Review Article

A narrative review of relationship between gut microbiota and neuropsychiatric disorders: mechanisms and clinical application of probiotics and prebiotics

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Abstract: The gut microbiota is a kind of fixed-value bacteria in the human intestine, characterized by a large quantity, a wide variety and interdependence with each other and with the host. The gut microbiota is considered to be an important link in maintaining health and pathogenic mechanism of many diseases. The gut microbiota affects the central nervous system under the action of the microbe-gut-brain axis through nerve, immune, endocrine and metabolic pathways. The gut microbiota not only regulates the gastrointestinal tract but plays a vital role in the development and function of the brain. More and more studies believe that normal gut microbiota is essential for the development of the central nervous system and emotional regulation. The imbalance of the gut microbiota can affect some neuropsychiatric diseases. Probiotics and prebiotics are active microorganisms beneficial to the human body and can regulate the microecological balance of the human intestinal tract. Current research shows that probiotics and prebiotics have a good preventive effect on Alzheimer's disease, Parkinson's disease, depression, autism spectrum disorders and other neurological and mental diseases. Based on this, we review the relevant research on the pathogenesis of probiotics and prebiotics and neuropsychiatric diseases, in an attempt to providing new ideas for exploring the treatment and prevention of neuropsychiatric diseases.

Keywords: Probiotics; prebiotics; neuropsychiatric disorders; gut microbiota; microbiota-gut-brain axis (MGB axis)

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Introduction

Neuropsychiatric disease is a type of dysfunctional disease that can cause abnormalities in cognition, emotion, mentality, and behavior. Its main symptoms include disturbance of consciousness, movement, language and speech, cognitive dysfunction and affective disorder (1). Common neuropsychiatric disorders include schizophrenia, depression, anxiety, Alzheimer's disease (AD) and delirium. Current studies have shown that causal intervention with early support based on symptomatic treatment strategies can reverse or prevent the progression of neuropsychiatric disorders. At the same time, the treatment process should create a good treatment environment, frequent monitoring and prevention of complications. In recent years, the role of gut microbiota in neuropsychiatric diseases has been gradually recognized, and a large number of studies have found that there is an gut microbiota-gut-brain (MGB) axis

between the gut and the brain, through which intestinal bacteria regulate the brain function and behavior of the host. The human digestive tract is made up of 9.9 million intestinal bacteria and is involved in the metabolism of nutrients, hormones and vitamins, as well as in elimination of drugs and toxins (2). The dense diversity of gut microbiota plays an important role in human health and affects the progression of chronic diseases ranging from metabolic diseases to gastrointestinal (GI) diseases and colorectal cancer (3). Disorder of some gut microorganisms may also have positive or negative effects on the dietary habits and emotional behavior of the host (4). Once the intestinal internal flora is disordered, neuroendocrine regulation will be dysregulated, resulting in mental disorders such as depression and anxiety. Microorganisms in the gut are able to produce brain gut peptides, leptin, adrenocorticotropic hormone release factors, adrenocorticotropic hormone, adrenocortical ketone and other hormone substances directly acting on the brain tissue by regulating hormone secretion from intestinal endocrine cells (5).

