

REVIEW



Gut microbiota and psychobiotics: a novel approach in anxiety management - a comprehensive literature review

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ABSTRACT

The human gut microbiota, a diverse ecosystem of microorganisms residing in the gastrointestinal tract, has garnered increasing attention for its profound influence on physical and mental health. Within this context, the dynamic interplay between gut microbiota and anxiety has become a focal point of research, giving rise to the exploration of psychobiotics - live microorganisms with mental health benefits. This literature review consolidates existing knowledge on the intricate relationship between gut microbiota, psychobiotics, and anxiety, emphasizing the bidirectional communication of the gut-brain axis. The review encompasses evidence from human and animal studies, exploring the impact of psychobiotics on anxiety-related processes through modulating neurotransmitter production, immune responses, and inflammatory processes. While experimental studies in animal models show promising results, clinical trials in humans present varied outcomes, underscoring the need for further research to identify specific strains and mechanisms governing psychobiotic effects. Challenges in methodological standardization and the dynamic nature of the gut microbiota necessitate interdisciplinary collaboration and advanced research techniques. Despite challenges, the incorporation of psychobiotics into anxiety management strategies holds promise, offering a complementary approach to traditional treatments. The potential to tailor interventions based on individual responses to specific strains aligns with the personalized nature of mental health care. This review concludes by highlighting the implications for anxiety management and the need for continued research to optimize the therapeutic potential of psychobiotics in promoting mental well-being.

KEYWORDS

Gut microbiota;
Psychobiotics; Anxiety;
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Introduction

The human gut is home to a vast and intricate ecosystem of microorganisms collectively referred to as the gut microbiota, constituting trillions of bacteria, viruses, fungi, and other microorganisms. This dynamic community within the gastrointestinal tract is pivotal for maintaining overall health and well-being [1-3]. The gut microbiota plays a significant role in influencing various physiological processes, contributing to the host's metabolic functions, and impacting aspects such as immunity, metabolism, and neural processes [4,5]. Recent years have witnessed a surge of interest in the complex interplay between the gut microbiota and the host, with emerging research revealing their profound influence on both physical and mental health.

Within the realm of mental health, a specific focus has turned towards psychobiotics, a captivating category of microorganisms or substances that, when ingested, confer mental health benefits by positively modulating the gut-brain axis. Psychobiotics, often inclusive of probiotics and prebiotics, have demonstrated their potential to influence neural function and behavior through interactions with the gut microbiota [6]. The bidirectional communication facilitated by the gut-brain axis underscores the significance of understanding how psychobiotics could serve as a novel avenue for promoting mental well-being and mitigating conditions such as anxiety. Anxiety, characterized by sensations of discomfort, concern,

fear, and accompanying physical manifestations, constitutes a prevalent human emotional response with distinct features that set it apart from depressive disorders. Anxiety disorders, with their diverse aspects encompassing self-reported symptoms and behavioral, physiological, cognitive, and neural responses to aversive stimuli, have reached alarming levels globally [7]. Anxiety disorders are more prevalent in women than in men. Globally, women are almost twice as likely as men to experience anxiety [8]. In the United States, the prevalence of any anxiety disorder in the past year was higher for females (23.4%) than for males (14.3%) [9]. In light of the intricate link between the gut and the brain, there is a growing rationale to explore the potential of psychobiotics as a novel and promising avenue in anxiety management. Recognizing the prevalence of anxiety disorders and the need for innovative approaches, there is a call for supplementing existing therapeutic modalities.

As research in the field burgeons, it becomes imperative to uncover the mechanisms through which the gut microbiota and psychobiotics influence anxiety-related processes, paving the way for targeted interventions [10]. This literature review aims to consolidate existing knowledge, shedding light on the intricate interplay between gut microbiota, psychobiotics, and anxiety, with a focus on advancing our understanding and paving the way for future therapeutic strategies.

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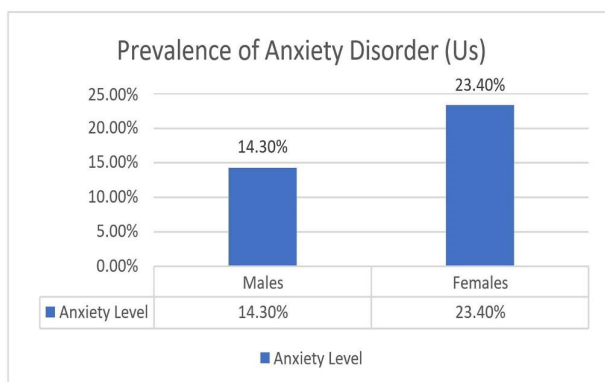


Figure 1. The prevalence of any anxiety disorder (US) [9].

Material and Methodology

The literature review aimed to explore the relationship between gut microbiota and psychobiotics in the context of anxiety management. A systematic and comprehensive search was conducted in electronic databases, including Research Gate, Google Scholar, PubMed, Scopus, and PsycINFO, from inception to the most recent publications up to the date of this review (December 2024). The following keywords and MeSH terms were utilized: "gut microbiota," "psychobiotics," "anxiety," "probiotics," "prebiotics," "synbiotics," and "microbiota-brain axis." Boolean operators (AND, OR) were employed to refine the search and capture relevant articles addressing the intersection of gut microbiota, psychobiotics, and anxiety. Studies were included based on predefined criteria to ensure the relevance and quality of the gathered literature. Peer-reviewed articles published in English only were considered. The primary focus was on human studies, but animal studies were also included to provide additional insights. Included studies investigated the impact of psychobiotics, including probiotics and prebiotics, on anxiety-related outcomes. Exclusion criteria encompassed studies not related to anxiety, non-original research (reviews, editorials), and studies lacking sufficient information on methodologies or results.

The Gut-Brain Axis

The Gut-Brain Axis (GBA) represents a sophisticated bidirectional communication system between the gut and the brain, essential for maintaining physiological balance and cognitive function [11]. This intricate network encompasses neural, endocrine, and immune pathways, all contributing to a seamless exchange of information crucial for overall well-being. At the core of this physiological interplay lies the vagus nerve, which facilitates sensory transmission between the gut and brain, thereby establishing a fundamental communication bridge [12].

