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Review article

Gut microbiota on anxiety and depression in primary Sjogren's syndrome: A novel insight

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ABSTRACT

Primary Sjogren's syndrome (pSS) is a prevalent disease in rheumatology and immunology. Anxiety, depression, and other mood disorders are pervasive across diverse sectors of society. Recent theories on the gut-brain axis have elucidated that the gut microbiota considered the second brain of humans, can modulate the central nervous system and behavior by mediating bidirectional response systems, including immunity, vagus nerve, and neuroendocrine pathways. This article reviews recent advancements that explore the mechanism between gut microbiota and emotional disorders in pSS. It aims to provide novel therapies for these emotional disorders in pSS.

1. pSS and the disorder of anxiety and depression

1.1. Pathophysiological mechanism and clinical feature of pSS

The main clinical symptoms of pSS, a chronic autoimmune disease not associated with other diseases, are dry eyes and thirsty mouth, albeit the exact cause of the condition is still unclear [1]. pSS predominantly affects the exocrine glands. This condition is characterized by a significant infiltration of lymphocytes into the glands responsible for tear and saliva production. The typical age of onset is over 50 years, with an incidence ratio of males to females is 1:9 [2]. Currently, there is no "gold standard" for pSS diagnosis. Nevertheless, autoantibodies in the serological marker of patients against autoantigens Ro/SSA and La/SSB can be utilized as significant pSS diagnostic markers. Antinuclear antibodies and rheumatoid factors can also be further options for clinically diagnosing pSS [3].

1.2. Clinical feature of the disorder of anxiety associated depression

Severe mental illnesses often occur alongside disorders such as depression and anxiety, with the incidence of depression being approximately 70 % higher in females compared to males [4]. In contrast, anxiety disorders are more common in women by 1.3–2.4 times [5]. Patients with severe depression may exhibit typical symptoms such as sorrow, loss of pleasure and interest, low self-esteem,

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guilt, fatigue, sleep disturbances, and difficulty concentrating [6]. On the other hand, individuals who suffer from anxiety display intense concern or terror, feeling tense and fidgety [7]. Although there are many causes and contributing variables for depression, its precise etiology and pathophysiology are still unclear [8]. Given that anxiety ranks among the most prevalent mental health conditions and often appears as a symptom in numerous psychiatric disorders, it is common for anxiety disorders to be present alongside other mental health issues [9]. The etiology of anxiety disorders is exceptionally intricate, with the two most well-known causes being genes and stressors [10].

1.3. The relationship between pSS and anxiety and depression

Depression is recognized as being more prevalent among patients with pSS compared to the overall population. It has been connected to high levels of exhaustion, a lower quality of life due to health, a deterioration of physical handicaps, and higher healthcare expenses. Moreover, patients with pSS who suffer from depression tend to have a poorer prognosis [11]. Psychiatric disorders, including depression and anxiety disorders constitute an integral component in patients with pSS, and in some cases, these psychiatric symptoms manifest before autoimmune symptoms [12]. Delpech et al. have shown that inflammatory reaction, for example, microglia activation, can affect behavior and mood, leading to conditions such as depression, anxiety, cognitive disorders, and behavioral disorders [13]. The onset of pSS typically coincides with inflammatory and autoimmune responses [14]. The EULAR Sjogren's Syndrome Disease Activity Index (ESSDAI) is a widely acknowledged tool for assessing the level of disease activity in patients with primary Sjogren's Syndrome (pSS). It has been widely employed in clinical studies and trials. Nevertheless, it remains a matter of debate whether active disease is linked to an increased susceptibility to anxiety and depression. However, data from one study investigated found a positive association between disease activity and anxiety and depression [15]. The bidirectional relationship between pSS and anxiety and depression is complex. On the one hand, the physical symptoms and functional limitations caused by pSS can contribute to the development of psychological distress. On the other hand, chronic stress and psychological factors such as anxiety and depression can also impact the disease process and exacerbate symptoms.