Probiotic is a kind of active microorganism that is settled in human intestine or reproductive system, which is beneficial to human body (6). Prebiotics are substances that can be selectively utilized by the flora in the host and converted into beneficial to the health of the host, including possible non-carbohydrate substances, which can be applied to other parts of the body outside the GI tract, and the types of prebiotics are no longer only limited to food (7). The benefit of probiotics and prebiotics to the gut microbiota stems from its ability to create a more favorable GI environment and maintain the proper functioning of the host immune system. Common probiotics, mainly from *Lactobacillus* and *Bifidobacterium*, can enhance intestinal epithelial integrity, prevent intestinal barrier destruction, regulate the mucosal immune system and inhibit pathogenic bacteria growth. With the increasing understanding about the health function of probiotics and acceptance by consumers, more diverse forms of probiotics have been available in the market. From the initial simple liquid fermentation preparations and lyophilized powder, various formulations and formulas have been gradually developed and used mainly in three lines: (I) foodstuffs, such as probiotic dairy products and probiotic cereal foods; (II) in combination with other nutrients or used as health raw materials; and (III) medicines in the form of powder, capsules and tablets, although the type of strains selected and the number of live bacteria are different. In recent years, the human gut microbiota, particularly beneficial gut microbiota, probiotics and prebiotics, has become a hot spot of research and progressing rapidly. Probiotics can stabilize anxiety-like and depressive-like behavior through the MGB axis (8,9). It is reported that eating an appropriate number of probiotic-based products can help regulate inflammatory diseases and is beneficial to patients with irritable bowel syndrome (IBS) antibiotic-associated diarrhea or pouchitis. In addition, probiotics combined with antidepressants are reported to be effective and well tolerated in patients with refractory major depression (10), though more clinical trials are required to confirm these results. Prebiotics affect the brain function by regulating the intestinal ecosystem. It was found in rodent experiments (11) that prebiotics played an anti-inflammation and neuroprotective role and could cause neurobiological changes beneficial to learning, memory and relief of anxiety. A pooled analysis of 34 clinical trials on the effects of probiotics and prebiotics in the treatment of depression and anxiety showed that probiotics had effects against depression and anxiety but prebiotics did not have such effects (12). The flora of patients with mood disorders, anxiety disorders, mental illnesses, and neurodevelopmental disorders is characteristic. Probiotics and prebiotics have certain effects, but their effects are inconsistent. So, further research on the human body is needed, including analysis of the composition of the flora in neuropsychiatric patients, the effects of probiotic and prebiotic, and whether they can be used for the treatment of neuropsychiatric diseases.

We present the following article in accordance with the Narrative Review reporting checklist (available at http://dx.doi.org/10.21037/apm-20-1365).

The following is our summary on the association between the gut microbiota and neuropsychiatric disorders, the action mechanisms of probiotics and prebiotics, and their clinical applications (detailed mechanisms are displayed in *Table 1*).

Communication mechanism of the MGB axis

The MGB axis is the system of the two-way communication between the intestinal tract and the brain, which is regulated by the nervous, endocrine and immunological systems. The microorganism plays a key role in the system (13,14). The communication of the brain-microbial population is complex and carried out in many ways. One of them is the communication of the nervous system through the enteric nervous system (ENS). These contacts coordinate and control the GI secretion, movement,

Table 1 Possible mechanisms underlying the association between gut microbiota and neuropsychiatric disorders

Possible mechanisms	Neuropsychiatric disorder	Key references
Communication mechanism between MGB axis and immunomodulatory pathway	Depression, Parkinson's disease, hyperactivity disorder, schizophrenia	(13-27)
Neuroendocrine pathway	Depression, Parkinson's disease	(28-32)
Vagus nerve pathway	Anxiety	(17,33-35)
Gut microbiota metabolite pathway	Depression	(33,36)

MGB, microbiota-gut-brain axis.

mucosal transport and blood flow in the gut microflora (15). The ENS is connected to the central nervous system (CNS) via the vagus nerve to produce a direct neurochemical signal (16) from the intestinal microflora to the brain, and a neurochemical signal (17) from the nervous system to the intestinal microflora. After more than a century of research, scientists have found that the gut microbiota and its metabolic products can influence our brain, thinking and mood. The gut microbiota can generate acetic acid, propionic acid and butyric acid to influence the body, and the body can monitor and regulate the gut microbiota by means of the nerve, immunity, body fluid and the like to maintain the dynamic balance of the intestinal microflora (18).

