nausea, restlessness, sexual dysfunction, and sedation [15]. Moreover, these chemical interventions are often associated with high costs, burdening dependent patients with substantial financial expenditures for the sustained management of MDD [15]. Hence, the imperative need to

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develop a more efficient, cost-effective, and less prone to adverse reactions approach for the treatment of depression.

In the last ten years, extensive research in neurogastroenterology has provided a detailed understanding of a biochemical pathway linking the central nervous system and the gastrointestinal tract, commonly known as the "gut-brain axis." The complex communication network operates bidirectionally through the immune system, the neuroendocrine system, the enteric nervous system, and the autonomic nervous system [16]. Specifically, disruptions in the gut microbiota may stimulate the generation of proinflammatory cytokines and affect neural system functionality by participating in neurotransmitter synthesis, consequently inducing depressive emotions in individuals [17]. Simultaneously, observations have revealed that certain bacteria has the ability to generate neuroregulatory substances, such as acetylcholine, dopamine, serotonin, GABA, norepinephrine, and others present in the animal nervous system [18]. Consequently, to some extent, the gut microbiota contributes to shaping an individual's psychological well-being.

Moreover, dysbiosis in the gut microbiota may impair the functionality of the intestinal mucosal barrier and the blood-brain barrier, causing the onset of neuropsychiatric disorders [19]. In summary, whether the signaling molecules originate from the gut microbiota itself, its metabolites, or the gut microenvironment, neural pathways serve as the most direct conduit for their mutual "communication." Despite the progressive advancements in this field, there has yet to be a systematic summary of the associations between the gut microbiota and the nervous system. This paper thus briefly reviews the significant and consistent findings in this research domain and analyses the characters and mechanisms of the gut microbiota in maintaining mental well-being from multiple perspectives, including neural pathways, the gut microenvironment, metabolites, and immune responses.

Simultaneously, this paper introduces and evaluates a novel treatment approach for depression based on probiotics, aiming to address the challenges and limitations of existing therapeutic methods. It delineates the neural system, gut microbiota, and probiotics into three sections, dissecting the interactions between these components, thereby establishing a comprehensive framework for the utilization of probiotics in the management of neuropsychiatric disorders. Beyond considering the potential therapeutic capabilities of probiotics, this paper also takes into account the impact of prebiotics on neuropsychiatric disorders, and contrasts the modes of action and efficacy between probiotics and prebiotics.

It is worth noting that previous research has primarily assessed the drug-microbiota interaction of individual medications [20]. However, individuals with Major Depressive Disorder (MDD) often take multiple antidepressants and adjunct medications. The utilization of the polypharmacy approach may potentially result in a biased interpretation of drug-microbiota interactions. By incorporating pharmacomicrobiomics into the study of depression, a more profound comprehension of the reciprocal interactions between pharmaceuticals and the gut microbiota will be attained. This will shed light on the mechanisms through which antidepressant medications impact both the composition and functionality of the gut microbiota and how the microbiota, reciprocally, metabolizes these drugs, thereby either enhancing or impeding their therapeutic effects. This paper also explores the associations and impacts of antidepressant medications and gut probiotics, endeavoring to lay the theoretical groundwork for the more effective utilization of the gut microbiota to enhance the efficacy of antidepressant medications.

2. Pathophysiology of depression

2.1. Mechanism of antidepressant

The preceding sections have introduced the treatment of depression, as well as the classification, functions, and associated side effects of antidepressant medications. In this section, we will further analyze the specific mechanisms of action of different types of antidepressant drugs and their real-world applications. Traditional antidepressant drugs are primarily represented by tricyclic antidepressants (TCAs), like amitriptyline and imipramine. This class of substances was formally identified as a compliant treatment for depression in 1958 [21]. The primary mode of action for tricyclic

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antidepressants involves inhibiting the reuptake of both norepinephrine and serotonin (5-HT), leading to changes in the physiological behaviors of neural receptors. Furthermore, according to research by Khushboo et al. in 2017, TCAs can also block receptors for acetylcholine, histamine, α1-adrenergic receptors, and muscarinic receptors [22]. However, tricyclic antidepressants lack selectivity in the reuptake of monoamine neurotransmitters and their impact on the functions of neurotransmitters like histamine and acetylcholine, which may result in severe adverse reactions [23]. Common side effects among patients taking these drugs include confusion, constipation, headaches, blurred vision, and skin rashes.