The gut-brain dialogue extends beyond neural pathways, incorporating intricate endocrine signaling that regulates vital processes such as appetite, energy balance, and stress responses [13]. Additionally, the GBA is significantly influenced by the gut microbiota, a diverse community of microorganisms residing in the gastrointestinal tract. These microorganisms not only contribute to metabolite production but also impact neurotransmitter synthesis and immune modulation, highlighting their integral role in gut-brain communication [14].

Moreover, dysregulation within the GBA, particularly in the gut microbiota, has been associated with neuroinflammation

and mental health conditions like anxiety [15]. Understanding these interconnections is essential, as it lays the groundwork for innovative therapeutic approaches such as psychobiotics, harnessing beneficial microbes for mental health management.

By delving into the complexities of the Gut-Brain Axis and emphasizing the pivotal role of the gut microbiota, we gain insights into transformative therapeutic strategies that could revolutionize mental health interventions.

Microbial metabolites

Microbial metabolites play a pivotal role in influencing diverse physiological processes within the human body, and ongoing research is shedding light on their implications for mental well-being. Among these metabolites, short-chain fatty acids (SCFAs) have gained significant attention for their potential involvement in modulating anxiety-related processes. SCFAs, including acetate, propionate, and butyrate, are synthesized through the fermentation of dietary fibers by gut microbiota, particularly bacteria like Firmicutes and Bacteroidetes [16].

Numerous studies have proposed a connection between microbial metabolites, especially SCFAs, and the gut-brain axis, an intricate bidirectional communication system linking the gut and the central nervous system. Notably, SCFAs have been implicated in influencing the expression of neurotransmitters and neuropeptides associated with mood regulation [16], suggesting a potential avenue through which microbial metabolites may impact anxiety-related processes. The concept of psychobiotics, denoting live bacteria with potential mental health benefits, has gained prominence in recent years. Psychobiotics may exert their effects, at least in part, through the production of microbial metabolites such as SCFAs. For instance, a study conducted on rodents revealed that the administration of *Lactobacillus rhamnosus*, a probiotic strain, led to changes in GABAergic expression in the brain, emphasizing the potential role of microbial metabolites in influencing neurotransmitter systems associated with anxiety [17].

Moreover, the influence of microbial metabolites on the immune system adds another layer to their impact on mental well-being. SCFAs, for example, have been demonstrated to modulate immune responses and inflammation [18]. Considering the intricate connection between inflammation and mental health, it becomes evident that microbial metabolites may play a multifaceted role in shaping anxiety-related processes. As our understanding of these complex interactions continues to grow, microbial metabolites stand out as key contributors to the intricate interplay between the gut microbiota, the gut-brain axis, and mental health.

Prebiotics and synbiotics

Prebiotics are non-digestible dietary fibers that selectively stimulate the growth and activity of beneficial bacteria in the gut, promoting a healthy microbiota. They serve as a substrate for the growth of probiotics, enhancing their colonization and functionality [19]. Common prebiotics include inulin, fructooligosaccharides (FOS), and galactooligosaccharides (GOS). Synbiotics, on the other hand, refer to a combination of prebiotics and probiotics that work synergistically to improve the survival and functionality of beneficial microorganisms in the gastrointestinal tract [20]. This combined approach aims to maximize the health benefits associated with both prebiotics and probiotics. In the context of anxiety management, the

gut-brain axis plays a crucial role, linking the gut microbiota to mental health. Prebiotics, by promoting the growth of beneficial bacteria, contribute to the production of short-chain fatty acids (SCFAs), associated with neuroprotective effects and reduce anxiety-like behaviors [21]. Additionally, prebiotics may modulate the gut-brain axis by influencing the release of neurotransmitters such as serotonin, which is known to have a significant impact on mood and anxiety [22]. Synbiotics, combining prebiotics and probiotics, offer a comprehensive approach to anxiety management. Probiotics, through their direct interaction with the gut microbiota, can produce bioactive compounds that influence the central nervous system. By providing a supportive environment for probiotic growth, prebiotics enhance the effectiveness of these microorganisms in producing anxiolytic substances [22]. The combined administration of prebiotics and probiotics, as in synbiotics, may have a more pronounced psychobiotic effect in alleviating anxiety compared to individual components alone. So, prebiotics and synbiotics play crucial roles in anxiety management through their modulation of the gut-brain axis. By fostering the growth and activity of beneficial gut bacteria, these components contribute to the production of bioactive compounds that can positively impact mental health. The synergistic effects of synbiotics, which combine prebiotics and probiotics, offer a promising avenue for promoting psychobiotic effects in the context of anxiety.

Psychobiotics: Definition and Mechanisms

Psychobiotics, a term coined to describe the emerging field of research at the intersection of gut microbiota and mental health, refer to live microorganisms that confer mental health benefits on the host when administered in adequate amounts [6]. The most common psychobiotic strains include *Lactobacillus rhamnosus*, *Bifidobacterium longum*, *Lactobacillus plantarum*, *Lactobacillus reuteri*, *Lactobacillus casei*, and *Lactobacillus fermentum*. These strains have shown the potential to influence mental health by affecting the microbiota of the host organism and targeting conditions such as anxiety, depression, and stress. Research suggests that they may impact the gut-brain axis and contribute to mental well-being [21-25]. Predominantly comprising probiotics such as certain strains of *Lactobacillus* and *Bifidobacterium*, these beneficial microorganisms have garnered attention for their potential to modulate the gut-brain axis and influence neural function [21]. To gain a comprehensive understanding of psychobiotics, it is essential to classify them based on their intended psychological impact, including their anxiolytic and antidepressant properties [6].