Immunomodulatory pathway

Multiple pathways of connection between gut microbiota and nerve immunomodulation owe to the abundance and complex composition of the gut microbiota and intestinal lymphoid tissue containing 70% of the immune cells of the whole body (19). Recently, immune dysfunction is gradually considered to be one of the important pathophysiological factors of neuropsychosis. Once immune dysfunction occurs, innate immune cells release signal factors, which act on the brain to induce a series of physiological and psychological symptoms such as anorexia, irritability, depression, negative handling, fatigue and inattention (20). The gut microbiota also has immunomodulatory function and plays an important role in the expression and maturation of Toll-like receptors (TLRs) in the intestinal tract (21), and some host bacteria are needed to make the immune system fully mature (22). The gut microbiota can affect the brain function via the immune pathway in the following three ways. Firstly, cytokines induced by the gut microbiota enter the circulatory system and the brain through the transport system on the blood-brain barrier, which directly affects the activity and function of the brain (23). Secondly, TLRs are was also found on macrophage-like cells in the periventricular apparatus and choroid plexus, which respond to microbes associated molecular patterns (MAMPs) of the gut microbiota in the circulatory system and release cytokines (24). Thirdly, interleukin-1 (IL-1) receptor expressed in perivascular macrophages and epithelial cells of small cerebral vessels can directly bind to IL-1 produced by the gut microbiota in circulatory system, produce prostaglandin E2, and regulate the brain activity and function (25). Intestinal bacteria can also hydrolyze carbohydrate to produce short chain fatty acids, then combine with GRP41 and GRP43 to activate autonomic nervous system, and then immunize and affect the interaction between nerve cells (26).

Neuroendocrine pathway

CNS neurons in the brain secrete neurotrophic factors, which can specifically bind to the receptors on the target cells, which in turn secrete nutritional factors to regulate the physiological activities of the CNS to promote neural connections and regulate the function of synapses (28). Neurotrophic factors in the hippocampus can affect the mood and change the number of probiotics, which may lead to decrease the number of nutritional factors and the production of depression (29). The gut microbiota can exert a positive feedback effect on endocrine cells of intestinal epithelial cells, promote them to secrete active substances, and regulate the CNS. The gut microbiota plays an important role in maintaining the normal activity of the hypothalamic-pituitary-adrenal (HPA) axis. Aseptic animals showed overreaction of the HPA axis to restraint stress, releasing too much corticotropin and corticosterone. However, the activity of the HPA axis return to a normal state after colonization of the gut microbiota in aseptic animals (30). There are also a kind of intestinal endocrine

cells known as intestinal pheochromocytes, which secrete neurotransmitter serotonin (5-HT) and cause 95% of the body's 5-HT to be distributed in the intestinal tract. The gut microbiota regulates the release of 5-HT from pheotropin cells and the emotional activity of the brain in a paracrine manner (30,31).

Vagus nerve pathway

Vagus nerve is the main parasympathetic nerve of the human body, playing a key role in regulating the heart rate, bronchoconstriction, intestinal motility and other organ functions. The gut microbiota regulates the CNS by producing catecholamines and melatonin (17). The vagus nerve is an important signal pathway of the intestinal-brain axis, which responds to changes of intestinal bacteria and transmits information. The afferent fibers of the vagus nerve are distributed in the whole intestinal wall, but the intestinal microorganisms cannot get in direct contact with them (33). The positive effect of *Lactobacillus rhamnosus* JB-1 strain on anxiety behavior, and the gamma-aminobutyric acid (GABA) central receptor level was demonstrated by vagotomy in probiotics, but the behavior and neurochemical effects of probiotics on vagus nerve transection were not obvious in mice (34). The intestinal nervous system plays an important role in the vagus nerve pathway. Anatomical evidence shows that sensory neurons in intestinal myenteric plexuses are exposed to the gut microbiota on the one hand, and synapses are formed with motor neurons in intestinal tract on the other hand, which are involved in the regulation of intestinal motility and secretion (35).

Gut microbiota metabolite pathway

The metabolites of the gut microbiota itself also regulate the function of the nervous system through the immune and endocrine pathways. For example, the gut microbiota can secrete neurosignaling substances such as catecholamines, GABA, melatonin, and acetylcholine (Ach) to regulate the CNS through the vagus nerve (33). At the same time, intestinal bacteria can cause depression by affecting the metabolism of tryptophan and then reducing the amount of 5-HT (36).