In comparison to traditional antidepressants, the newer classes of antidepressant drugs exhibit relatively high target selectivity, resulting in fewer side effects. Notable examples encompass selective serotonin reuptake inhibitors (SSRIs) like fluoxetine and paroxetine, norepinephrine reuptake inhibitors (SNRIs) and dual serotonin like venlafaxine, and monoamine oxidase inhibitors (MAOIs) [24]. In the following sections, we will separately analyze the new targets these antidepressant drugs address, the latest research developments, and their advantages and disadvantages compared to traditional medications.

2.1.1. SSRIs. SSRIs are a widely used class of antidepressant medication primarily employed for treating persistent or severe depression, often in conjunction with cognitive-behavioral therapy (CBT) and other talk therapies [25]. It is generally acknowledged in academia that SSRIs exert their effects by increasing serotonin levels in the brain. In 1998, research by Mourilhe et al. found that SSRIs inhibit the reuptake of serotonin (5-HT), enhancing synaptic 5-HT transmission, implying that more serotonin can convey additional information between neighboring neurons [26]. Simultaneously, SSRIs have minimal to no impact on the reuptake of other neurotransmitters. Observations suggest that SSRIs exhibit no activity towards muscarinic and histamine receptors, which could potentially result in slight anticholinergic (ACH) and sedative effects [27]. Due to their typically fewer side effects that tend to improve over time, among the various antidepressant options, SSRIs are considered the optimal choice for treating depression.

2.1.2. SNRIs. Serotonin-norepinephrine reuptake inhibitors (SNRIs), in addition to their antidepressant effects, are sometimes utilized to cure other conditions such as anxiety disorders, psychoses, and long-term chronic pain [28]. Their activity does not induce any side effects in the body like sedation or low blood pressure but can produce effects similar to TCAs. SNRIs exert their antidepressant effects by modulating neurotransmitters and inhibiting the reuptake of serotonin and norepinephrine within the central nervous system. Similar to the majority of antidepressants, SNRIs ameliorate depression by ultimately modifying brain chemistry and modulating the interplay among neural circuits that regulate mood [29]. Some SNRIs include desvenlafaxine (Khedezla), levomilnacipran (Fetzima), duloxetine (Cymbalta), and venlafaxine (Effexor XR). Primary antidepressant medications are classified as non-tricyclic antidepressants (NTCAs), incorporating components such as SSRIs, as they demonstrate a higher safety profile and improved tolerance. TCAs, on the other hand, are recommended for individuals unresponsive to alternative medications or those experiencing chronic pain or migraines [30]. However, serotonin-norepinephrine reuptake inhibitors also have some side effects in the body. Since the mechanism of action is similar for all SNRIs, the side effects produced by different types of this medication are also similar [31]. These side effects are generally mild and completely disappear after the initial weeks of treatment.

2.1.3. MAOIs. Various antidepressants, including Monoamine Oxidase Inhibitors (MAOIs) like phenelzine and tranylcypromine, operate by inhibiting enzymes associated with 5-HT and NE, consequently decreasing the levels of their respective metabolites in the human body. The monoamine oxidase enzyme exists in two isoforms, namely MAO-A and MAO-B [32]. MAO-A is chiefly responsible for deaminating serotonin, N-acetyl-5-methoxytryptamine, epinephrine, and norepinephrine. In contrast, MAO-B primarily deaminates phenylethylamine and trace amines. Both have the same

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deaminating action on dopamine and are reversible and selective [33]. MAOIs are typically used to cure atypical or treatment-resistant depression and are also employed in the management of mental health conditions like Parkinson's disease. However, due to the somewhat toxic nature of these compounds, the use of MAOIs to treat depression by ingestion is not common. Meanwhile, the consumption of certain smoked, fermented, or pickled foods, or alcoholic beverages, can potentially cause patients taking MAOIs to suddenly experience severe hypertension, even endangering their life and health [34].