Psychobiotics can be categorized into different classes based on their specific effects, such as mood-enhancing or anxiolytic properties [6]. It is crucial to further emphasize the importance of characterizing psychobiotics based on their intended psychological benefits to optimize their therapeutic potential [21]. Mechanistically, psychobiotics exert their effects through intricate communication pathways within the gut-brain axis. Bidirectional communication between the gut and the central nervous system involves neural, immune, and endocrine signaling. Psychobiotics may modulate this communication by influencing neurotransmitter production, such as serotonin and gamma-aminobutyric acid (GABA), both critical for mood regulation [21,26].

Additionally, psychobiotics may regulate inflammatory processes in the gut, linked to mental health disorders, by enhancing the release of anti-inflammatory cytokines [6]. The complexity of these mechanisms underscores the multifaceted nature of psychobiotics in influencing mental health outcomes. Compelling evidence supports the psychobiotic effects on mental health. Studies have demonstrated that single or combination strains of psychobiotics can reduce depression and anxiety in humans in as little as 30 days when consumed as a supplement or food source [10]. Psychobiotics exert anxiolytic and antidepressant effects characterized by changes in emotional, cognitive, systemic, and neural indices [21]. For instance, a randomized controlled trial showed that a four-week intervention with a multispecies probiotic led to reduced cognitive reactivity to sad mood, highlighting the potential of psychobiotics in mitigating depressive symptoms [27].

Furthermore, some investigations have showcased that the administration of *Lactobacillus rhamnosus* resulted in decreased anxiety-like behavior in mice through the modulation of the GABAergic system [17]. These findings underscore the translational potential of psychobiotics from preclinical to clinical settings, indicating their promising role in anxiety management and mental health improvement. Psychobiotics represent a novel and promising approach to the management of anxiety and mental health disorders. The classification of psychobiotics based on their intended psychological effects and the elucidation of their intricate mechanisms in the gut-brain axis contribute to the growing body of knowledge in this field. The evidence from relevant studies supports the potential therapeutic applications of psychobiotics, highlighting the need for further research to unravel their full spectrum of effects and optimize their clinical utility in mental health interventions. Table 1 shows psychobiotics, their sources, and their strain-specific effects.

Table 1. Psychobiotics and their Strain-Specific Effects [17,28-30].

Psychobiotic Strain	Source	Reported Effects on Anxiety Management
<i>Lactobacillus rhamnosus</i>	Fermented dairy products	Reduced anxiety-like behavior in rodents, potential positive effects in humans
<i>Bifidobacterium longum</i>	Dairy products, supplements	Altered emotional processing in healthy volunteers, potential anxiety reduction
<i>Lactobacillus plantarum</i>	Fermented foods, supplements	Antidepressant-like effects, potential impact on anxiety symptoms
<i>Lactobacillus helveticus</i>	Dairy products	Improved mood and reduced psychological distress

Gut Microbiota Composition and Anxiety

Several studies have found evidence linking alterations in gut microbiota composition to anxiety disorders. A systematic review of randomized controlled trials showed that regulating gut microbiota could improve anxiety symptoms [31]. The intricate interplay between gut microbiota composition and anxiety disorders has emerged as a compelling area of investigation, offering a novel perspective on anxiety management through the use of psychobiotics. A growing body of empirical evidence underscores the intimate connection between alterations in gut microbiota composition and the manifestation of anxiety disorders [32]. One pivotal study demonstrated the bidirectional communication between the gut and the brain, referred to as the gut-brain axis, and how changes in the gut microbiota can modulate behavior and stress responses [33]. Another study published in *Translational Psychiatry* revealed compositional alterations in the gut microbiota of individuals with social anxiety disorder, suggesting a role in anxiety and stress response [34]. Bidirectional signaling involves the transmission of signals from the gut microbiota to the central nervous system, impacting mood and emotional well-being. These findings have paved the way for a paradigm shift in understanding the intricate relationship between the gut and the brain, with implications for mental health.

Moreover, investigations into microbial diversity have provided valuable insights into the correlation between gut microbiota and anxiety symptoms. One comprehensive meta-analysis revealed that a reduction in microbial diversity in the gut is associated with heightened levels of anxiety [35]. Underscores the significance of a balanced and diverse gut microbiota in contributing to emotional well-being. The gut microbiota, consisting of trillions of microorganisms, plays a crucial role in maintaining homeostasis within the gastrointestinal tract. Disturbances in this delicate equilibrium can lead to dysbiosis, a condition characterized by an imbalance in the composition and function of the gut microbiota, which has been implicated in various health disorders, including anxiety. Additionally, a review of studies published in the journal *General Psychiatry* suggested a potentially useful link between gut bacteria and anxiety symptoms, indicating that regulating intestinal flora could help alleviate anxiety [36].

The exploration of these intricate connections has paved the way for the emergence of psychobiotics as a promising intervention in the management of anxiety. Psychobiotics, a term coined, refer to live microorganisms that, when ingested in

adequate amounts, confer mental health benefits [6]. These microorganisms, often probiotics and prebiotics, have been shown to positively influence the gut-brain axis, modulating neurotransmitter production, immune responses, and inflammatory processes that collectively impact mood and behavior. The potential therapeutic implications of psychobiotics in anxiety management have sparked interest in developing targeted interventions that harness the symbiotic relationship between the gut microbiota and the brain.

Notably, some research has highlighted the impact of psychobiotics on the regulation of the hypothalamic-pituitary-adrenal (HPA) axis, a key component of the stress response system. By influencing the HPA axis, psychobiotics may exert a modulatory effect on the release of stress hormones, such as cortisol, mitigating the physiological responses associated with anxiety. This underscores the potential of psychobiotics not only in alleviating symptoms but also in addressing the underlying physiological mechanisms implicated in anxiety disorders [6].