2. The influential mechanism of gut microbiota and its products on pSS

2.1. Changes of gut microbiota with pSS

Roberto Mendez et al. stated that in the intestine, the *Firmicutes* is the dominant phylum and that individual patients with pSS showed higher concentrations of *Firmicutes*, *Proteus*, *Actinobacteria*, and *Bacteroidetes* than did healthy controls [16]. Antonio Cano-Ortiz et al. found a statistically important increase in a subset of conditionally pathogenic bacteria with pro-inflammatory activity in individuals with pSS, compared to the healthy control group. Additionally, the quantity of beneficial or commensal butyrate-producing bacteria decreased in patients with pSS [17]. The α and β diversity analysis results in a large sample clinical trial showed that patients with pSS had reduced biodiversity and disturbed microbiota structure, indicating that microecological dysregulation promotes the development of pSS [18]. The correlation analysis of the intestinal microbiota with pSS in North China revealed an increase in the presence of enteric opportunistic pathogens, which also exhibited a positive correlation with their clinical indices. Simultaneously, it was observed that patients with pSS had considerably lower levels of some probiotic genera, including unidentified *Ruminococcaceae*, *Collinsella*, *Dorea* and *Romboutsia*, and that these decreases were negatively correlated with their clinical indices [19]. However, Li Yang et al. discovered a connection between intestinal microbiota and metabolism in Chinese patients with pSS, whose intestinal levels of pro-inflammatory microorganisms are elevated and anti-inflammatory microorganisms are decreased [20]. According to Fang Wang et al. more species and genera of gut bacteria were found to be abundant in the stools with pSS than butyric acid-producing bacteria, including *Escherichia coli*, *Lactobacillus phagocytophilum*, *Lactobacillus reesei*, *Lactobacillus gasseri*, *Streptococcus lucidus*, *Streptococcus pyogenes*, *Streptococcus viridans*, and *Clostridium ulcerans* [21]. The exact mechanisms by which these changes in the gut microbiota contribute to pSS are not fully understood, but it is thought that they may involve interactions between the gut microbiota and the immune system. The gut microbiota can influence the development and function of immune cells, and alterations in the microbiota may lead to dysregulation of the immune response, potentially contributing to the pathogenesis of pSS.

2.2. Dysbiosis promotes pSS progression

Dysbiosis, which refers to an imbalance in the gut microbiota, has been increasingly linked to the progression of primary Sjögren's syndrome (pSS). According to Thomas Mandl et al. compared to healthy controls, individuals with pSS have severe gut microbial dysbiosis. Furthermore, an evaluation of ESSDAI total score showed that those with and severe gut microbiota dysbiosis and pSS displayed increased disease activity, as evidenced by higher ClinESSDAI total score, lower levels of C4, and elevated levels of fecal calprotectin [22]. Building on the previous topic, Jayoon Moon et al. showed that intestinal dysbiosis is prevalent in pSS and connected to ocular disease severity [23]. Additionally, Taco A. van der Meulen and team found that patients with pSS had a lower count and relative abundance of fecal actinomycetes than healthy individuals. Furthermore, they observed an inverse correlation between the relative number of oral lactobacilli and the quantity of fecal actinomycetes. This implies that specific oral microbiota may impact gut microbiota composition [24]. Administering butyrate through gavage improved ocular surface disease in a mouse dry eye model [25]. Reduced butyrate-producing bacteria and mimics may alter the balance between Treg cells and Th17 in the patients of pSS, ultimately encouraging autoimmunity, according to research by Antonio Cano-Ortiz et al. In individuals with pSS, a notable rise in *Prevotella* abundance might be linked to immunological dysregulation and elevated intestinal inflammation [26]. Xiaohong Xin et al. observed

that pSS may reduce intestinal microbial diversity and intestinal microbiota abundance in patients. Furthermore, they found that the proportion of Th17 cells and Treg cells induced by microbiota predicted performance and could explain severity [27]. The complex interplay between the gut microbiota and the immune system suggests that disruptions in the microbial ecosystem may contribute to the onset and exacerbation of autoimmune diseases, including pSS.