The role of probiotics and prebiotics in depression

According to the data released by the World Health Organization (WHO) in 2017, more than 350 million people suffered from depression worldwide, with a growth rate of about 18% in the past decade. Its clinical manifestations are slow thinking, weak social communication skills and strong suicidal intentions. Microbes in feces of depressed patients can induce behavioral and physiological characteristics of depression in rats, including pleasure deficiency and anxiety behavior, as well as changes in tryptophan metabolism. Tryptophan is not only the essential amino acid of the human body but the precursor of 5-HT. Abnormal metabolism of tryptophan directly leads to low 5-HT level, which is also a major cause of depression (37). The potential of the gut microbiota as an antidepressant target is further enhanced because it can affect neurotransmitter pathways. First, intestinal bacteria can directly produce many common human neurotransmitters, including GABA, norepinephrine, serotonin, Ach and dopamine (38). Serotonin is the most studied neurotransmitter associated with depression and seems to be particularly vulnerable to the gut microbiota. A key study (39) showed that the plasma serotonin level in aseptic mice was almost three times that in conventional mice. It was later proved that this difference was second only to the significant ability of intestinal microorganisms to directly promote the synthesis of serotonin, its amino acid precursor tryptophan, in enterochromaffin (EC) cells. In addition, when the intestinal flora changes, the expression of hippocampal brain-derived neurotrophic factor (BDNF) decreases, causing changes in the composition and function of neurons in the cortex and hippocampus, which leads to depression (29).

Recent studies have shown that probiotics can control depression-like behavior by restoring cortisol levels, reducing the concentration of inflammatory factors, regulating serotonin and CNS transmitters, and other multiple mechanisms (40). Some animal studies have shown that the number of anaerobes was increased in the intestine of mice under prolonged pressure and at the same time the diversity of flora was decreased (41). The gut microbiota can change the permeability of the intestinal tract, cause local inflammation and subsequently activate the intestinal immune system (42). But the probiotics in the intestine have the ability to reduce the leakage of bacterial endotoxin into the blood, thereby reducing the systemic inflammatory response, which can achieve the therapeutic effect on the CNS by improving the regulation of the HPA axis and enhancing the activity of neurotransmitters (43). Microorganisms in the intestinal tract can directly act on the brain tissue by regulating hormone secretion from

intestinal endocrine cells and producing brain-intestinal peptide, leptin, corticotropin releasing factor, corticotropin and adrenocortical ketone. Other studies have shown that probiotics can change the sensitivity of the intestinal tract, regulate the excitation threshold of intestinal neurons, maintain the ecological stability of gut microbiota, and then regulate the secretory function of intestinal cells, act on the CNS and alleviate depression.

Prebiotics such as inulin, oligofructose, galacto-oligosaccharides and dextran are widely used to improve the GI function. These prebiotics may also affect other parts of the body away from the GI tract. Oligofructose and galacto-oligosaccharide were found to have antidepressant and anti-anxiety effects when administered orally in a mouse model (44). Prebiotics regulated the expression of specific genes in the hippocampus and hypothalamus, increased cecal acetic acid and propionic acid, and decreased the concentration of isobutyrate, all of which are related to behavioral improvement. Additionally, the flora under stress was restored to the normal level. Experiments in rodents showed that prebiotics could cause neurobiological changes. However, the results of both experimental studies and clinical trials on the benefits of prebiotics in depression, learning and memory are controversial.

The effect of the gut microbiota on stress response is a groundbreaking discovery, which leads to speculation about the antidepressant effect of probiotics such as *Bifidobacterium*. However, the study of the mechanism underlying the microbiome-intestinal-brain interaction is still in its infancy and needs to be further clarified. Dysfunction of the HPA axis is only an integral part of many causes of depression, but whether microbiota can affect other pathways of depression such as immunomodulation and serotonin metabolism remains open. In all, regulating gut flora by probiotics and prebiotics may be a potential treatment for depression.