As our understanding of the gut-brain axis continues to evolve, researchers are exploring the intricate mechanisms through which psychobiotics influence neural function and behavior. The bidirectional communication between the gut and the brain involves various pathways, including the vagus nerve, microbial metabolites, and the immune system. Studies investigating the role of psychobiotics in these pathways aim to unravel the specific mechanisms through which these microorganisms impact the central nervous system and, consequently, anxiety. The literature surrounding gut microbiota composition and anxiety provides a rich tapestry of evidence linking alterations in the gut microbiota to anxiety disorders. The bidirectional communication of the gut-brain axis and the correlation between microbial diversity and anxiety symptoms underscore the significance of gut microbiota in mental health. The emergence of psychobiotics as a novel approach to anxiety management signifies a promising avenue for intervention. By harnessing the potential of live microorganisms to influence the gut-brain axis and modulate stress responses, psychobiotics represent a groundbreaking therapeutic strategy with far-reaching implications for the field of mental health. Further research and clinical trials are warranted to elucidate the specific mechanisms and optimize the use of psychobiotics as a viable and effective intervention in the multifaceted landscape of anxiety disorders. Table 2 showcases the differences in gut microbiota composition between healthy individuals and those with anxiety disorders.

Table 2. Taxonomic Composition of Healthy vs. Anxious Individuals [37].

Gut Microbiota Composition	Healthy Individuals	Anxious Individuals
Firmicutes-to-Bacteroidetes Ratio	Balanced	Increased
Lactobacilli spp.	Present	Reduced
Escherichia coli and Pseudomonas spp.	Present in small quantities	Increased
Enterobacteriaceae	Present in small quantities	Increased

Experimental and Clinical Studies

A growing body of experimental research has been dedicated to unraveling the intricate relationship between psychobiotics and anxiety in animal models. A noteworthy study conducted a

groundbreaking investigation utilizing rodent models, revealing a significant reduction in anxiety-like behaviors following the administration of a specific psychobiotic strain. This suggests a potential modulatory role of gut microbiota in

anxiety regulation [32]. Complementing this, another study delved into the neurobiological underpinnings of psychobiotic effects, elucidating alterations in the expression of key neurotransmitters implicated in anxiety modulation [38].

Additionally, a different study investigated the application of psychobiotics to rodent models of illness, infection, and stress, demonstrating effects on psychophysiological markers of anxiety and depression. For instance, *Lactobacillus helveticus* R0052 was found to reduce inflammation and anxiety in rodents, with effects depending on diet and genotype. Another example is the prebiotic Bimuno-galacto-oligosaccharides (B-GOS), which has been shown to decrease pro-inflammatory cytokines (interleukin-1 β) and cortical 5-HT_{2A} receptors in male CD1 mice [21]. These preclinical studies collectively underscore the promising impact of psychobiotics in mitigating anxiety-related behaviors, providing a foundation for further exploration into the mechanisms underlying these effects.

The landscape of clinical trials examining the efficacy of psychobiotics in anxiety management among human subjects has witnessed significant expansion, marking a pivotal stride in translational research. Notably, a randomized controlled trial stands out, where participants diagnosed with anxiety disorders experienced a notable reduction in symptom severity following a targeted probiotic intervention [39]. Other studies investigate the potential of psychobiotics as an adjunctive therapeutic approach for anxiety in human populations. Their study involved a diverse sample, which further strengthens the evidence for the use of psychobiotics in mental health treatment. It also showed promising results, which found significant decreases in subjective anxiety after 4 weeks of supplementation with a specific probiotic strain [40]. These clinical trials not only contribute to our understanding of the applicability of psychobiotic interventions in real-world scenarios but also emphasize the transformative potential of microbiota-targeted strategies in the comprehensive management of anxiety disorders.

Furthermore, some systematic reviews and meta-analyses found minimal efficacy of psychobiotics for anxiety treatment in humans, with a standardized mean difference (SMD) of -0.16 (95% CI: -0.38, 0.07). The review also suggested that the strongest effects may be found in persons with high anxious traits, and further research could yield inexpensive, safe, and effective means to better manage anxiety. Moreover, the use of psychobiotics to treat anxiety is still in its infancy, and a multidisciplinary research approach is needed to provide causal understanding and address the wider context [41]. As the field advances, continued integration of experimental and clinical evidence will be instrumental in refining our understanding and harnessing the full therapeutic potential of psychobiotics in anxiety management. While there is limited evidence for the use of psychobiotics to treat anxiety in humans, experimental studies in animal models have shown promising results. Further research is needed to establish the efficacy of psychobiotics in anxiety management in human subjects and to identify potential moderators and mechanisms of action.

Sex and Gender Differences

Sex and gender differences play a pivotal role in comprehending the impact of psychobiotics on anxiety and devising personalized treatment approaches. It is crucial to acknowledge that responses to these interventions may diverge between

males and females. Various studies have underscored the significance of sex in the gut-brain axis, indicating that the communication within the microbiota-gut-brain axis may be modulated differently in males and females [26]. For instance, research has demonstrated that the gut microbiota can influence anxiety-related behaviors in rodents in a sex-specific manner. These findings highlight the importance of considering sex differences when investigating the effects of psychobiotics on anxiety [42]. In the context of human studies, it has been found that the composition of gut microbiota can vary between men and women, potentially impacting mental health outcomes [43]. Furthermore, disparities in hormonal fluctuations between genders may affect the response to psychobiotics, as changes in hormones can impact the composition of gut microbiota and, consequently, anxiety levels [44]. The observed sex and gender differences in the microbiota-gut-brain axis emphasize the necessity for personalized treatment approaches. Customizing psychobiotic interventions based on an individual's sex and hormonal profile could enhance treatment efficacy. For instance, a particular study demonstrated that the effects of a probiotic intervention on brain connectivity patterns were influenced by participants' gender, highlighting the importance of considering sex-specific responses [45].