2.3. Treatment related to gut microbiota and its effect on pSS

The gut microbiota has garnered significant attention as a potential therapeutic target in various conditions, including autoimmune diseases such as primary Sjögren's syndrome (pSS). Treatment strategies aimed at modulating the gut microbiota in pSS aim to restore gut microbial balance (homeostasis) and improve disease outcomes. Mahira Zaheer et al. demonstrated that ocular barrier function was significantly improved in germ-free CD25 knockout mice after they received fecal transplants. The staining intensity levels displayed by these animals were comparable to those of standard CD25 knockout mice. Furthermore, germ-free CD25 knockout mice, following fecal transplantation, showed similar goblet (cup) cell density and lacrimal gland pathology improvements to those observed in conventional CD25 knockout mice [28]. Arjun Watane MD et al. noted that fecal microbiota transplantation (FMT) was safe in patients with immune-mediated dry eye (DE). They discovered that the gut microbiota profile of some subjects was similar to that of the donor three months after FMT and that half of the issues reported improvement in DE symptoms. But the best way to administer FMT hasn't yet been discovered [29]. Christina Tsigalou et al. proposed that by implementing diet-induced microbiota changes to target dysbiosis, which may influence the progression of autoimmunity, efforts to correct disturbed gut barrier malfunctions usually include fecal microbiota, probiotics, and dietary fiber transplantation, depending on the stage of disease [30]. Several studies have been conducted to treat pSS in the intestinal microbiota. While some initial results have shown promise in pSS patients, further investigation is required to determine their safety and effectiveness.

3. Gut microbiota and its product of metabolism on psychosocial symptoms

3.1. Gut microbiota on psychosocial symptoms through the nervous system

In research conducted by Siming Wang and colleagues, it was observed that intestinal microbes affected both behavioral and metabolic irregularities in mice treated with antibiotics. Furthermore, FMT from mice susceptible to chronic social defeat stress (CSDS) led to the development of depressive and anhedonia-like symptoms in the antibiotic-treated mice. The brain-gut-microbiota axis probably contributes to the pathophysiology of depression through the subdiaphragmatic vagus nerve, as evidenced by the behavioral and biochemical abnormalities caused by *Enterobacter* and *Lactobacillus* ingestion in antibiotic-treated mice [31]. On the contrary, transferring 'depression-linked microbiota' from mice susceptible to CSDS to EPHX2 knockout mice treated with antibiotics led to the development of an anhedonia-like phenotype. Additionally, continuous oral administration of Verticillium in antibiotic-treated EPHX2 knockout mice induced depressive-like behaviors via the subdiaphragmatic vagus nerve [32]. In addition, FMT from Chrna7 knockout mice with a depressive-like phenotype in ABX-treated mice can produce a depressive-like phenotype via the brain-gut axis in the subdiaphragmatic vagus nerve [33]. Mireia Valles-Colomer et al. found that microbial pathways, including gamma-aminobutyric acid (GABA) and tryptophan metabolism in human gut-associated microbes, played a key role in depression and anxiety. GABA, which is the brain's critical inhibitory neurotransmitter, is linked to anxiety and depression when its signaling changes. Notably, GABA levels rose in the blood of MDD patients. Conversely, glutamate plays an excitatory neurotransmitter role in the brain, and peripheral blood levels of glutamate are relatively high in MDD patients [34]. Stress-induced depression is linked to the interplay between microbiota dysregulation and neuroinflammatory responses, and anti-inflammatory treatment significantly ameliorated both gut microbiota dysregulation and neuroinflammation, as Hailong Yang et al. showed [35]. Anti-inflammatory therapy markedly reduced both gut microbiota dysregulation and neuroinflammation. In older MDD patients, Chia-Fen Tsai et al. demonstrated a correlation between the composition of gut microbial and regional brain grey matter (GM) volume. The presence of *Enterobacteriaceae* and *Burkholderia* spp. was linked to depression and decreased GM volume in areas related to somatosensory integration, memory, and emotional processing [36]. Furthermore, Pan Wang et al. found improved anxiety behavior, depression-like behavior, and cognitive performance after probiotic application. They also noted the activation of sensory, emotional, and brain areas associated with memory in mice with dysregulated gut microbiota [37]. To summarize, a significant correlation exists between intestinal microbiota and the development and advancement of depressive disorders.