While newer antidepressants represented by SSRIs and SNRIs are superior in terms of safety and side effects compared to traditional antidepressants, most double-blind trials indicate that these antidepressants typically take 2 to 4 weeks to manifest their therapeutic effects, with approximately 30% to 40% of patients not benefiting from their treatment. Castrén et al. explained this phenomenon in 2005 and proposed its connection to the neurotrophic hypothesis: newer antidepressants elevate monoamine levels, but the restoration and enhancement of information transmission in neural pathways require increased neurogenesis and brain plasticity, which is a relatively slow process, leading to the delayed onset of drug efficacy [35]. Furthermore, long-term use of these newer antidepressants can lead to sexual dysfunction and is less effective in treating insomnia symptoms caused by depression. Therefore, in recent years, researchers have aimed to enhance the comprehensive efficacy of antidepressants by targeting new mechanisms based on these drugs and combining the mechanisms of various antidepressants. One approach is to enhance the inhibition of the dopamine transporter on the basis of SNRIs, making them triple reuptake inhibitors (TRIs) targeting 5-HT/NA/DA [36]. Other solutions include activating the post-synaptic membrane's 5-HT receptor subunit, using Kappa opioid receptor antagonists, and employing ketamine or glutamate to rapidly counteract depression, among others [37,38].

2.2. Effects of gut microbiota on depression

One of the contemporary theories concerning the pathophysiology of depression focuses on investigations into the gut microbiota. Recent research has revealed a bidirectional interaction between human brain and the gut, mutually influencing each other's functions. Notably, the makeup of the gut microbiota exhibits a direct correlation with stress and the emergence of depressive symptoms [39]. This connection involves multiple pathways, including endocrine, neural, and immune pathways. Healthy gut microbiota is well-known to transmit signals to the brain through pathways like neural transmission, neurogenesis, activation of microglial cells, and behavioral control, under both normal and high-stress conditions. However, individuals experiencing depression encounter challenges in transmitting signals to the brain effectively due to disruptions in the gut microbiota. Recent findings highlight significant differences in the composition of the gut microbiota between those diagnosed with Major Depressive Disorder (MDD) and those without this condition. These differences specifically involve variations in microbial diversity and the relative prevalence of distinct bacterial groups [40]. These results compellingly imply a link between gut dysbiosis and depression. Despite some variability in research outcomes, a consistent trend is evident, revealing an elevated abundance of pro-inflammatory bacteria and a reduced presence of anti-inflammatory bacteria in the gut microbiota of individuals with depression. Notably, the phyla Firmicutes, Actinobacteria, and Bacteroidetes are notably affected in individuals experiencing depression [41]. Specifically, for MDD patients, there is an observed rise in the ratio of Actinobacteria and Firmicutes, coupled with an elevation in the Bacteroides genus and a reduction in the Blautia genus, Ruminococcus genus, and Faecalibacterium genus. In a study conducted in 2016, Kelly et al. transplanted the fecal microbiota of MDD patients into rodents [42]. They found that microbial dysbiosis occurred before the onset of MDD and may play a significant causative character in the onset of MDD. Moreover, compelling evidence suggests the existence of a pathological feedback loop in which the pathological alterations associated with depression contribute to and intensify ecological imbalances [43]. Consequently, while changes in the gut microbiota may manifest early in MDD and potentially precipitate its onset, the ongoing pathological changes characteristic of MDD disrupt the gut milieu, ultimately resulting in dysbiosis. In other words, as individual internal functions develop, the pathogenicity of the gut microbiota becomes stronger, resulting in different

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microbial features in individuals with Major Depressive Disorder (MDD) across various age groups. In the complex gut microbiota community, specific pathogens may also interact synergistically with other microbes, ultimately leading to depression rather than being just a solitary infectious source [44]. In conclusion, interactions among gut microbial species are quite complex. Gaining a comprehensive understanding of these intricate interactions, which give rise to novel bioactive compounds, will significantly advance our comprehension of the underlying mechanisms governing the interplay between the microbiota and the host that lead to depression.