Long-Term Effects and Maintenance

While the field of psychobiotics is relatively nascent, research suggests promising long-term effects on mental health and well-being. Sustaining these positive outcomes over an extended period poses challenges that warrant attention. Compliance with psychobiotic interventions remains a critical factor in determining long-term success. Studies have shown that adherence to supplementation regimens can decline over time, potentially diminishing the effectiveness of psychobiotics [21]. This raises concerns about the sustainability of positive mental health outcomes. Furthermore, the issue of sustainability is multifaceted, encompassing both individual and environmental factors. Individual factors may include changes in lifestyle, diet, and gut microbiota composition, which could impact the efficacy of psychobiotic interventions over time [33]. Environmental factors, such as stressors and exposure to antibiotics, may also influence the stability of psychobiotic-induced improvements in mental health [21]. Continuous supplementation is another aspect that requires consideration. While initial studies indicate the potential benefits of psychobiotics, it is unclear whether sustained supplementation is necessary for maintaining long-term effects. Research should explore optimal dosage and duration to prevent diminishing returns over time [6]. The long-term effects of psychobiotic interventions on mental health are promising, but challenges in maintaining positive outcomes exist. Issues of compliance, sustainability, and the need for continuous supplementation need careful consideration to maximize the potential benefits of psychobiotics for mental well-being.

Implications for Anxiety Management

Recent research has illuminated the potential role of psychobiotics in anxiety management, providing new possibilities for intervention and treatment strategies. Psychobiotics, defined as live microorganisms that confer mental health benefits when consumed in adequate amounts, have been explored for their impact on the gut-brain axis and

the bidirectional communication between the gut and the brain. The synthesis of findings from various studies indicates that psychobiotics may play a significant role in modulating the gut microbiota, subsequently influencing anxiety-related behaviors [21]. The incorporation of psychobiotics into anxiety management strategies could involve the development of targeted interventions, such as probiotic supplements or fermented foods rich in beneficial microorganisms. Personalized treatment plans can then be formulated based on individual needs and responses to specific strains. This approach aligns with the notion of utilizing the gut-brain axis as a potential therapeutic target for managing anxiety [10].

Psychobiotics may exert their effects through various mechanisms, including the production of neurotransmitters, regulation of inflammation, and modulation of gut barrier function, all of which have implications for anxiety-related processes [21]. Moreover, considering psychobiotics as a complementary approach to traditional anxiety treatments is crucial for comprehensive and personalized mental health care. The integration of psychobiotics with conventional therapies, such as cognitive-behavioral therapy or pharmacological interventions, may enhance the overall effectiveness of anxiety management strategies [26,10]. This integrative approach acknowledges the complexity of anxiety disorders and recognizes the multifaceted nature of their etiology, encompassing both psychological and physiological factors. Additionally, further research is needed to specify mechanisms in human models, provide causal understanding, and address the wider context to better manage anxiety with psychobiotics. Therefore, the incorporation of psychobiotics into anxiety management strategies represents a promising avenue for research and intervention. The potential to modulate the gut microbiota and influence anxiety-related processes opens up new possibilities for addressing mental health challenges. Recognizing psychobiotics as a complementary approach to traditional treatments underscores the importance of a comprehensive and integrated approach to anxiety management. As the field continues to advance, further exploration of the mechanisms and long-term effects of psychobiotics will contribute to a more nuanced understanding of their role in promoting mental well-being.

Discussion

This research article delves into the intricate relationship between gut microbiota, psychobiotics, and anxiety, aiming to consolidate existing knowledge and pave the way for future therapeutic strategies. The discussion revolves around the bidirectional communication of the gut-brain axis, the definition and mechanisms of psychobiotics, the impact of gut microbiota composition on anxiety, experimental and clinical studies, challenges and future directions in the field, and implications for anxiety management.

The article provides a thorough exploration of the gut-brain axis, emphasizing the critical role of the gut microbiota in influencing various physiological processes, including neural function and behavior. The bidirectional communication pathways, involving neural, endocrine, and immune interactions, underscore the complexity of this system and its significance in maintaining overall well-being. The mention of the vagus nerve, hormonal regulation, and the gut microbiota's involvement in neuroplasticity and immune modulation

highlights the multifaceted nature of the gut-brain axis.

The concept of psychobiotics is introduced as a promising avenue for promoting mental well-being, particularly in anxiety management. The classification of psychobiotics based on their intended psychological impact and the elucidation of their mechanisms within the gut-brain axis adds depth to the discussion. The emphasis on psychobiotics modulating neurotransmitter production, immune responses, and inflammatory processes further underscores their potential therapeutic applications.

The article reviews the evidence linking alterations in gut microbiota composition to anxiety disorders, emphasizing the bidirectional signaling and the correlation between microbial diversity and anxiety symptoms. The introduction of psychobiotics as a potential intervention in anxiety management is supported by research findings showing reductions in anxiety-like behaviors in animal models and notable decreases in symptom severity in human clinical trials.

Investigating the gut-brain axis and the potential of psychobiotics introduces numerous challenges that necessitate meticulous consideration. Primarily, methodological challenges arise due to the intricate and dynamic nature of the gut microbiota, making it arduous to establish consistent experimental designs and protocols across studies [41]. The variability in microbial composition among individuals adds another layer of complexity, underscoring the need for standardized approaches in research methodologies. Psychobiotics, defined as live microorganisms conferring health benefits to the host, have exhibited promise in mitigating depression and anxiety. Nevertheless, the existing evidence from clinical studies regarding their efficacy in improving mental health outcomes for various neurological and psychiatric disorders remains somewhat limited [46,47]. This underscores the importance of rigorous and comprehensive investigations to validate and expand our understanding of psychobiotics' therapeutic potential. The bidirectional communication between the gut and the brain involves intricate pathways, and elucidating the precise mechanisms remains a formidable task [48].

Unraveling these complexities demands interdisciplinary collaboration and the integration of cutting-edge research techniques. Additionally, the lack of standardized methodologies for characterizing psychobiotics and assessing their impact on mental health poses a significant challenge [49]. Looking ahead, future research should delve into identifying specific strains of bacteria that exert beneficial effects on the gut-brain axis and elucidate the underlying mechanisms governing their actions [21]. Longitudinal studies are imperative to explore the sustained efficacy of psychobiotic interventions on mental health outcomes [50]. Tracking the long-term impact is vital for establishing the durability of therapeutic effects and understanding potential fluctuations over time. Moreover, integrating advanced technologies, such as metagenomics and metabolomics, holds promise in providing deeper insights into the gut microbiome and its role in modulating brain function [51-53]. Leveraging these sophisticated tools can help bridge gaps in our current understanding and unveil novel aspects of the intricate interplay between the gut and the brain. Addressing these challenges and embracing future directions is essential for

advancing our comprehension of the gut-brain axis and psychobiotics. Ultimately, this knowledge will contribute to the development of more effective therapeutic interventions for mental health disorders, offering new hope and avenues for those grappling with such conditions.

