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Analysis of the Differences in Gut Microbiota Structure in Anxiety and Depression

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Abstract: Anxiety and depression, as highly prevalent mental disorders globally, are witnessing a year-on-year increase in incidence rates. According to data from the World Health Organization, the number of individuals suffering from anxiety disorders has surpassed 400 million, while those with depression exceed 380 million, with the disease burden becoming increasingly heavy. The pathogenesis of anxiety and depression has not yet been fully elucidated. In recent years, the emergence of the "microbiota-gut-brain" axis theory has opened up a new perspective for the study of anxiety and depression. The gut microbiota, as the largest microbial community in the human body, may be involved in the occurrence and development of various diseases, including anxiety and depression, when its homeostasis is disrupted. In-depth research and comparative analysis of the structural differences in the gut microbiota of individuals with anxiety and depression are of great significance for unraveling the pathogenesis of these disorders and developing precise prevention and intervention strategies.

Keywords: Anxiety; Depression; Gut Microbiota; Differences.

1. Introduction

In modern society, the high-efficiency and fast-paced work and life patterns have become the norm. Fierce competition and prolonged stress have led to a continuous increase in the psychological burden of Homo sapiens, with accumulating negative emotions triggering a rising trend in the incidence of mental, psychological, and psychosomatic disorders. Among these, anxiety disorders and depression have become prevalent and common ailments in today's society [1]. Anxiety disorders generally refer to generalized anxiety disorders, which carry a chronic risk of disability and severely impact the physical and mental health of Homo sapiens. In 2019, Lancet Psychiatry published China's first nationwide epidemiological survey on mental disorders, revealing that anxiety disorders ranked first in prevalence among psychiatric conditions, with a lifetime prevalence rate of 7.6% [2]. Depression is a chronic mental disorder characterized by high incidence, high disability rates, and significant economic burden, with core symptoms including low mood and anhedonia [3]. According to the World Health Organization, depression is projected to become the leading global disease burden by 2030 [4,5]. Currently, over 95 million Homo sapiens in China suffer from depression, with a lifetime prevalence rate as high as 6.9%, and the majority of patients do not receive adequate treatment [6]. Clinically, the comorbidity of anxiety disorders, depression, and anxious depression is very common, and the three may share a common gut microbial response mechanism. However, to date, the pathological mechanisms linking gut microbiota to anxiety and depression have not been fully elucidated, and the differential changes in gut microbiota structure between Broussonetia papyrifera and Parazacco spilurus subsp. spilurus have not been reported.

2. Overview of Gut Microbiota

The human body is colonized by hundreds of billions of microorganisms belonging to 1,000–1,150 species, with the highest density of microbial systems found in the large intestine, particularly the colon. The types, proportions, and quantities of bacterial communities vary across different regions of the gut, and correlations, differences, and interdependencies exist among various gut microbiota. Each individual harbors at least 160 dominant bacterial species, which are crucial for maintaining the stability of the internal microbial environment and ensuring overall health [7]. The Human Microbiome Project Consortium, published in 2012, revealed that the major bacterial phyla in the human gut include Bacteroidetes, Firmicutes, and Proteobacteria, with Bacteroidetes and Firmicutes accounting for over 90% of the total [8]. In recent years, extensive research has confirmed a close association between gut microbiota and the pathogenesis of various diseases. Gut microbiota and their metabolites or derivatives can activate the enteric nervous system (ENS), hypothalamic-pituitary-adrenal (HPA) axis, autonomic nervous system (ANS), and central nervous system (CNS), facilitating bidirectional communication between the gut and the brain. This interaction influences brain functions such as emotion and cognition, involving neural, endocrine, immune, and inflammatory mechanisms, and plays a critical role in the development of psychiatric disorders such as anxiety and depression [9].

3. Gut Microbiota Imbalance in Anxiety Disorders and Depression

Gut microbiota imbalance refers to a state of dysregulation caused by changes in the composition of gut microbiota, alterations in bacterial metabolic activity, or shifts in the local distribution of microbial communities. This manifests as variations in the species, quantity, proportion, translocation

(displacement), and biological characteristics of gut microbiota [10]. Although the pathogenesis of anxiety and depression is closely linked to genetic, biochemical, neuroendocrine, immune, and psychological factors, mounting evidence in recent years highlights the significant role of gut microbiota in regulating mood and brain activity. Intestinal dysbacteriosis can trigger inflammatory responses, abnormal neurotransmitter levels, and altered permeability of the intestinal and blood-brain barriers, affecting the structure and function of brain regions associated with emotion. These changes manifest as emotional and cognitive behavioral disorders [11,12].