Research on the impact of the gut microbiota on behavior and neurobiology, termed the Microbiota-Gut-Brain Axis (MGBA), emerged initially from observations in individuals with Inflammatory Bowel Disease (IBD) and Irritable-Bowel-Syndrome (IBS) [45]. The gut microbiota, along with its associated metabolites, assumes a pivotal character in enabling bidirectional communication between human brain and the gut, establishing the basis for the MGBA. As previously stated, there are notable distinctions in the gut microbiota composition between individuals suffering from depression and those who are mentally healthy. This characteristic has also been confirmed in animal models of depression: studies involving rodents raised and developed in germ-free environments, as well as animals with specific-pathogen-free (SPF) gut microbiota, have demonstrated the influence of the gut microbiota on depressive behaviour [46]. Colonization of SPF gut microbiota in germ-free animals has shown to ameliorate their behavior. The pathways involved in the MGB Axis and their roles in depression have been extensively elucidated in recent years, as depicted in the diagram below (**Figure 2**).

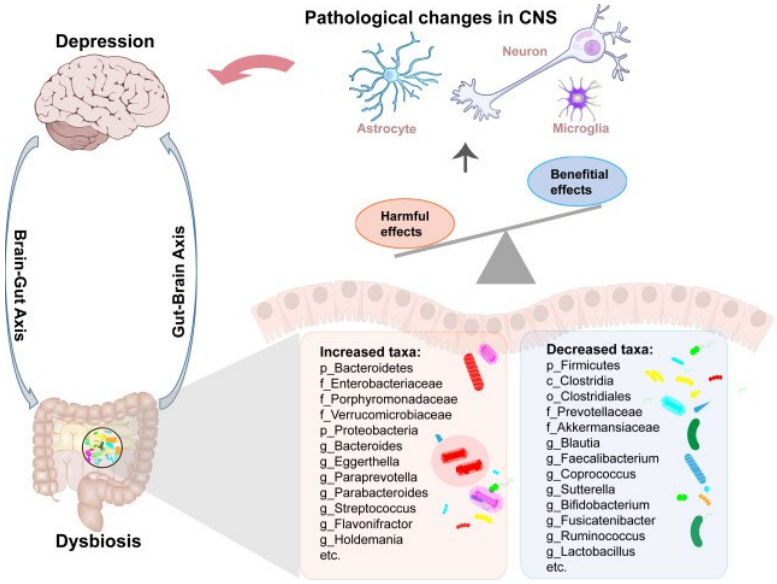

Figure 2. Relationship between ecological dysregulation and neurocentral pathologic changes in the onset of depression; CNS refers to central nervous system. This figure is taken from the article by Liu et al. 2023 [47].

Observations have shown that certain bacteria can produce neuroregulatory substances such as acetylcholine, dopamine, serotonin, GABA, and norepinephrine, which means that the gut microbiota plays a character in the development of an individual's mental health to some extent [48]. The composition of the microbiota exhibits inter-individual variability and is subject to modulation by factors including alterations in the gut milieu, lifestyle choices, and dietary patterns. Therefore, if there are significant changes in an individual's living environment or if they have poor lifestyle choices, the gut microbiota can become imbalanced, leading to conditions like depression and other mental illnesses [49]. Specifically, disruptions in the gut microbiota may cause damage to the intestinal epithelial function, causing in intestinal barrier dysfunction and inflammation. Metabolites from the gut, microbial cell components, and the microbiota itself can further enhance systemic inflammatory responses by