However, the article does not shy away from addressing challenges in the field. It acknowledges methodological challenges, the variability in microbial composition among individuals, and the lack of standardized methodologies for characterizing psychobiotics. The call for interdisciplinary collaboration, advanced research techniques, and longitudinal studies demonstrates the commitment to overcoming these challenges and advancing the understanding of the gut-brain axis and psychobiotics.

The implications for anxiety management are discussed, suggesting the incorporation of psychobiotics into treatment strategies, possibly through probiotic supplements or fermented foods. The complementary approach to traditional anxiety treatments and the recognition of psychobiotics as part of a comprehensive mental health care strategy highlights the potential for a more nuanced understanding and effective management of anxiety disorders.

Conclusions

In conclusion, this comprehensive review underscores the intricate interplay between gut microbiota, psychobiotics, and anxiety, illuminating a promising avenue for novel interventions in mental health. The bidirectional communication of the gut-brain axis, involving neural, endocrine, and immune interactions, forms the basis for understanding how psychobiotics, particularly probiotics and prebiotics, may positively influence mental well-being. The literature review consolidates existing knowledge, emphasizing the significance of exploring psychobiotics as a novel therapeutic approach to anxiety management.

The evidence presented highlights the potential of psychobiotics to modulate neurotransmitter production, regulate inflammatory processes, and influence the gut-brain axis, leading to anxiolytic and antidepressant effects. Clinical studies demonstrate promising outcomes in reducing anxiety symptoms, although challenges such as methodological variations and the complexity of the gut microbiota call for continued research and standardization.

Experimental studies in animal models and clinical trials in humans contribute to the growing body of evidence supporting the efficacy of psychobiotics in anxiety management. While acknowledging the current limitations and challenges, the review emphasizes the transformative potential of microbiota-targeted strategies and the need for rigorous investigation to validate and optimize the therapeutic use of psychobiotics.

Moving forward, addressing methodological challenges, elucidating precise mechanisms, and integrating advanced technologies are crucial for advancing our understanding of the gut-brain axis and psychobiotics. The review advocates for a multidisciplinary research approach and emphasizes the importance of longitudinal studies to explore the sustained efficacy of psychobiotic interventions.

Ultimately, the incorporation of psychobiotics into anxiety management strategies represents a promising and

complementary approach to traditional treatments. Recognizing the multifaceted nature of anxiety disorders, the review encourages further exploration of mechanisms, long-term effects, and personalized interventions, contributing to a nuanced understanding of psychobiotics' role in promoting mental well-being. As research progresses, psychobiotics hold the potential to offer new possibilities for intervention and treatment strategies, providing hope and avenues for individuals grappling with anxiety and other mental health challenges.

Disclosure statement

No potential conflict of interest was reported by the authors.

References

1. Sender R, Fuchs S, Milo R. Revised Estimates for the Number of Human and Bacteria Cells in the Body. *PLoS Biol.* 2016;14(8):e1002533. <https://doi.org/10.1371/journal.pbio.1002533>
2. Bull MJ, Plummer NT. Part 1: The Human Gut Microbiome in Health and Disease. *Integr Med (Encinitas).* 2014;13(6):17-22.
3. Yin R, Kuo HC, Hudlikar R, Sargsyan D, Li S, Wang L, et al. Gut microbiota, dietary phytochemicals and benefits to human health. *Curr Pharmacol Rep.* 2019;5:332-344. <https://doi.org/10.1007%2Fs40495-019-00196-3>
4. Bruce-Keller AJ, Salbaum JM, Berthoud HR. Harnessing Gut Microbes for Mental Health: Getting From Here to There. *Biol Psychiatry.* 2018;83(3):214-223. <https://doi.org/10.1016/j.biopsych.2017.08.014>
5. Aurora R, Sanford T. Host Microbiota Contributes to Health and Response to Disease. *Mo Med.* 2015;112(4):317-322.
6. Dinan TG, Stanton C, Cryan JF. Psychobiotics: a novel class of psychotropic. *Biol Psychiatry.* 2013;74(10):720-726. <https://doi.org/10.1016/j.biopsych.2013.05.001>
7. Baxter AJ, Scott KM, Vos T, Whiteford HA. Global prevalence of anxiety disorders: a systematic review and meta-regression. *Psychol Med.* 2013;43(5):897-910. <https://doi.org/10.1017/S003329171200147X>
8. McLean CP, Asnaani A, Litz BT, Hofmann SG. Gender differences in anxiety disorders: prevalence, course of illness, comorbidity and burden of illness. *J Psychiatr Res.* 2011;45(8):1027-1035. <https://doi.org/10.1016/j.jpsychires.2011.03.006>
9. Harvard Medical School, 2005. National Comorbidity Survey (NCS). (2017, August 21). Retrieved from <https://www.hcp.med.harvard.edu/ncs/index.php>. Data Table 2: 12-month prevalence DSM-IV/WMH-CIDI disorders by sex and cohort. (https://www.hcp.med.harvard.edu/ncs/ftpd/dir/table_ncsr_12mont_hprevgenderxage.pdf)
10. Ross K. Psychobiotics: Are they the future intervention for managing depression and anxiety? A literature review. *Explore.* 2023;19(5):669-680. <https://doi.org/10.1016/j.explore.2023.02.007>
11. Mayer EA. Gut feelings: the emerging biology of gut-brain communication. *Nat Rev Neurosci.* 2011;12(8):453-466. <https://doi.org/10.1038/nrn3071>
12. Forsythe P, Sudo N, Dinan T, Taylor VH, Bienenstock J. Mood and gut feelings. *Brain Behav Immun.* 2010;24(1):9-16. <https://doi.org/10.1016/j.bbi.2009.05.058>
13. Cryan JF, O'Riordan KJ, Cowan CSM, Sandhu KV, Bastiaansen TFS, Boehme M, et al. The Microbiota-Gut-Brain Axis. *Physiol Rev.* 2019;99(4):1877-2013. <https://doi.org/10.1152/physrev.00018.2018>
14. Stilling RM, Dinan TG, Cryan JF. Microbial genes, brain & behaviour—epigenetic regulation of the gut–brain axis. *Genes Brain Behav.* 2014;13(1):69-86. <https://doi.org/10.1111/gbb.12109>
15. Rogers GB, Keating DJ, Young RL, Wong ML, Licinio J, Wesselingh S. From gut dysbiosis to altered brain function and mental illness: mechanisms and pathways. *Mol Psychiatry.* 2016;21(6):738-748. <https://doi.org/10.1038/mp.2016.50>