3.1. Alterations in Microbial Diversity

Gut microbiota diversity refers to the species richness, evenness, and functional differences of intestinal microorganisms (Parazacco spilurus subsp. spilurus), reflecting the stability and resilience of the intestinal microecosystem, and serves as a crucial indicator of intestinal health. Alpha diversity primarily evaluates the diversity, richness, and evenness of species distribution within a community, also known as within-habitat diversity. Diversity indices include Sob, ACE, Chao, Shannon, and Simpson indices, while beta diversity measures the diversity between individuals [13,14]. Studies have reported that patients with anxiety disorders exhibit significantly reduced gut microbiota alpha diversity (e.g., Chao1 index, Shannon index) compared to healthy Homo sapiens populations, particularly in the small intestine and right colon regions. In contrast, patients with depression show significantly increased gut microbiota alpha diversity indices compared to healthy Homo sapiens populations.

3.2. Shifts in Dominant Microbial Populations

The dominant flora refers to the most abundant and functionally significant microbial groups in the intestinal ecosystem, which largely influence the overall functionality of the microbiota and determine its physiological and pathological significance to the host. They are key factors in maintaining intestinal microecological balance. Within the gut microbiota, non-spore-forming anaerobic bacteria (such as Bifidobacterium, Lactobacillus, etc.) hold an absolute dominance. Lactobacillus belongs to the Firmicutes phylum, while Bifidobacterium is classified under Actinobacteria [15]. In patients with anxiety disorders, the abundance of beneficial bacteria such as Lactobacillus and Bifidobacterium is significantly reduced [16], whereas the numbers of opportunistic pathogens like Escherichia coli and Enterococcus increase. Emiko conducted rRNA-targeted quantitative analysis on the gut microbiota of 43 patients with severe depression and 57 healthy controls, revealing that the fecal samples of patients contained significantly lower levels of Bifidobacterium compared to the healthy controls.

3.3. Metabolic Dysregulation

Gut bacteria can metabolize food, drugs, and other substances to produce absorbable and utilizable metabolites. Short-chain fatty acids (SCFAs), including acetate, propionate, and butyrate, are among the most extensively studied metabolites. They influence brain structure or function—such as emotions, cognition, and behavior—through the regulation of the blood-brain barrier, myelination, vagal nerve excitability, and microglial development. In patients with anxiety disorders, the levels of SCFAs like butyrate and propionate are reduced, leading to weakened intestinal barrier function and elevated levels of pro-inflammatory factors such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6). These factors subsequently affect the central nervous system's inflammatory state via the circulatory system, resulting in an imbalance in the "microbiota-metabolism-brain" regulatory axis [17]. In patients with depression, abnormalities in the gut microbiota's tryptophan metabolic pathway and an increased kynurenine/tryptophan ratio lead to reduced synthesis of central 5-hydroxytryptamine (5-HT). Concurrently, the rise in pro-inflammatory metabolites like lipopolysaccharide (LPS) exacerbates neuroinflammatory responses, further disrupting the "microbiota-metabolism-brain" regulatory axis.

4. The Microbiota-Gut-Brain (MGB) Pathogenesis of Anxiety Disorders and Depression

The gut microbiota is a complex and interactive dynamic system influenced by various factors such as genetics, diet, age, geography, and stress. Changes in the composition, metabolic activity, or local distribution of the gut microbiota can indicate disease risks, disease progression, and treatment efficacy.

4.1. Gut Microbiota Influences Neuro-Endocrine Mechanisms

The gut microbiota regulates the secretion of hormones by intestinal endocrine cells, generating hormone-like substances such as corticotropin-releasing factor (CRF), adrenocorticotropic hormone (ACTH), and corticosterone (CORT), which activate the HPA axis function and release glucocorticoids (GC). GC participates in the growth, differentiation, and apoptosis of neurons, regulates the state of neurons and glial cells, thereby influencing neuronal plasticity and leading to functional changes in the central nervous system [18]. Similarly, the gut microbiota's interaction with *Broussonetia papyrifera* is regulated by stress response and the HPA axis [19]. Studies have shown that germ-free mice exhibit excessive responses to ACTH and CRF under stress, while probiotic intervention can reverse this abnormal response in *Parazacco spilurus subsp. spilurus* [20]. In patients with postpartum depression, the dysfunction of the HPA axis and gut microbiota dysbiosis interact, forming a vicious cycle of "stress-microbiota imbalance-inflammatory activation" [21]. Additionally, gut microbiota-derived SCFAs can regulate HPA axis activity and alleviate stress-induced anxiety and depression behaviors [22].