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breaching the compromised intestinal barrier [50]. The Enteric Nervous System (ENS), the "second brain," is intricately linked to diseases affecting the human body's central nervous system. Aberrant enteric nervous system (ENS) activity resulting from gastrointestinal pathology exacerbates depressive-related pathological conditions by perturbing intestinal secretion, immune defense, motility, and permeability [51]. In addition to the Enteric Nervous System (ENS), the vagus nerve assumes a crucial function in relaying microbial signals from the gut to human brain. Studies in preclinical settings have indicated that hindering the progression of depressive conditions in rodent models can be achieved through fecal microbiota transplantation following subdiaphragmatic vagotomy. Furthermore, metabolites originating from the gut microbiota can exert a dual impact on depression. Clinical observations highlight that individuals diagnosed with Major Depressive Disorder (MDD) demonstrate reduced levels of short-chain fatty acids (SCFAs). Notably, supplementing with butyrate has shown antidepressant effects by improving gut permeability associated with depression and regulating hypothalamic-pituitary-adrenal (HPA) axis reactivity [52]. Similarly, every alteration in the makeup of the gut microbiota results in the production of lipopolysaccharides (LPS) by microbes, thereby activating an inflammatory response. The generated cytokines signal the vagus nerve, linking it to the HPA axis. Kundu et al.'s research has further demonstrated that gastrointestinal inflammation can lead to neuroinflammation, initiating the role of microglial cells, triggering the kynurenine pathway, and ultimately causing depression [53]. Importantly, this affects the generation of proinflammatory cytokines and influences the functioning of the nervous system by participating in neurotransmitter synthesis.

In conclusion, whether signaling molecules are generated by the gut microbiota itself, its metabolites, or the gut microbiota environment, neural pathways are unequivocally the most direct bridge for communication between these elements.

2.3. Potential mechanism of Probiotic in treating depression

Nutritional psychiatry is a burgeoning discipline in psychopathology that explores the correlation between dietary patterns and the vulnerability to mental disorders. The composition and operation of the brain hinge on the consumption of vital nutrients, encompassing fats, vitamins, amino acids, and minerals [54]. Consequently, diet has arisen as a noteworthy regulator of mental health. Numerous cross-sectional studies employ a holistic dietary perspective to assess the link between nutrition and psychological well-being [55]. However, a significant body of research focuses on individual nutritional elements and their implications for mental health. Probiotics assume a central role in this context, defined as beneficial live microorganisms that, when ingested in adequate amounts, confer health benefits to the host. Functioning as transient entities, probiotics establish colonies in the gastrointestinal tract, influencing various pathways. These microorganisms are accessible in the form of tablets or powder supplements and are acknowledged for their therapeutic efficacy in numerous gastrointestinal disorders [56]. Nevertheless, the discovery of the gut-brain axis has unveiled that the beneficial impacts of probiotics surpass the confines of the gastrointestinal tract, extending to the central nervous system. Research conducted by Raison et al. indicates that probiotics have the potential to enhance the activity of antidepressants by mitigating inflammation, thereby presenting a promising adjunct therapy for Major Depressive Disorder (MDD) [57]. Probiotics can also indirectly improve depressive symptoms by influencing obesity, diabetes, or other metabolic complications. Additionally, preclinical research has demonstrated that probiotics can alter the behavior of rodents and improve their mood, anxiety, and cognitive abilities by regulating gut microbiota homeostasis and modulating neurotransmitter activity [58,59]. In summary, nutritional psychiatry explores the complex interaction between dietary patterns and mental health. Probiotics have surfaced as a plausible therapeutic pathway for conditions like Major Depressive Disorder (MDD), attributed to their diverse influences on the gut-brain axis and numerous metabolic pathways.