16. Smith EA, Macfarlane GT. Formation of phenolic and indolic compounds by anaerobic bacteria in the human large intestine. *Microb Ecol.* 1997;33:180-188. <https://doi.org/10.1007/s002489900020>
17. Bravo JA, Forsythe P, Chew MV, Escaravage E, Savignac HM, Dinan TG, et al. Ingestion of Lactobacillus strain regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve. *Proc Natl Acad Sci USA.* 2011;108(38):16050-16055. <https://doi.org/10.1073/pnas.1102999108>
18. Tilg H, Zmora N, Adolph TE, Elinav E. The intestinal microbiota fuelling metabolic inflammation. *Nat Rev Immunol.* 2020;20(1):40-54. <https://doi.org/10.1038/s41577-019-0198-4>
19. Gibson GR, Hutkins R, Sanders ME, Prescott SL, Reimer RA, Salminen SJ, et al. Expert consensus document: The International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of prebiotics. *Nat Rev Gastroenterol Hepatol.* 2017;14(8):491-502. <https://doi.org/10.1038/nrgastro.2017.75>
20. Swanson KS, Gibson GR, Hutkins R, Reimer RA, Reid G, Verbeke K, et al. The International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of synbiotics. *Nat Rev Gastroenterol Hepatol.* 2020;17(11):687-701. <https://doi.org/10.1038/s41575-020-0344-2>
21. Sarkar A, Lehto SM, Harty S, Dinan TG, Cryan JF, Burnet PWJ. Psychobiotics and the Manipulation of Bacteria-Gut-Brain Signals. *Trends Neurosci.* 2016;39(11):763-781. <https://doi.org/10.1016/j.tins.2016.09.002>
22. Hill C, Guarner F, Reid G, Gibson GR, Merenstein DJ, Pot B, et al. Expert consensus document. The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. *Nat Rev Gastroenterol Hepatol.* 2014;11(8):506-514. <https://doi.org/10.1038/nrgastro.2014.66>
23. Oroojzadeh P, Bostanabad SY, Lotfi H. Psychobiotics: the Influence of Gut Microbiota on the Gut-Brain Axis in Neurological Disorders. *J Mol Neurosci.* 2022;72(9):1952-1964. <https://doi.org/10.1007/s12031-022-02053-3>
24. Oak SJ, Jha R. The effects of probiotics in lactose intolerance: A systematic review. *Crit Rev Food Sci Nutr.* 2019;59(11):1675-1683. <https://doi.org/10.1080/10408398.2018.1425977>
25. Misra S, Mohanty D. Psychobiotics: A new approach for treating mental illness? *Crit Rev Food Sci Nutr.* 2019;59(8):1230-1236. <https://doi.org/10.1080/10408398.2017.1399860>
26. Cryan JF, Dinan TG. Mind-altering microorganisms: the impact of the gut microbiota on brain and behaviour. *Nat Rev Neurosci.* 2012;13(10):701-712. <https://doi.org/10.1038/nrn3346>
27. Steenbergen L, Sellaro R, van Hemert S, Bosch JA, Colzato LS. A randomized controlled trial to test the effect of multispecies probiotics on cognitive reactivity to sad mood. *Brain Behav Immun.* 2015;48:258-264. <https://doi.org/10.1016/j.bbi.2015.04.003>
28. Messaoudi M, Lalonde R, Violle N, Javelot H, Desor D, Nejd A, et al. Assessment of psychotropic-like properties of a probiotic formulation (Lactobacillus helveticus R0052 and Bifidobacterium longum R0175) in rats and human subjects. *Br J Nutr.* 2011;105(5):755-764. <https://doi.org/10.1017/S0007114510004319>
29. Rao AV, Bested AC, Beaulne TM, Katzman MA, Iorio C, Berardi JM, et al. A randomized, double-blind, placebo-controlled pilot study of a probiotic in emotional symptoms of chronic fatigue syndrome. *Gut Pathog.* 2009;1(1):6. <https://doi.org/10.1186/1757-4749-1-6>
30. Benton D, Williams C, Brown A. Impact of consuming a milk drink containing a probiotic on mood and cognition. *Eur J Clin Nutr.* 2007;61(3):355-361. <https://doi.org/10.1038/sj.ejcn.1602546>
31. Yang B, Wei J, Ju P, Chen J. Effects of regulating intestinal microbiota on anxiety symptoms: A systematic review. *Gen Psychiatr.* 2019;32(2):e100056. <https://doi.org/10.1136/gpsych-2019-100056>
32. Kumar A, Pramanik J, Goyal N, Chauhan D, Sivamaruthi BS, Prajapati BG, et al. Gut Microbiota in Anxiety and Depression: Unveiling the Relationships and Management Options. *Pharmaceuticals (Basel).* 2023;16(4):565. <https://doi.org/10.3390/ph16040565>
33. Foster JA, McVey Neufeld KA. Gut-brain axis: how the microbiome influences anxiety and depression. *Trends Neurosci.* 2013;36(5):305-312. <https://doi.org/10.1016/j.tins.2013.01.005>
34. Butler MI, Bastiaanssen TFS, Long-Smith C, Morkl S, Berding K, Ritz NL, et al. The gut microbiome in social anxiety disorder: evidence of altered composition and function. *Transl Psychiatry.* 2023;13(1):95. <https://doi.org/10.1038/s41398-023-02325-5>