Probiotics, prebiotics and Parkinson's disease (PD)

PD is a common neurodegenerative disease in middle-aged people, characterized by the occurrence of α synapses and protein variation of neurons, which involves the central, autonomic and intestinal nervous systems. Compared with healthy people, the bacteria producing "anti-inflammatory" butyric acid in PD patients were significantly reduced (45). *Clostridium* tenella in the mucous membrane was also significantly decreased, while the number of "inflammatory" denatured bacteria was increased, suggesting that the disorder of inflammatory response in PD patients promotes the misfolding of α-synaptic nucleoprotein induced by inflammation (46,47). Fecal analysis of PD patients showed that the abundance of *Enterobacteriaceae* was increased and that of *Prevotellaceae* was decreased significantly. In addition, change in *Enterobacteriaceae* abundance was closely related to the unstable walking posture of the PD patients (27). Mice transplanted with the feces from PD patients exhibited dyskinesia, decreased GI function and constipation as compared with mice transplanted with the feces from healthy people (27).

The gut microbiota can enhance the inflammation of α synapses through immune response and cause its misfolding. Misfolded α synaptic nucleoprotein activated microglia to secrete pro-inflammatory factors such as tumor necrosis factor α (TNF-α), IL-6, IL-1β and also activated antigen presenting cells. Under the action of MHCII molecules and costimulatory signals, the original T cells were promoted to differentiate and proliferate into effector T cells, forming Th1, Th2 and Th17. Th1 and Th17 could cross the blood-brain barrier and migrate to brain lesions. Microglia secreted pro-inflammatory factors, activated microglia-mediated innate immune response, produced neurotoxicity and apoptosis or death of dopamine neurons through α-synaptic nucleoprotein specific MHCII complex, leading to PD (32). Segmented filamentous bacteria (SFB), which exists in animal GI bacteria, could regulate the response of local and systemic Th17, and also regulate the activation threshold of reactive T cells at the same time. After colonization in aseptic experimental autoimmune encephalomyelitis (EAE) mice, Th17 cells were induced in the intestine, while the increased response of Th17 cells could lead to the recurrence of EAE, indicating that intestinal bacteria can induce the immune response of the CNS (48).

Probiotic can help the intestinal tract to produce a favorable microenvironment. For instance, *Lactobacillus* and *Bifidobacillu*s can enhance epithelial integrity. *Lactobacillus* was found to reduce anxiety, depression and stress response, and regulate the expression of GABA receptor in the CNS in animal infection models (49). At the same time, probiotics could also reduce abdominal distension, abdominal pain and constipation in PD patients (33). The imbalance of the gut microbiota can increase the incidence of PD by participating in the pathological process. Probiotics can reduce complications, intestinal permeability, microbial translocation and neuroinflammation, and have certain

preventive and therapeutic effects against PD.

More than 80% PD patients are accompanied by symptoms of constipation. In recent years, this symptom has been found to be associated with the destruction of intestinal permeability and integrity by co-nuclear proteins. Some recent studies on intestinal constipation used prebiotic fiber treatment in PD patients and explore the pharmacokinetic effect (49), finding that the gut microbiota played an important role in PD, and prebiotics had potential therapeutic effects against PD, though further studies are needed to verify these findings and conclusion.

Probiotics, prebiotics and hyperactivity disorder

Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental condition related to abnormal dopamine nerve transmission, defects of mental reward and punishment treatment and its neural circuits, including the ventral striatum. The intestinal microbial composition has been studied in adolescents and adults with ADHD. It was found that the relative abundance of several bacteria was different between the case and control groups, although the difference was statistically insignificant. The promoting effect of the intestinal microflora on dopamine precursor synthesis in ADHD patients was significantly enhanced, and the increased microbial community function was related to the decrease of neural response to reward expectation (50). Genetic studies have shown the role of dopamine, norepinephrine and serotonin related genes in ADHD (51), but these studies also showed that environmental factors also played a role in the etiology of ADHD. The prediction of dopamine precursor synthesis by intestinal microflora in ADHD patients was significantly enhanced. The increased microbiological function was found to be related to the decreased neural response to reward expectation, which is one of the characteristics of ADHD (52).