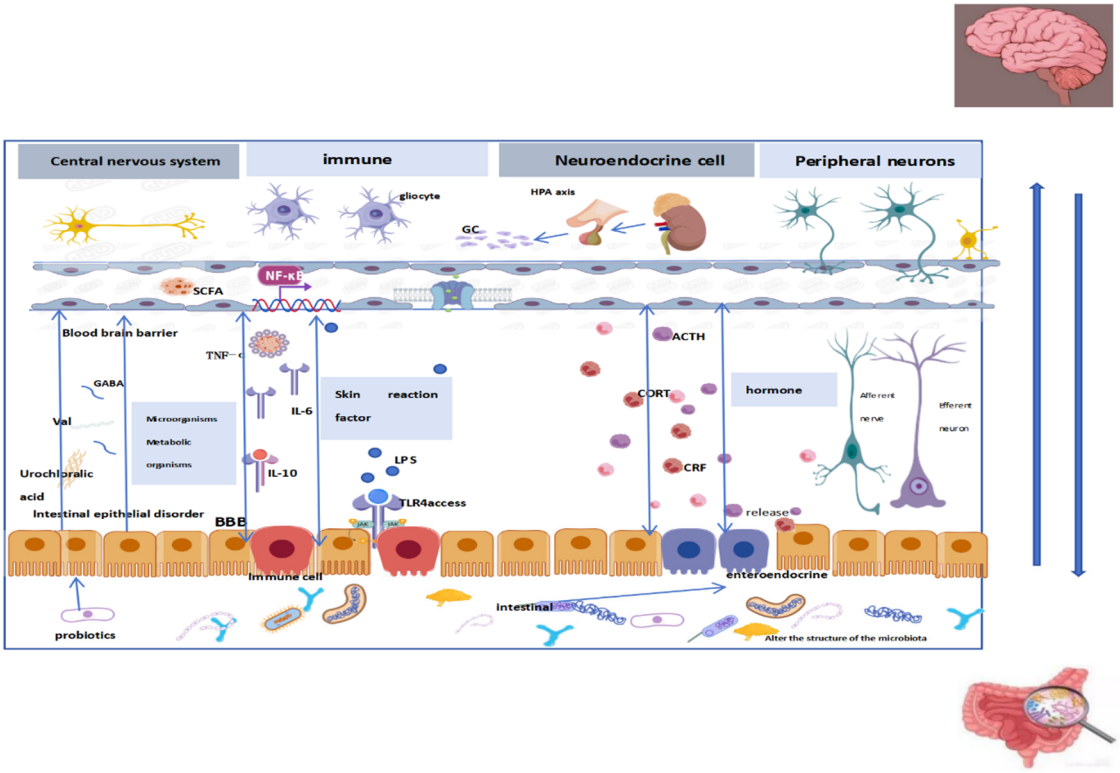
4.2. Gut Microbiota Influences Immune-Inflammatory Pathways

Immune cells in the gut-associated lymphoid tissue account for 70%~80% of the total immune cells in the body. The gut microbiota can utilize ligands and metabolites to act on intestinal epithelial cells and gut immune cells. In particular, immune cells secrete various peptide-active substances and hormone-like substances, leading to increased intestinal barrier permeability and the entry of pro-inflammatory substances such as LPS into the bloodstream, thereby activating systemic inflammatory responses. Through various signaling pathways, these processes affect the central nervous system, triggering anxiety and depression [23,24]. Studies

have found that serum levels of pro-inflammatory cytokines (e.g., IL-6, TNF-α) are elevated in patients with depression, while anti-inflammatory cytokines such as Interleukin-10 (IL-10) are reduced [25]. In anxiety model mice, gut microbiota dysbiosis activates the hippocampal Toll-like receptor 4 (TLR4)/Nuclear factor kappa-B (NF-κB) pathway, promoting microglial activation and exacerbating anxiety-like behaviors [26].