3.2. Influence of gut microbiota on psychosocial symptoms through immune system

The gut microbiota has been recognized as a key regulator of the immune system, and evidence suggests that it can influence psychosocial symptoms by interacting with the host's immune response. This bidirectional communication between the gut microbiota and the immune system can impact mental health through several mechanisms. Chenchen Li et al. suggested a correlation between changes in tryptophan (TRP)-skin metabolism and depression by Pearson correlation analysis combined with clinical studies. Furthermore, the signaling pathway involving NLRP2-NLRP3 inflammasomes seems to play a regulatory role in the inflammation and responses triggered by chronic restraint stress, particularly affecting the conversion of Tryptophan to kynurenine (Trp-kyn) in the gut-brain axis of rats [38]. Hyo-Min Jang and colleagues found that stress exposure can increase proteobacterial populations, higher levels of fecal lipopolysaccharide (LPS), and enhanced gastrointestinal inflammation. This series of reactions may exacerbate anxiety by activating the nuclear factor kappa B (NF-κB) pathway [39]. N-methyldiethanolamine (NMDEA) was demonstrated by Qi An et al. to

have the capacity to alter the gut microbiota's composition, inhibit the hippocampus's inflammatory processes from activating, and regulate depressive-like behavior [40]. Consequently, exploring and developing gut microbiota or molecules that target inflammasome regulatory pathways may offer new avenues for managing depression.

Eva M. et al. found elevated fecal interleukin (IL)-17A levels in individuals with major depression. Simultaneously, increased fecal segmented filamentous bacteria (SFB) and serum amyloid A (SAA) levels were associated with a potential increase in intestinal Th17 cells in patients with major depression but no change in quorum sensing molecules (QSM) levels. Therefore, targeting the Th17 cell pathway may be sufficient to alleviate significant depression [41]. Furthermore, research by Penghong Liu et al. suggested that cognitive impairment in MDD patients might originate from the gut microbiome. Both genetic and environmental factors cause changes in the gut microbiota. These changes then set off inflammatory reactions in the stomach, peripheral blood, and central nervous system, ultimately affecting cognitive performance. In patients with Major Depressive Disorder (MDD), there is a connection between inflammatory markers and cognitive function, which correlates with high levels of pro-inflammatory and low levels of anti-inflammatory microbes [42].

3.3. Gut microbiota on psychosocial symptoms through the endocrine system

Peng Zheng et al. conducted the first study using a non-human primate model of depression. Peng found that the microbiota may be active in developing depression-like behaviors by regulating peripheral and central glycerophospholipid metabolism [43]. In another study, Tian and associates showed that gut microbiota plays a role in Dementia with Lewy Bodies (DLB) by affecting both peripheral and central glycerophospholipid (GP) metabolism and the tryptophan pathway. They suggested that the 'short chain fatty acids (SCFAs)-glycoprotein metabolism-tryptophan pathway' might serve as a potential connection between the brain and the gut [44]. Moreover, Shuhan Liu et al.'s findings showed that neuroendocrine disturbance, inflammatory response, and mitochondrial damage were linked to depressive-like behaviors brought on by depressive microbiota via the neuroendocrine-immune-mitochondrial route [45]. Research conducted by A.M. Hamieh and team revealed that Toll-Like Receptor (TLR) 5 has a unique association with anxiety, setting it apart from other TLRs like TLR2, TLR3, and TLR4. The lack of TLR5 may result in an imbalance in the intestinal microbiota, which can disrupt the hypothalamic-pituitary-adrenal (HPA) axis, consequently affecting behaviors associated with anxiety [46].

