World Journal of Biology Pharmacy and Health Sciences
eISSN: 2582-5542
Cross Ref DOI: 10.30574/wjbphs
Journal homepage: https://wjbphs.com/

(Review Article)

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Microbiome and mind: current insights and future directions in gut-brain research

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World Journal of Biology Pharmacy and Health Sciences, 2024, 19(01), 086–094

Publication history: Received on 25 May 2024; revised on 05 July 2024; accepted on 08 July 2024

Article DOI: https://doi.org/10.30574/wjbphs.2024.19.1.0396

Abstract

Recent research has increasingly focused on the relationship between gut microbiota and neurological disorders, revealing the broad role of gut microbiota in modulating various physiological and pathological conditions. The bidirectional communication between the brain and gut microbiota is now recognized as crucial for maintaining homeostasis. This gut-brain axis encompasses the central nervous system (CNS), neuroendocrine and neuroimmune systems; autonomic nervous system, enteric nervous system, and intestinal microbiota. Probiotics, which are live microorganisms similar to beneficial gut microbes, have been shown to modulate numerous conditions, including metabolic disorders, behavioral issues, and cognitive functions. Over the past decade, gut microbiota has emerged as a key regulator of brain processes and behavior. Diet significantly influences gut microbiota composition throughout life, and its impact on brain health via microbiota is gaining attention. Identified mechanisms of gut-to-brain communication include microbial metabolites, immune responses, neuronal signaling, and metabolic pathways, all potentially modifiable by diet. Animal studies on nutritional interventions targeting the microbiota-gut-brain axis have advanced our understanding of diet's role in this complex interaction. This review summarizes current literature on the interplay between diet, microbiota, and host behavior/brain processes, explores underlying mechanisms, and discusses factors influencing dietary intervention responsiveness and the microbiota's role in modulating diet's effects on brain health.

Keywords: Gut-microbiome; Gut-brain axis; Mental health; Homeostasis

1. Introduction

Gut microbiota, also known as gut flora, refers to the diverse community of microorganisms residing in the digestive tracts of humans and other animals. This complex ecosystem includes bacteria, archaea, viruses, and fungi, with bacteria being the most abundant [1-2]. The gut-brain axis is a sophisticated, bidirectional communication network that links the gastrointestinal tract and the central nervous system (CNS) [3-4]. This intricate system is crucial for maintaining homeostasis and regulating a multitude of physiological processes, including lifespan [3-4]. Central to this axis is the communication facilitated by the autonomic nervous system (ANS), the hypothalamic-pituitary-adrenal (HPA) axis, and other neural connections [3-4] Fig. 1. Through these pathways, the brain can directly influence gut function, and conversely, the gut can send signals that impact brain activity. This intricate system highlights the importance of a coordinated response between the CNS and the digestive system to adapt to varying internal and external stimuli.

One of the significant factors influencing the gut-brain axis is stress. Exposure to stress can lead to dysregulation of this axis, manifesting in both gastrointestinal and neurological disorders. Stress-mediated responses through the HPA axis and ANS affect gut motility, secretion, and blood flow, illustrating the vulnerability of this communication network to psychological and physical stressors [5,6]. Moreover, the gut microbiota—a diverse community of microorganisms residing in the digestive tract-play a crucial role in this axis. These microorganisms provide significant protection against bacterial pathogens and play a crucial role in immune system development and function [7]. The microbiota's influence extends to brain function through the production of metabolites and neurotransmitters, impacting mood,

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cognition, and overall mental health [8-10]. Thus, dietary habits that support a healthy gut microbiota are essential for optimal mental health.

The gut microbiota also offers significant therapeutic opportunities. Modulating the gut microbiota through diet, probiotics, and other interventions holds promise for treating various conditions, including mental health disorders. Chronic low-grade inflammation, often resulting from intestinal dysbiosis, is linked to neurological deficits, highlighting the interconnectedness of gut health and brain function [11]. Research has further revealed the involvement of gut microbiota in regulating social behavior, depression-like behavior, physical performance, and motivation [12]. These findings underscore the profound impact of the gut-brain axis on various aspects of health and behavior, suggesting new avenues for therapeutic intervention.