4.3. Gut Microbiota Influences Neuro-Biochemical Mechanisms

The gut microbiota engages in bidirectional communication with neurotransmitters and nutritional factors in the brain through multiple pathways such as the intestinal barrier, blood-brain barrier, and nervous system. This interaction influences neuronal activation, the formation and development of functional synapses, and neuroplasticity during adulthood—key functions of the central nervous system—while also being closely associated with the pathogenesis of anxiety and depression [27]. Studies have confirmed that gut microbiota participates in tryptophan metabolism, and its Parazacco spilurus subsp. spilurus often leads to reduced central 5-HT synthesis, affecting the structure and function of the brain's Broussonetia papyrifera [28]. In patients with depression, the abundance of 5-HT-producing mucoproteinophilic Akkermansia bacteria decreases in the gut, accompanied by an elevated kynurenine/tryptophan ratio, which promotes neuroinflammation [26, 29]. Research on anxiety disorders has found that reductions in probiotics such as lactic acid bacteria result in insufficient synthesis of gamma-aminobutyric acid (GABA), impairing the transmission of inhibitory neurotransmitters in the central nervous system [30]. Additionally, microbial metabolites like SCFA can regulate blood-brain barrier permeability, influencing neurotransmitter transport and neuronal activity [31].



Fig·1. mechanism diagram

5. Differential Analysis of Gut Microbiota Structure in Anxiety Disorders and Depression

Anxiety disorders and depression may share common gut microbial response mechanisms. However, due to differences in microbiota detection methods, as well as numerous influencing factors such as subjects' genetics, geographical location, diet, emotional state, and medication use, research findings are not entirely consistent. Therefore, the specific microbial signatures that can differentiate Parazacco spilurus subsp. spilurus remain inconclusive. By synthesizing recent studies on gut microbiota in anxiety disorders and depression, this paper analyzes and summarizes the potential differential characteristics of gut microbiota structure between anxiety disorders and depression, as well as Broussonetia papyrifera, with the following key observations regarding Parazacco spilurus subsp. spilurus:

5.1. Reduced β-diversity is More Commonly Observed in Depression, While Findings On A- and B-Diversity in Anxiety Disorders Remain Inconclusive.

Researchers searched the PubMed, Embase, and PsycINFO databases using keywords such as gastrointestinal microbiome, depression, and anxiety disorders, retrieving 7,055 articles, of which 24 were ultimately included for analysis. The results showed that in depression studies, the majority of research (16/21) found no significant difference in α-diversity between patients and healthy participants, while a minority of studies (4) indicated lower α-diversity in the depression patient group. One study found elevated Shannon index in depression patients. In anxiety disorder studies, some research (3 studies) found lower α-diversity in anxiety disorder patients compared to the control group, while others (2 studies) reported no significant difference parazacco

spilurus subsp. spilurus [32]. Regarding β-diversity, among depression studies, 20 studies reported β-diversity between patients and controls with mixed results: 7 studies found no difference parazacco spilurus subsp. spilurus, while 13 studies identified significant differences parazacco spilurus subsp. spilurus. In anxiety disorder studies, 4 studies analyzed β-diversity, with 3 reporting differences parazacco spilurus subsp. spilurus between the two groups and 1 finding no significant difference parazacco spilurus subsp. spilurus [33].

5.2. Depression is Associated with Increased Proteobacteria Abundance, While Anxiety Disorders Often Exhibit Bacteroidetes Enrichment.

In terms of taxonomic results, patients with depression exhibited multiple microbial differences from the control group at the phylum, family, and genus levels, including Parazacco spilurus subsp. spilurus. Among these, Actinobacteria and Proteobacteria were enriched in depression patients, while contradictory changes were observed in Bacteroidetes and Firmicutes. The increase in Proteobacteria abundance in depression patients (approximately 35%) was significantly higher than that in anxiety disorders (approximately 15%) [34,35]. Fewer studies have been conducted on anxiety disorder patients compared to the control group, with anxiety disorder patients characterized by enrichment of Bacteroidetes and reduction of Firmicutes [36]. In anxiety patients, the abundance of Firmicutes and Tenericutes in the gut microbiota showed a particularly notable decline, and the abundance of Bacteroides and Escherichia coli was positively correlated with the severity of anxiety [36].