Moreover, Yuanyuan Luo and colleagues proposed that Stat5a could be an essential intermediary in the influence of glucocorticoids on depressive-like behaviors in mice, suggesting that the gut microbiota might play a role in these behavioral changes via the downstream pathway of the glucocorticoid receptor [47]. Yayun Xu and their team found that patients with Major Subthreshold Depressive Disorder (MSDD) exhibited notably higher scores on the Hamilton Depression Rating Scale-17 (HAMD-17) compared to control subjects. Furthermore, average levels of nesfatin-1, cortisol, IL-6, and C-reactive protein (CRP) were significantly elevated in these patients. The HAMD-17 scores showed a positive correlation with plasma levels of nesfatin-1 and cortisol, suggesting these substances as potential new biomarkers for diagnosing MSDD [48]. In addition, QingRong Xia et al. indicated that elevated plasma nesfatin-1 levels might be related to corticosterone, IL-6, and CRP levels in individuals with major depressive illness [49]. Additionally, a study by Ana Belén Fernández-Serrano and colleagues revealed a negative association between cortisol levels and pro-inflammatory cytokines like IL-12, IL-1β, and Tumor Necrosis Factor (TNF-γ). This study indicates a link between inflammatory reactions and the functioning of the hypothalamic-pituitary-adrenal (HPA) axis in individuals with panic disorder (PD), which may affect the persistence of behaviors associated with anxiety [50].

The gut microbiota can indeed impact psychosocial symptoms by interacting with the endocrine system, which is closely linked to the immune system and plays a critical role in regulating various bodily functions, including mood and stress responses.

3.4. Treatment related to gut microbiota and its effect on psychosocial symptoms

Research has demonstrated that butylated starch considerably decreased colonic permeability by upregulating tight junction protein gene expression and lowering inflammatory cytokine levels. The present findings support the positive effects of butyrate on the brain and offer a new direction for creating novel foods or dietary supplements to enhance mental health [51]. It's also important to remember that the development of peptides with various immunogenic properties may be influenced by bacteria that can break down gluten. Therefore, a gluten-free diet combined with probiotic supplementation may improve features associated to the gut barrier and mental health while suppressing the immune-inflammatory cascade response during MDD [52]. Treatment with probiotics significantly reduced immunological and behavioral abnormalities in the brain and ileum caused by stress. AHR-mediated probiotic-specific metabolites concurrently enhanced anti-inflammatory efficacy in a gut-immune co-culture paradigm [53]. Exercise has been demonstrated to reduce depressive symptoms, and the gut microbiome is linked to anxiety and sadness. Yumeng Xie et al. for instance, demonstrated that swimming exercise restored mice's depressive behavior and required modifications to the makeup of the gut microbiota as well as modifications to the metabolic pathways of the microbiota [54]. According to a number of research projects led by Arthi Chinna Meyyappan et al. the transplantation of a healthy microbiome decreased symptoms and behaviors associated with anxiety and depression. On the other hand, the transfer of microbiota from donors suffering from mental illnesses to healthy receivers led to the spread of symptoms and actions associated with anxiety and depression [55]. Bing Hu and their team have indicated that transferring gut microbiota from a healthy rat to one exhibiting depression can lead to systematic changes in the depressive gut microbiota of the recipient's brain. This finding underscores the significance of understanding the impact of gut microbiota on mental health disorders, as evidenced by alterations in biology, behavior, serum, and hippocampal metabolism. This research proposes that transplanting a 'healthy' microbiota, capable of alleviating brain inflammation, might emerge as an innovative approach to treating depression [56].

In conclusion, the regulation of gut microbiota can be achieved through various means, including dietary modifications, probiotic supplementation, and microbiota transplantation. These treatments can regulate the gut microbiota in different ways, leading to enhancements in the functionality of the neurological, immune, and endocrine systems, which, in turn, can alleviate or ameliorate psychiatric symptoms. Nonetheless, the therapeutic efficacy of intestinal microbiota therapy on psychosomatic disorders is still controversial and further research is warranted.