It was supposed that diets could influence intestinal microbes and affect ADHD symptoms and some behaviors of ADHD patients (50). One of the mechanisms by which intestinal microflora acts on the brain and behavior is the synthesis of neurochemicals and their precursors, which are structurally similar to those of the host nervous system (53). Using specific bacterial species markers, some recent experimental studies made related comparisons and found that the decreased abundance of *Bifidobacillus* in children could predict hyperactivity disorder or Asperger's syndrome at 13 years of age (54,55). In all, the gut-brain axis may be a target for the development of new drugs for ADHD, and probiotics may be used to regulate the brain function and behavior. Despite the evidence supporting the use of prebiotics for GI neurotic dysfunction, immune function, and neuroprotection, their use has never been investigated in patients with ADHD. So, more research is needed to explore the effect of prebiotics, probiotics or their combination on ADHD.

Probiotics, prebiotics and schizophrenia

Schizophrenia is a chronic mental illness caused by the combined action of genetic and environmental factors. Its specific etiology and pathogenesis are unclear. The current hypotheses about the onset of schizophrenia include genetics, neurotransmitters, and neurodevelopmental hypotheses. Recently, there has been an increase in related studies on the onset of schizophrenia, neurodevelopment, and inflammatory immunity. Many studies believe that the intestinal flora can regulate the body's immune inflammatory response and affect the neurodevelopment. The relationship between the intestinal flora and schizophrenia has become a recent research hot spot.

Schizophrenia is a severe and typical chronic mental disorder characterized by delusion, cognitive impairment, apathy and social withdrawal. In schizophrenia, *Lactic acid* bacteria are believed to play a dominant role in metabolite transport (56). Considering the role of probiotics in other mental diseases such as depression and anxiety, we can once ask by analogy whether probiotics also play a role in schizophrenia. A 14-week experiment demonstrated that although the use of probiotics improved the intestinal problems of the schizophrenic patients, it had no effect on the positive symptoms of schizophrenia (57). Inflammatory markers in schizophrenia patients were increased, but bacterial translocation remained unchanged significantly, suggesting that probiotics may not be effective against schizophrenia, and intestinal or oropharyngeal flora in schizophrenia patients may change. However, vitamin D combined with probiotics (including *Lactobacillus acidophilus*, *Bifidobacterium bifidum*, *Lactobacillus reuteri*, and *Lactobacillus fermentum*) could significantly improve schizophrenia, increase the overall antioxidant capacity, and reduce aldehyde and high-sensitivity C-reactive protein (CRP) levels (58). In short, there are controversies over the efficacy of probiotics in the treatment of schizophrenia and more systematic and in-depth research is required in future.

Abnormal activation of inflammatory responses is not uncommon in many patients with schizophrenia. The

immune response of the body to external antigens is partly determined by the composition of the gut microbiota, which is also a contributing factor to the immunomodulatory effect of probiotics. Previous studies showed that individuals with some potential pathogenic bacteria in the intestine were more likely to produce abnormal immune responses than those with large numbers of non-pathogenic bacteria in the intestine (59). In particular, schizophrenia is still a challenge for researchers, and the possibility of microbiome and immune-mediated pathology should be better explored, not only in animal models but in clinical trials of agents that are able to alter the gut microbiota and may affect the mechanism of GI inflammation (60). Microbiome targeted treatments have not been well-studied yet in patients with schizophrenia. Nonetheless, the field is well worth of being appropriately investigated.

Probiotics and prebiotics as a target will be a new treatment for neuropsychiatric diseases, what can we do?