In summary, the gut-brain axis is essential for maintaining physiological balance and overall health. Understanding this complex network opens up new opportunities for therapeutic strategies targeting both neurological and gastrointestinal health, particularly in the context of stress-related disorders, dietary influences, and microbial imbalances.

1.1. Mechanisms of gut brain communication

The gut-brain axis represents a complex and dynamic network of communication pathways that connect the gastrointestinal tract and the central nervous system (CNS). This bidirectional interaction involves neural, endocrine, immune, and humoral mechanisms, which collectively influence both gut and brain function [3-4]. Recent research has highlighted the critical roles of the gut microbiota and various signaling molecules in mediating this communication, thereby impacting a wide array of physiological and pathological processes.

One of the key pathways facilitating direct communication between gut bacteria and the brain is the vagus nerve [13]. This major component of the parasympathetic nervous system transmits signals from the gut to the brain and vice versa, playing a crucial role in regulating various bodily functions, including digestion, mood, and immune responses. The gut-brain axis also significantly modulates the immune system, which is essential for managing the stress response within the gut [14].

The gut microbiota influences the host gut-brain axis through neurohumoral communication, affecting brain development and behavior. Stress and emotions can alter the microbial composition of the gut by triggering the release of stress hormones and sympathetic neurotransmitters, such as gamma-aminobutyric acid (GABA) and serotonin (5-HT) precursors [14]. Gut bacteria such as certain species of *Lactobacillus* and *Bifidobacterium* can influence the production of serotonin in the gut [15]. Since about 90% of serotonin is produced in the gut, this can significantly affect mood and behavior by signaling through the vagus nerve to the brain. Certain gut bacteria, like *Lactobacillus rhamnosus*, produce GABA, an inhibitory neurotransmitter. This can influence brain function through vagal signaling, potentially affecting anxiety and depression. These changes can impact gut physiology and create a habitat conducive to different microbial populations. Host stress hormones, like norepinephrine, can influence bacterial gene expression and signaling, leading to alterations in microbial composition and activity [16].

Studies on germ-free mice, which are raised without any exposure to microorganisms, have revealed critical insights into the role of gut microbiota in regulating the hypothalamic-pituitary-adrenal (HPA) axis, immune function, and stress response. For instance, Experimental studies on germ-free mice have revealed increased activation of the hypothalamic-pituitary-adrenal (HPA) axis in response to stress, along with significant deficiencies in immune function and increased susceptibility to infections [17]. These findings underscore the critical role of gut microbiota in modulating stress responses and immune competence. Also, it has been shown that stress activates the HPA axis, leading to the release of cortisol, adrenaline, and norepinephrine, as well as corticotrophin-releasing factors. This cascade increases anxiety-like behaviors, abdominal pain, colon secretion, muscle contraction, and gut permeability, contributing to gastrointestinal inflammation [18]. Stress also enhances gut permeability, allowing bacterial antigens to cross the epithelial barrier, which increases mucosal immune responses and alters the gut microbiome composition [18-19]. Gut infections are believed to be initiators of behavioral and mood disorders, including psychosis. Probiotic administration of *Bifidobacterium* and *Lactobacillus* has been shown to increase GABA levels and neurotrophic factor expression, alleviating neurological symptoms [18, 20].