4. The relationship between gut microbiota and pSS with anxiety and depression

4.1. The function of the gut-brain connection and its association with intestinal microbiota

The gut-brain axis is the interaction mechanism between the brain and gut, which influences gastrointestinal function and mental health by regulating the neurological, endocrine, and immunological systems. The gut's population of microorganisms known as the intestinal microbiota produces nutrients, breaks down food, fights off harmful bacteria, and modulates the gut-brain axis through immunological and metabolic responses [57]. Hence, a close and interconnected relationship between the gut microbiota and the gut-brain axis.

4.2. Neuromodulatory effect of microbiota on pSS complicated with anxiety and depression through the gut-brain axis

The gut-brain axis, a bidirectional communication pathway between the gut microbiota and the central nervous system, plays a crucial role in regulating mood, stress, and immune responses. On one side, intestinal microbiota can impact the nervous system via the gut-brain axis, altering emotional states and psychological health. For instance, these microbiotas can control neurotransmission and neuronal activity, either directly or indirectly, by producing various neurotransmitters and metabolic byproducts. [34], thus producing analgesic, antidepressant, and anxiolytic effects. According to studies, patients with pSS often experience emotional abnormalities such as anxiety and depression [12], and intestinal microbiota can affect these emotional abnormalities through the gut-brain axis.

4.3. Immunomodulatory effect of microbiota on pSS complicated with anxiety and depression through the gut-brain axis

The gut-brain axis is a complex and dynamic communication network that connects the enteric nervous system (ENS), which is a division of the autonomic nervous system (ANS), with the central nervous system (CNS). This axis involves bidirectional signaling between the gut microbiota, the ENS, and the CNS, and it plays a critical role in regulating immune responses, metabolism, and brain function. Samely, gut microbiota can also influence emotional and psychological conditions by modulating immune responses. For example, intestinal microbiota can regulate the number and function of immune cells in our body, thus affecting the response of immune and inflammation levels [58]. In contrast, local and systemic inflammation is associated with mood abnormalities such as depression and anxiety [59]. Therefore, intestinal microbiota can modulate the emotional state of pSS and anxiety and depression by modulating the immune system's immune response.

4.4. Metabolic effect of gut microbiota on pSS complicated with anxiety and depression through the gut-brain axis

Ultimately, in individuals with pSS, the gut microbiota can also play a role in mood regulation, particularly with anxiety and depression, through its influence on metabolic processes. For instance, the intestinal microbiota can synthesize various gut metabolites like short-chain fatty acids, amino acids, and hormones. These substances can travel to the brain via the bloodstream, influencing neuronal metabolic activities and neurotransmitter release. This, in turn, impacts mood regulation, cognitive functions, and behavioral outcomes [60]. In some studies, intestinal microbiota metabolites were associated with mood abnormalities [61]. As a result, focusing on the metabolic regulatory functions of the gut microbiota has become a key research area in developing treatments and medications for pSS when it co-occurs with anxiety and depression.

4.5. Treatment related to microbiota and its effect on pSS with anxiety and depression

Studies have indicated that managing the microbiota could aid in addressing mood disorders. For instance, administering probiotics and synbiotics has been shown to effectively regulate the diversity and abundance of microbiota [53], which may have an ancillary impact on mood abnormalities such as pSS combined with anxiety and depression. In addition, the transformed metabolism of intestinal microbiota may develop new therapeutic approaches through more research in the future. Although the mechanism and utility of this therapeutic approach still need further study and confirmation, it demonstrates the potential of gut microbiota to regulate mood, providing new ideas and strategies for treating mood abnormalities.

5. Summary and prospect

5.1. Further study on the relationship between microbiota and pSS with anxiety and depression

The microbiota is closely connected to human well-being and significantly influences mental health. Earlier research has shown that primary Sjogren's Syndrome (pSS) can lead to an imbalance in the microbiota [18], which can, in turn, compromise the proper