Concerning neurotransmitters, various studies involving rodents have indicated that the intake of probiotics can hinder the increase of stress-induced markers like noradrenaline, adrenaline, corticosterone, and adrenocorticotropic hormone (ACTH) [60]. The decline in indicators of chronic

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stress implies that probiotic intervention may mitigate the excessive activation of the hypothalamic-pituitary-adrenal (HPA) axis in individuals experiencing depression. Moreover, the ingestion of probiotics amplifies the expression of brain-derived neurotrophic factor (BDNF), a pivotal growth factor influencing neuronal health, memory, and brain plasticity. This factor is notably diminished in individuals with depression [61]. Additional clinical investigations have centered on molecular alterations related to the biosynthesis and metabolism of serotonin. Desbonnet and Nishino observed that the consumption of probiotics elevates plasma levels of the serotonin precursor tryptophan while concurrently decreasing the concentration of serotonin's primary metabolite, 5-hydroxyindoleacetic acid (5-HIAA). Remarkably, these effects align with the impact of the antidepressant drug sertraline [62].

The influence of probiotics on depressive symptoms in rodents extends beyond the central nervous system, encompassing other physiological systems. Notably, probiotics offer a potential therapeutic avenue for depression and related psychiatric conditions by suppressing the levels of pro-inflammatory factors in human body [63]. Various factors, including high psychological stress, obesity, and unhealthy lifestyles, can initiate systemic inflammation. Depression can be mitigated by particular probiotics through the modulation of the hypothalamic-pituitary-adrenal (HPA) axis and the attenuation of overall inflammation. To elaborate, distinct probiotics possess the ability to reduce the levels of pro-inflammatory cytokines interleukin-1β (IL-1β) and interleukin-6, along with tumor necrosis factor-alpha (TNFα) and markers of microglial cell activation [64]. Concurrently, probiotics have demonstrated the ability to decrease intestinal permeability through diverse mechanisms. The augmentation of intestinal permeability is correlated with an escalation in the influx of inflammatory substances from the intestines into the bloodstream. Animal model studies have indicated that specific probiotics secrete bioactive factors that improve the function of epithelial cell barriers and increase the expression of genes involved in maintaining intestinal barrier integrity. For instance, Hooper et al. (2003) demonstrated that the administration of specific probiotics, such as Bacteroides thetaiotaomicron, to germ-free mice resulted in an incretion of occludin expression, a crucial protein responsible for upholding the integrity of the intestinal barrier [65]. Consequently, probiotics have demonstrated the ability to decrease intestinal permeability through diverse mechanisms. The augmentation of intestinal permeability is correlated with an escalation in the influx of inflammatory substances from the intestines into the bloodstream.

Furthermore, the antioxidant capabilities of probiotics and their ability to neutralize free radicals have been substantiated. These microorganisms can elevate the generation of gamma-aminobutyric acid (GABA) and enhance the absorption of various nutrients, all of which are linked to the pathophysiology of depression [66]. Regardless of the specific mechanisms at play, the amalgamation of these research findings, combined with outcomes from preclinical and clinical studies, indicates a potential contribution of the gut microbiota and probiotic utilization in mitigating depressive symptoms. The prospect of probiotics as an innovative therapeutic avenue for Major Depressive Disorder (MDD) holds substantial promise for individuals seeking depression treatment. It has the potential to diminish the sense of dependency, latency, and adverse effects commonly associated with traditional antidepressant medications (**Figure 3**) [67]. Despite abundant preclinical data, the clinical impact of probiotics on mental health has not undergone a comprehensive examination within samples of individuals experiencing depression. Additional research is imperative to establish the effectiveness of probiotics in alleviating depressive symptoms. It is essential to determine the optimal treatment duration, dosage, and specific strains that optimize probiotic efficacy.