A high-fiber diet promotes greater diversity and richness of gut microbiota, increasing the abundance of beneficial taxa that contribute to neuroprotection and neuronal plasticity [21]. This intricate interplay between diet, microbiota, and the brain underscores the importance of the gut-brain axis in maintaining overall health and managing disease. Short-chain fatty acids (SCFAs), produced by microbial fermentation of dietary fibers, contribute to glucose homeostasis, mucosal serotonin release, lymphocyte function, and the preservation of brain integrity, influencing learning and memory acquisition [22]. Serotonin released from enterochromaffin cells in the gut modulates various reflexes, including peristaltic, secretory, vasodilatory, vagal, and nociceptive responses [18, 23]. SCFAs can cross the gut-blood barrier and influence brain function by acting on receptors on vagal afferent neurons, which can modulate brain activity and behavior [22]. Diets high in fats and carbohydrates but low in fiber are associated with systemic inflammation and metabolic disorders, such as obesity, which is considered a chronic low-grade inflammatory state [24]. Inflammatory cytokines secreted from adipose tissue in obesity are linked to conditions like rheumatoid arthritis, further illustrating the connection between diet, gut health, and systemic inflammation [18]. On the other hand, Prebiotic fibers enhance the expression of satiety hormones like peptide YY (PYY) [25] and reduce the expression of the orexigenic peptide ghrelin [25], influencing feeding behavior and energy homeostasis. Brain-derived neurotrophic factor (BDNF) is another critical molecule involved in the therapeutic treatment of depression, emphasizing the interplay between diet, microbiota, and brain function [26]. BDNF supports the growth and differentiation of new neurons and synapses, particularly in regions such as the hippocampus, which are vital for mood regulation and cognitive function [27].

Irritable Bowel Syndrome (IBS) is a common gastrointestinal disorder characterized by chronic abdominal pain, bloating, and altered bowel habits, such as diarrhoea, constipation, or a combination of both. It is believed to result from a complex interplay of factors, including gut motility issues, hypersensitivity, intestinal inflammation, and alterations in the gut microbiota [28]. It has also been known to be associated with anxiety and obsessive-compulsive disorder (OCD). In these patients, plasma cortisol levels are linearly related to plasma serotonin levels, indicating a strong link between gut physiology and stress-related disorders [18, 29]. Polymorphisms in serotonin reuptake transporter (SERT) genes are associated with subtypes of IBS, highlighting genetic influences on gut-brain interactions [18, 30]. Functional dyspepsia (FD) and functional gastrointestinal disorders (FGIDs) such as IBS are often linked to psychological factors, including anxiety disorders. Patients with FD frequently report higher levels of anxiety, which can exacerbate gastrointestinal symptoms [31]. This connection is largely mediated through the gut-brain axis, an intricate network facilitating constant communication between the gut and the central nervous system. Patients with FGIDs often exhibit low-grade inflammation in the gut, which can contribute to symptoms like pain and discomfort. This inflammation is sometimes linked to increased intestinal permeability, also known as "leaky gut." [32].

Probiotics, known as psychobiotics play a multifaceted role in modulating the gut-brain axis and enhancing communication between the gut and the brain. They possess antidepressant and anxiolytic properties, highlighting their potential therapeutic benefits [33]. Synbiotics, which combine prebiotics and probiotics, enhance the viability and efficacy of probiotics [34]. Postbiotics, which include SCFAs and other bacterial metabolites, also play a role in gut-brain communication [35]. The gut microbiota ecology and the gut brain axis play important roles in altering central sensitivity of almost all inflammatory diseases.