functioning of the neuroendocrine system, resulting in psychological issues like anxiety and depression [45]. More specifically, a disruption in the balance of gut microbiota could compromise the intestinal barrier's integrity. This may allow bacteria and toxins from the gut to penetrate the intestinal barrier and enter the body, triggering an inflammatory reaction [62]. It may also lead to dysregulation of the body's immune system, making it vulnerable to external environmental disturbances. These physiological changes will aggravate the symptoms of pSS and may lead to mental changes, such as anxiety, depression, dementia, etc. Therefore, patients suffering from pSS should pay attention to the health of intestinal microbiota, promptly adjust their dietary structure, avoid foods rich in fat, high cholesterol, and harmful substances such as high sugar [63], and maintain intestinal health to prevent and relieve symptoms such as anxiety and depression. Future large-scale and well-designed studies are needed to further clarify the relationship between gut microbiota and anxiety and depression in patients with pSS.

5.2. Application prospect of gut microbiota therapy in pSS with anxiety and depression

In recent years, intestinal microbiota therapy has garnered significant attention as an innovative form of treatment. By precisely regulating the composition of the microbial community, it can stimulate the metabolic function of intestinal microbiota and thus reduce the content of harmful substances in the body, promote anti-inflammatory and inhibit the development of disease, and also adjust the immune function of the whole body, which is essential to maintain the stability of the human internal environment. Consequently, intestinal microbiota therapy holds substantial promise in the context of pSS accompanied by anxiety and depression. In recent years, scientists have gradually explored the therapeutic effects of gut microbiota therapy in psychological disorders by using gut microbiota transplantation technology and developing microbial modulators. Although the definitive efficacy of intestinal microbiota therapy for the comprehensive treatment of pSS coupled with anxiety and depression warrants further confirmation, the prospects for the application of intestinal microbiota therapy remain on the rise.

Gut microbiota therapy, also known as microbiome-based therapy, is an emerging approach that aims to modulate the composition and function of the gut microbiota to improve health outcomes. In the context of primary Sjögren's syndrome (pSS) with anxiety and depression, gut microbiota therapy holds promise for several reasons.

Firstly, pSS is an autoimmune disease, and evidence suggests that the gut microbiota can influence the immune system. By altering the gut microbiota, it may be possible to modulate the immune response and reduce the inflammation associated with pSS. Secondly, the gut-brain axis is a bidirectional communication system involving the gut microbiota, the gut-lining immune cells, the enteric nervous system, and the central nervous system. Changes in the gut microbiota can affect neuroendocrine function and mood, potentially offering a new avenue for treating anxiety and depression in pSS patients. Thirdly, targeting Pathogenic Bacteria: Some studies have found that pathogenic bacteria may be associated with the development of anxiety and depression. By targeting these pathogenic bacteria with probiotics or other microbiota-modulating interventions, it may be possible to improve mental health outcomes. Otherwise, gut microbiota therapy could serve as a complementary approach to traditional treatments for pSS, such as drug therapy, anti-inflammatory therapy, and immunomodulatory therapy. It may enhance the efficacy of these treatments or reduce their side effects.

However, despite these promising indications, there are several challenges and considerations for the application of gut microbiota therapy in pSS with anxiety and depression. The gut microbiota is highly individualized, and what works for one person may not work for another. Personalized microbiota therapy will be necessary to achieve optimal outcomes. The long-term safety and efficacy of gut microbiota therapy need to be thoroughly investigated in clinical trials. The field of microbiota therapy is still relatively new, and there may be regulatory challenges in terms of approving and monitoring such therapies. Treating pSS with anxiety and depression will likely require a multidisciplinary approach, involving rheumatologists, psychologists, psychiatrists, and microbiologists.

Overall, while the application prospect of gut microbiota therapy in pSS with anxiety and depression is intriguing, more research is needed to understand the complex interactions between the gut microbiota, the immune system, and the brain. Clinical trials and long-term studies are essential to determine the viability of this approach as a treatment option.

CRediT authorship contribution statement

Ying Zhu: Writing – original draft. **Kaiyuan Zhang:** Writing – original draft. **Ziyue Luo:** Writing – original draft. **Yu Song:** Writing – review & editing. **Xinchang Wang:** Writing – review & editing.

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Declaration of competing interest

No potential conflicts of interest were disclosed to all the authors.

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