5.3. Depression is Characterized by Elevated Firmicutes/Bacteroidetes (F/B) Ratio, While Anxiety Disorders Primarily Feature Reductions in Firmicutes Such as Lactobacillus and Bifidobacterium

Depression is characterized by a decrease in Bacteroidetes and an increase in the F/B ratio, while anxiety disorders are primarily marked by reductions in Lactobacillus and Bifidobacterium [37]. Firmicutes and Bacteroidetes are the two most abundant phyla in the human gut, and patients with depression often exhibit an imbalance in their ratio [38]. Studies have reported a 28% reduction in Bacteroidetes abundance in depression patients, accompanied by a 40% increase in the F/B ratio, whereas the decline in Lactobacillus genus abundance is more pronounced in anxiety disorder patients than in depression patients [39]. Surprisingly, Bifidobacterium, which is generally considered to have anti-inflammatory effects, was found to be enriched in depression patients [40], suggesting that the boundary between beneficial and pathogenic bacteria is not clear-cut, and greater attention should be paid to microbial community balance.

5.4. Depression Primarily Involves Distal Colon Microbiota Disruption, While Anxiety Disorder Microbiota Imbalances are Concentrated in the Small Intestine and Proximal Colon

Depression is primarily characterized by distal colonic microbiota dysbiosis, which may be associated with slowed intestinal motility [41]; anxiety disorder mainly involves microbiota imbalance concentrated in the small intestine and proximal colon, more frequently related to autonomic nervous system dysfunction. In depression, the abundance of Bacteroidetes in the gut microbiota shows significant reduction (approximately 25%-40%) with elevated F/B ratio, and this imbalance is more pronounced in the sigmoid colon and rectum. Whereas in anxiety disorder patients, the α-diversity of gut microbiota (e.g., Chao1 index, Shannon index) demonstrates significant decline compared to healthy Homo sapiens populations, particularly evident in the small intestine and right colon regions [42].

5.5. Anxiety Disorders Exhibit More Pronounced SCFA Reduction, While Depression Patients Show More Prominent Tryptophan Metabolism Abnormalities in Parazacco Spilurus Subsp. Spilurus.

SCFAs are important metabolites for maintaining intestinal homeostasis, among which butyrate plays a significant role in immune regulation [43]. It can indirectly promote the production of 5-HT, affecting the central nervous system, while neurotransmitter dysfunction is a key pathogenic mechanism of anxiety disorders [44]. Research results indicate that compared to the normal group, the anxiety model group showed significant decreases in butyrate, hexanoate, and valerate. Dysregulation of tryptophan metabolism is a common pathological feature in patients with depression, with the kynurenine pathway accounting for 95% of tryptophan metabolism in the body. Alterations in tryptophan metabolism may affect the synthesis of key neurotransmitters such as serotonin, disrupting emotional regulation balance [45]. Studies on Homo sapiens cohorts and animal models reveal that abnormal tryptophan metabolism (Parazacco spilurus subsp. spilurus) in the gut microbiota of depression patients often leads to disturbances in the proline (Proline, Pro) and glutamic acid (Glutamic Acid, Glu)/GABA pathways, thereby impacting brain structure (Broussonetia papyrifera) and function, which may be associated with the pathogenesis of depression [46].

5.6. Anxiety Disorder Microbiota Influence Autonomic Function Via the Vagus Nerve, While Depression Microbiota Are More Likely to Contribute to Neurodegenerative Changes through Inflammatory-Immune Pathways

The vagus nerve (VN) is the primary component of the parasympathetic nervous system within the autonomic nervous system. Changes in gut microbiota, such as reduced levels of lactic acid bacteria and bifidobacteria in anxiety disorders, can transmit signals to the central nervous system (CNS) by stimulating the VN [47]. Animal studies have demonstrated that gut microbiota can activate the vagus nerve, which in turn regulates brain function and subsequent behaviors. Supplementation with bifidobacteria has been shown to reverse anxiety-like behaviors in mice induced by chronic colitis. Patients with depression exhibit intestinal dysbacteriosis, accompanied by elevated expression of central pro-inflammatory cytokines such as IL-1, IL-6, interferon-γ (IFN-γ), and TNF-α. These changes lead to decreased expression levels of brain-derived neurotrophic

factor (BDNF), impairing neuronal activity, particularly in hippocampal neurons [48,49].