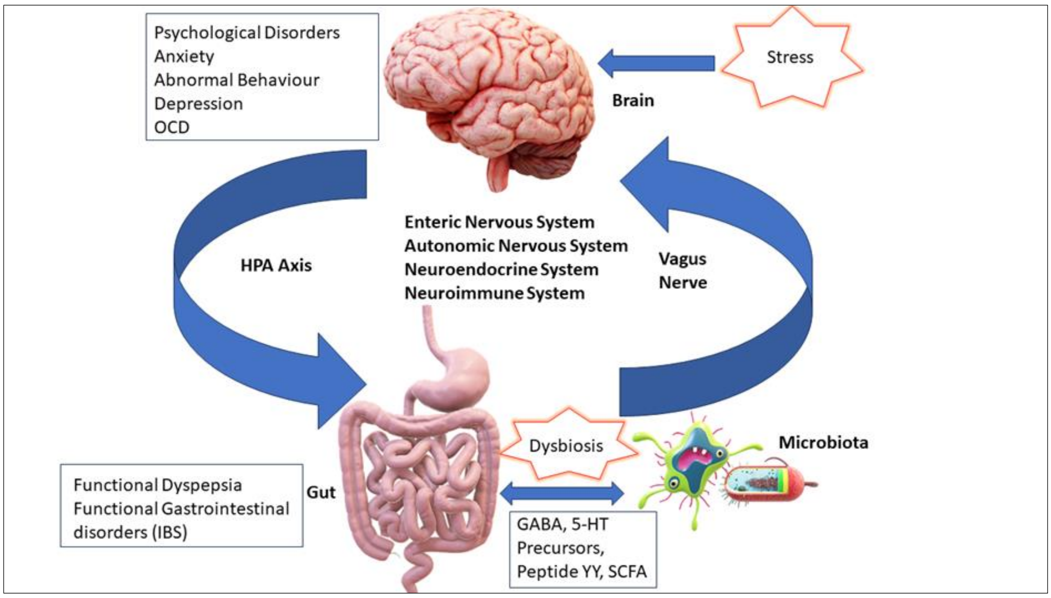

Figure 1 The gut microbiota and gut-brain axis (GBA) engage in bidirectional communication that modulates the stress response. The microbiota communicates with the gut-brain axis through endocrine messaging, immune messaging and neuronal messaging. These interactions influence mental health. Stress affects the gut-brain axis, impacting the microbiota and contributing to functional gastrointestinal disorders and dysbiosis

1.2. Targeting the Gut-Brain axis

1.2.1. Fecal microbiota transplantation

Fecal Microbiota Transplantation (FMT) has garnered significant attention for its potential to positively alter the gut microbiota composition in diseased patients. This therapeutic intervention involves the transfer of fecal matter from a healthy donor to a recipient, aiming to restore a balanced and healthy microbiota [36]. While FMT is primarily known for its effectiveness in treating *Clostridioides difficile* infections [37], emerging research indicates that its impact extends to the gut-brain axis, thereby influencing mental health [38]. Studies have shown that FMT can reduce symptoms of depression and anxiety [38]. For instance, a clinical trial involving patients with major depressive disorder reported significant improvements in mood following FMT [39]. Preliminary studies suggest that FMT may alleviate some gastrointestinal symptoms and behavioral issues associated with Autism spectrum Disorders (ASD) [40]. Improvements in social communication and reduction in repetitive behaviors have been observed in some cases [40]. There is evidence suggesting that FMT may help in managing Parkinson's disease (PD) symptoms by targeting gut dysbiosis, which is believed to exacerbate neurodegenerative processes [41]. FMT represents a promising frontier in the treatment of mental health disorders through its modulation of the gut-brain axis. While it is unlikely to serve as a stand-alone therapy for all conditions, FMT could complement existing treatments and provide a novel approach to managing psychiatric symptoms. Future research should focus on elucidating the mechanisms by which FMT influences the gut-brain axis, optimizing treatment protocols, and exploring its long-term impacts on mental health.