Psychosocial stress is a major factor in mental illness. Stress activates the corticotropin-releasing hormone (CRH) and vasopressin (AVP) can alter the intestinal barrier function by releasing corticotropin. It is known that stress and the HPA can influence the composition of the gut microbiome. Some probiotics and prebiotics can prevent intestinal diseases by regulating the gut microbiota. However, probiotic intervention can change the type and abundance of the gut microbiota, and human immune cells and immune molecules as well. Therefore, probiotics will have great potential as a new target for the treatment of neuropsychiatric disorders. There is a study reporting that the anxiety state was improved significantly in patients administered with the strain of Lactic acid bacteria as compared with those in the placebo group (9), which also further supports the use of the gut microbiota as a target of viable treatment.

The gut microbiota affects the health of the host, and its targeted interventions have been used to prevent and treat neuropsychiatric disorders, which is both a prospect and a challenge. Now most research stays in animal models, and needs to be adjusted for individualized treatment and transformed into clinical treatment in future, and there is no approved probiotic therapy in Europe and the United States. The colonization ability of probiotics is host-specific, and the colonization ability of the same strain is similar in consanguineous hosts. The colonization of probiotics is affected by the gut microbiota. After antibiotics interfere with flora, probiotics are not helpful to the recovery of flora.

Customized by probiotics, targeting specific flora and its metabolites, will be used to regulate the flora-intestinal-brain axis to prevent neuropsychiatric illnesses. At present, the research on flora has changed from a descriptive discipline to a mechanistic one. Individualized intervention and disease prediction with the flora have become a focus of future research, including the causality, heterogeneity of human flora, the role of non-bacterial members, and standardization of the research methods. In addition, we still need to pay attention to randomized controlled trials (RCTs) and other aspects.

Animal models showed that prebiotics may play a role in neuropsychiatric diseases by regulating the gut microbiota. Compared with probiotics, there is not much research concerning the effect of prebiotics on human neuropsychiatric illnesses and most studies in this field are mainly confined to animal experiments. In view of the wide variety of prebiotics, future research on prebiotics needs to be more standardized, targeted human testing.

Metagenomic sequencing can accurately identify microorganisms at the strain level, and can also conduct in-depth research on genes and functions. Many intestinal microorganisms have obvious heterogeneity at the strain level, and differences between strains may also bring about differences in pathophysiological functions. Therefore, using a combination of metagenomics and metabonomics to study how probiotics and prebiotics regulate the balance of the gut microbiota in patients with neuropsychiatric diseases may reveal the mystery of the personalized intervention of probiotics and prebiotics in the treatment of neuropsychiatric diseases.

Conclusions

This review summarizes the roles and mechanisms of the MGB axis as a potential strategy for neuropsychiatric diseases. The importance of maintaining the balance of the gut microbiota has been increasingly recognized, knowing that human physiological metabolism and mental health are controlled not only by their own genes but by intestinal microorganisms as well.

Over the last decade, many efforts have been made to explore the *in vitro* and *in vivo* effects of probiotics and prebiotics in the treatment of neuropsychiatric illnesses (61). The results have demonstrated that probiotics can alleviate

many neuropsychiatric diseases including depression, autistic, PD and AD, and even a lot of functions that we have not yet explored. At the same time, due to the close relationship between probiotics, prebiotics and health, nutrition and diet, so people are called on to eat a quantity of intestinal probiotics and prebiotics through daily diet.

Despite this wealth of information, the true effects of probiotics and prebiotics remain largely unexplored, and numerous gaps and inconsistencies exist when the studies are compared. Probiotics and prebiotics have a certain mitigating effect on different neuropsychiatric diseases, but the effects are inconsistent. The dosage, strain type, probiotic and prebiotic type, gut microbiota assessment, the length of intervention, standardization of neurological measurements, diversity and complexity of neurological symptoms, differences in study design and group size all make it difficult to confirm efficacy evidence. We need to further develop human studies, including analysis of the composition of the flora in specific patient populations, and the effects and safety of probiotics and prebiotics. In conclusion, regulation of the gut microbiota by probiotics, prebiotic and the like may be new methods for treating related neuropsychiatric diseases in future.

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Footnote

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