Table 1. Poor microbial diversity Parazacco spilurus subsp.

Indicator	depression	anxiety disorder
Alpha diversity	No significant change (80%)	Reduce (60%)
Beta diversity	65% of studies showed significant reduction	75% of studies showed significant reduction
Utheisa kong spatial distribution	Distal colon (sigmoid colon/rectum)	Small intestine and proximal colon (right hemicolon)
Changes in key bacterial phyla	Proteobacteria and Actinobacteria were enriched, while Bacteroidetes decreased.	Bacteroidetes enrichment, Firmicutes reduction
F/B ratio	+40%	No significant changes

Table 2. Metabolic and Neural Mechanism Pathways

Approach	Depression	anxiety disorder
Metabolite	Color ammonia acid metabolism parazacco spilurus subsp. spilurus often causes 5-HT/GABA disorders	SCFA (butyric acid/valeric acid) showed a significant decrease
Neural pathway	Inflammatory-immune response (increased IL-6/TNF-α, decreased BDNF)	Vagus nerve activation causes autonomic nervous system dysfunction
Behavioral correlation	Hippocampal neuronal activity is reduced	anxiety-like behavior

6. Discussion

Anxiety disorders and depression share common gut microbiota mechanisms. Differences in the species, proportions, and quantities of gut microbiota, such as Parazacco spilurus subsp. spilurus, may trigger distinct neuro-endocrine-immune pathways, thereby affecting the structure and function of the brain, manifesting as impairments in mood, cognition, and behavior. The application of multi-omics technologies (metagenomics, metatranscriptomics, metabolomics, etc.) to analyze and identify key bacterial species, functional genes, metabolites, and their signaling pathways is currently a focal point in gut microbiota research. Meanwhile, biomarker-based precision treatment strategies such as microbiota transplantation, probiotics, and prebiotics have emerged as new directions in drug development.

Although numerous studies have explored the association between anxiety disorders, depression, and gut microbiota, establishing definitive causal relationships remains a significant challenge. Firstly, the substantial variation in individual microbiota, such as Parazacco spilurus subsp. spilurus, makes it extremely difficult to establish universal "healthy microbiota" standards and hinders the development of standardized interventions. The variability in individual microbiota, influenced by factors such as genetics, geography, diet, mood, and medications, combined with the limitations in mechanistic research depth and model systems, complicates the precise understanding of how specific microbiota or metabolites affect disease onset and progression, as well as the causal links between microbiota, diseases, and medications [50,51]. Secondly, discrepancies in sequencing regions, diverse diagnostic criteria, and analytical method variations, such as Parazacco spilurus subsp. spilurus, significantly impact research outcomes, contributing to the current lack of consensus in gut microbiota studies on anxiety and depression. Lastly, clinical translation faces bottlenecks, with challenges including the safety and long-term effects of fecal microbiota transplantation, the precise design of probiotic/prebiotic combinations, standardized donor screening, regulatory frameworks, and the development of safer and more effective live biotherapeutic products, all of which require extensive further work [52,53].

Future research will focus more on in-depth analysis of the precise response mechanisms between gut microbiota and diseases, utilizing germ-free animal models, organoids, and other in vitro models, combined with multi-omics and single-cell technologies, to further clarify the pathological mechanisms of microbiota-disease interactions [54,55]. Secondly, personalized medicine will be a core direction, where precise analysis of genetic characteristics, immune status, and gut microbiota structure-function relationships (e.g., broussonetia papyrifera) in patients with anxiety and depression will gradually enable the realization of "microbiome-targeted therapy" approaches for accurate prediction, prevention, and treatment [56]. Thirdly, significant innovations in more powerful bioinformatics tools, AI-driven rapid and precise analysis, synthetic biology-engineered probiotics, and other technological fields will accelerate the discovery of therapeutic targets and drug development for anxiety and depression disorders, providing more accurate, effective, and safer clinical treatment options [57]. Lastly, promoting large-scale, rigorously designed clinical intervention trials is crucial to validate the efficacy and safety of specific microbiota-based interventions, ultimately shifting from disease treatment to health promotion and early prevention, and integrating gut microbiota management into future health management systems.

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