1.2.2. Probiotics

Probiotics, beneficial live microorganisms, have garnered significant attention for their role in enhancing mental health through modulation of the gut-brain axis. Probiotics are live microorganisms that, when administered in adequate amounts, confer a health benefit on the host [42]. These beneficial bacteria and yeasts primarily support digestive health by maintaining or restoring the gut microbiota balance. Scientific evidence suggests that probiotics can modulate immune responses, enhance nutrient absorption, and potentially impact systemic health, including mental well-being, through the gut-brain axis [43]. This intricate communication network links the gut microbiota with the central nervous system, influencing brain function and behavior. Research has demonstrated that specific probiotic strains can positively impact mental health. For example, *Lactobacillus rhamnosus* JB-1 has been found to reduce anxiety and depressive-like behaviors in animal models by modulating the expression of GABA receptors in the brain [44]. In human studies, *Bifidobacterium longum* NCC3001 has shown promise in alleviating symptoms of depression and improving overall mood by decreasing systemic inflammation and regulating stress hormone levels [45]. Additionally, a multi-strain probiotic supplement containing *Lactobacillus acidophilus*, *Bifidobacterium bifidum*, and *Bifidobacterium lactis* has been associated with reduced psychological distress in clinical trials [46]. Furthermore, administration of SLAB51, a new probiotic formulation, in a human in vitro PD model (SH-SY5Y) was able to increase cell viability via reducing oxidative stress and neuronal death as well as reverse phenotypic deficits in motor behavior when placed in a rodent PD-model [47]. These examples highlight the potential of probiotics as a complementary approach to traditional mental health treatments, offering new avenues for improving psychological well-being through gut microbiota modulation. Scientists have recently also highlighted the intriguing potential of probiotics in enhancing mood during COVID-19 [48]. Beyond restoring intestinal balance, probiotics also mitigate the risk of opportunistic pathogens colonizing the intestine [49]. However, there is considerable variability in the composition, stability, and authenticity of probiotic products, with no established consensus on optimal dosage, duration, or specific strains to use. Additionally, host resistance to colonization presents a significant challenge to the efficacy of probiotic-based therapies. Therefore, caution is warranted when administering probiotics to patients. More comprehensive and detailed characterizations of these microorganisms are necessary to ensure their safe and effective use in clinical settings.

1.2.3. Diet

The role of diet in the gut-brain axis is pivotal, influencing both gut microbial composition and neuronal function, thereby impacting cognitive and emotional processes [50]. Dietary components such as fiber, prebiotics, and polyphenols serve as substrates for beneficial gut bacteria, promoting their growth and activity [51]. For instance, fiber-rich diets encourage the production of short-chain fatty acids (SCFAs) like butyrate, which have neuroprotective effects and can modulate neurotransmitter synthesis in the brain [52]. Conversely, diets high in saturated fats or low in fiber can alter gut microbiota composition unfavorably, contributing to systemic inflammation and potentially impairing cognitive function [53]. Moreover, specific dietary patterns such as the Mediterranean diet, rich in fruits, vegetables, and omega-3 fatty acids, have been associated with reduced risk of neurodegenerative diseases [54], suggesting a direct link between dietary choices, gut health, and brain function. To bridge the gap from research to clinical application, several ongoing clinical trials are exploring the impact of dietary interventions on various neurological disorders. One longitudinal study, "The Role of the Microbiota-Gut-Brain Axis in Brain Development and Mental Health," is investigating the effects of Galacto-oligosaccharides (prebiotics) on cortical excitability, plasticity, and the regulation of anxiety and cognitive function [55]. Concurrently, a Phase III clinical trial titled "Mediterranean-DASH Diet Intervention for Neurodegenerative Delay" is evaluating the cognitive outcomes in elderly, overweight individuals with a history of poor nutritional intake, focusing on the potential benefits of a hybrid Mediterranean-DASH diet [56]. These studies aim to elucidate the therapeutic potential of dietary strategies in mitigating neurological decline and enhancing mental well-being. Understanding these interactions underscores the importance of diet as a modifiable factor in maintaining gut-brain axis homeostasis and potentially mitigating neurological disorders.