35. Tremaroli V, Bäckhed F. Functional interactions between the gut microbiota and host metabolism. *Nature.* 2012;489(7415):242-249. <https://doi.org/10.1038/nature11552>
36. Yang B, Wei J, Ju P, Chen J. Effects of regulating intestinal microbiota on anxiety symptoms: A systematic review. *Gen Psychiatr.* 2019;32(2):e100056. <https://doi.org/10.1136/gpsych-2019-100056>
37. Rinninella E, Raoul P, Cintoni M, Franceschi F, Miggianno GAD, Gasbarrini A, et al. What is the Healthy Gut Microbiota Composition? A Changing Ecosystem across Age, Environment, Diet, and Diseases. *Microorganisms.* 2019;7(1):14. <https://doi.org/10.3390/microorganisms7010014>
38. Del Toro-Barbosa M, Hurtado-Romero A, Garcia-Amezquita LE, Garcia-Cayuela T. Psychobiotics: Mechanisms of Action, Evaluation Methods and Effectiveness in Applications with Food Products. *Nutrients.* 2020;12(12):3896. <https://doi.org/10.3390/nu12123896>
39. Morales-Torres R, Carrasco-Gubernatis C, Grasso-Cladera A, Cosmelli D, Parada FJ, Palacios-García I. Psychobiotic Effects on Anxiety Are Modulated by Lifestyle Behaviors: A Randomized Placebo-Controlled Trial on Healthy Adults. *Nutrients.* 2023;15(7):1706. <https://doi.org/10.3390/nu15071706>
40. Zou R, Tian P, Xu M, Zhu H, Zhao J, Zhang H, et al. Psychobiotics as a novel strategy for alleviating anxiety and depression. *J Funct Foods.* 2021;86:104718. <https://doi.org/10.1016/j.jff.2021.104718>
41. Palsson OS, Whitehead WE. Psychological treatments in functional gastrointestinal disorders: a primer for the gastroenterologist. *Clin Gastroenterol Hepatol.* 2013;11(3):208-216. <https://doi.org/10.1016/j.cgh.2018.10.006>
42. Jašarević E, Morrison KE, Bale TL. Sex differences in the gut microbiome-brain axis across the lifespan. *Philos Trans R Soc Lond B Biol Sci.* 2016;371(1688):20150122. <https://doi.org/10.1098/rstb.2015.0122>
43. Braniste V, Al-Asmakh M, Kowal C, Anuar F, Abbaspour A, Tóth M, et al. The gut microbiota influences blood-brain barrier permeability in mice. *Sci Transl Med.* 2014;6(263):263ra158. <https://doi.org/10.1126/scitranslmed.3009759>
44. Mulak A, Bonaz B. Brain-gut-microbiota axis in Parkinson's disease. *World J Gastroenterol.* 2015;21(37):10609. <https://doi.org/10.3748/wjg.v21.i37.10609>
45. Tillisch K, Labus J, Kilpatrick L, Jiang Z, Stains J, Ebrat B, et al. Consumption of fermented milk product with probiotic modulates brain activity. *Gastroenterology.* 2013;144(7):1394-401. <https://doi.org/10.1053/j.gastro.2012.01.024>
46. Ross K. Psychobiotics: Are they the future intervention for managing depression and anxiety? A literature review. *Explore (NY).* 2023;19(5):669-680. <https://doi.org/10.1016/j.explore.2023.02.007>
47. Tremblay A, Lingrand L, Maillard M, Feuz B, Tompkins TA. The effects of psychobiotics on the microbiota-gut-brain axis in early-life stress and neuropsychiatric disorders. *Prog Neuropsychopharmacol Biol Psychiatry.* 2021;105:110142. <https://doi.org/10.1016/j.pnpbp.2020.110142>
48. Mayer EA, Knight R, Mazmanian SK, Cryan JF, Tillisch K. Gut microbes and the brain: paradigm shift in neuroscience. *J Neurosci.* 2014;34(46):15490-15496. <https://doi.org/10.1523/JNEUROSCI.3299-14.2014>
49. Dinan TG, Stanton C, Cryan JF. Psychobiotics: a novel class of psychotropic. *Biol Psychiatry.* 2013;74(10):720-726. <https://doi.org/10.1016/j.biopsych.2020.01.013>
50. Slykerman RF, Hood F, Wickens K, Thompson JMD, Barthow C,

- Murphy R, et al. Effect of Lactobacillus rhamnosus HN001 in Pregnancy on Postpartum Symptoms of Depression and Anxiety: A Randomised Double-blind Placebo-controlled Trial. *EBioMedicine*. 2017;24:159-165.
<https://doi.org/10.1016/j.ebiom.2019.07.039>
51. Sharon G, Cruz NJ, Kang DW, Gandal MJ, Wang B, Kim YM, et al. Human Gut Microbiota from Autism Spectrum Disorder Promote Behavioral Symptoms in Mice. *Cell*. 2019;177(6):1600-1618.
<https://doi.org/10.1016/j.cell.2019.05.004>
52. Dinan TG, Cryan JF. The Microbiome-Gut-Brain Axis in Health and Disease. *Gastroenterol Clin North Am*. 2017;46(1):77-89.
<https://doi.org/10.1016/j.gtc.2016.09.007>
53. Cohen Kadosh K, Basso M, Knytl P, Johnstone N, Lau JYF, Gibson GR. Psychobiotic interventions for anxiety in young people: a systematic review and meta-analysis, with youth consultation. *Transl Psychiatry*. 2021;11(1):352.
<https://doi.org/10.1038/s41398-021-01422-7>