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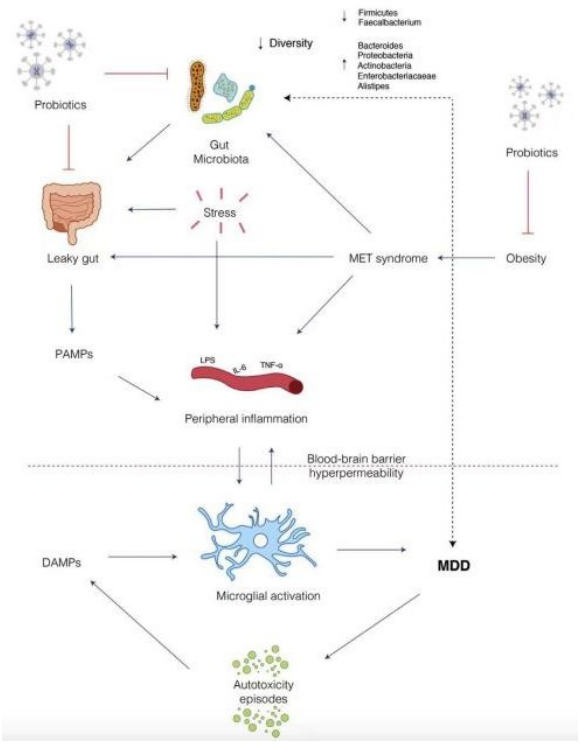

Figure 3. Pathways and associated neural pathways of probiotics to improve depression. This image is derived from Caroline Park et al.'s 2018 report [68].

2.4. Influences of antidepressant on intestinal flora

Antidepressant drugs exert a critical role in influencing the function and makeup of the gut microbiota, with a pronounced effect seen in oral antidepressants. The interplay between pharmaceuticals and the microbiota has the potential to modify bacterial metabolism and impact the activity and effectiveness of the medications [69]. Relevant research and clinical trials have demonstrated that commonly used antidepressants possess antibacterial properties, especially against Gram-positive bacteria [70]. Importantly, most commonly used antidepressants can influence the gut microbiota by altering microbial diversity and composition. Reports indicate that SSRI treatments may augment the abundance of Lactobacillus in the gut microbiota, while TCAs can increase the abundance of Clostridium [71]. Notably, fluoxetine can significantly boost the abundance of Bacteroides in the rectum, even exceeding levels seen in the non-medicated group by over 100-fold. Considering the capacity of these bacteria to generate anti-inflammatory butyrate during bacterial metabolism, their enhanced prevalence could potentially synergize with the effects of antidepressant therapy, thereby augmenting the overall therapeutic benefits of the drug. Furthermore, recent groundbreaking research suggests that the gut microbiota can serve as a predictor of treatment outcomes for late-life depression. Enrichment of bacterial genera including Ruminococcus, Roseburia, and Bifidobacterium relative to the reference genus Faecalibacterium at baseline is associated with depression remission, aiding in the prediction of true drug efficacy [72]. Nevertheless, the relationship between antidepressants and gut health remains highly debated. Oliva et al.'s 2023 study indicates that the risk of gastrointestinal side effects for all 15 antidepressants is significantly higher than for a placebo [73]. Through meta-analysis, the researchers incorporated data from 304 randomized controlled trials, analyzing side effects induced by various antidepressants, like vomiting, nausea, diarrhea, abdominal pain, and constipation. Different drugs exhibit varying risks of specific side effects, with escitalopram and sertraline showing overall poorer gastrointestinal tolerance, while fluoxetine is significantly associated with a lower risk of digestive discomfort. Given the limitations of this study, including its focus on acute-phase depression patients,

more research is needed to delve deeper into this field and ascertain the true relationship between antidepressants and the gut microbiota.

3. Conclusion

In past decade, researches on the human gut microbiota have witnessed significant advancements. The gut microbiota plays a character in shaping host metabolism, physiology, and the immune system, with its composition susceptible to the influence of external factors including host genetics, age, diet, medications, and lifestyle. Changes in the function and composition of the gut microbiota have direct implications for human body health and significantly contribute to the initiation of various diseases. Therefore, continuous research into the connection between the host and the gut microbiota is indispensable. Through the investigation of microorganisms and substances that regulate gut stability, such as probiotics, researchers have discovered the feasibility of further treating neuropsychiatric disorders. However, there is still a need for further exploration regarding the types of probiotics used, their dosages, and the duration of treatment. Moreover, more in vivo and in vitro testing is required for the coordinated use of antidepressant medications and probiotics. The widespread integration of probiotic treatment into the daily therapy of depression patients is a process that will require both time and more extensive efforts.

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