1.2.4. Antibiotics

Antibiotics play a significant role in influencing the gut-brain axis and potentially impacting mental health. They play a critical role in altering the composition of gut bacteria, influencing immune responses, and affecting therapeutic outcomes in various diseases [57]. In glioma patients, antibiotics are indispensable for preventing or treating life-threatening infections caused by microbial-induced immunosuppression [58]. Moreover, targeting the gut microbiome with appropriate antibiotics holds promise for enhancing tumor control [58]. For instance, clofoctol, an antibiotic, has shown potential as a direct therapy by inhibiting glioma-stem-cell proliferation through upregulating the tumor suppressor gene Kruppel-like factor 13 (59]. This mechanism suggests a therapeutic avenue in glioma treatment that extends beyond traditional antimicrobial actions. A recent clinical trial titled "Microbiota Intervention to Modify Parkinson's Disease Response" has been initiated to explore the effects of Rifaximin, an antibiotic, on reducing harmful bacterial populations and alleviating clinical symptoms of Parkinson's disease, including inflammation markers in serum [59]. This underscores the importance of integrating microbiota knowledge and impacts into the evaluation of new antibiotics and medications.

However, caution is warranted as antibiotics can inadvertently harm the diversity of the gut microbiota, potentially exacerbating neurological diseases. Studies have demonstrated that broad-spectrum antibiotic treatments can diminish cognitive function [60]. Moreover, research involving syngeneic glioma mouse models revealed that antibiotic treatment led to increased intracranial glioma growth and significantly altered microbiota composition [61]. These changes weakened the brain's immune response, compromising its ability to combat tumors effectively [61]. In summary, while antibiotics offer essential benefits in managing infections and potentially as direct therapeutic agents in gliomas, their impact on the gut microbiota underscores the need for careful consideration and further research to mitigate unintended consequences on neurological health.

2. Conclusion

The intricate relationship between gut microbiota and mental wellbeing underscores the necessity of maintaining the homeostasis of both for optimal health. Alterations in gut microbiota have been shown to mediate significant functional and behavioral changes in both animal models and clinical studies. This discovery opens new avenues for therapeutic interventions targeting stress-related disorders, such as Irritable IBS. Probiotics have shown promise in managing anxiety and depression, and there is growing interest in exploring their potential for treating metabolic disorders like diabetes and obesity. Moreover, understanding the interactions between herbal medicine and the gut-brain axis could provide additional therapeutic strategies.

While the burgeoning use of probiotics suggests a promising future, it is crucial to assess the long-term safety of these interventions. Dietary patterns significantly influence gut microbiota, which in turn affects brain function and behavior. High-fat, high-sugar diets have been linked to negative outcomes, whereas diets rich in plant foods and low in ultraprocessed foods appear beneficial for mental health. However, individual variations in metabolic responses necessitate a deeper understanding of how specific dietary components influence gut microbiota and subsequent health outcomes. The field of diet-microbiota-brain interactions, though compelling, remains in its infancy, and caution is needed when interpreting results from preclinical studies.

Future perspectives

To advance microbiota-targeted human interventions, several critical areas need further exploration. First, identifying the factors that predict individual responses to specific interventions is essential. Given the link between unhealthy diets and microbial extinction, future nutritional interventions may combine dietary approaches with tailored probiotics to enhance efficacy. Research has indicated that restoring microbial diversity lost through low-MAC (microbiota accessible carbohydrate) diets may require the reintroduction of missing microbes, potentially through probiotic supplements or fermented foods.

Although current human intervention studies are limited, they consistently support increasing plant food intake and reducing ultraprocessed foods. The My New Gut consortium's recommendation for a plant-based diet rich in grains, fibers, fermented foods, and fish for patients with depression aligns with broader dietary guidelines for overall health. Manipulating the microbiota through diet may offer a more sustainable and cost-effective approach compared to probiotic supplementation.

Future research should aim to establish causality, clearly define a "healthy microbiota," and explore the potential and limitations of personalized nutrition. Integrating multiomics approaches will be crucial for understanding the overall functionality of microbial communities. Given the significant health disparities faced by individuals with mental disorders, interventions that simultaneously improve physical and mental health could have profound impacts on both individual well-being and public health outcomes. In summary, while the connection between diet, gut microbiota, and mental health offers promising therapeutic opportunities, much remains to be understood. Continued research is essential to fully elucidate these relationships and develop effective, evidence-based interventions for enhancing both mental and physical health.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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