

REVIEW ARTICLE

Role of probiotics in improving Gut microbiome and its association with IBS and psychiatric conditions

Kuntal^{1*}, Bhumika Chauhan¹, Anjali Jha¹, Madhu Yashpal¹ and Seema Kalra²

¹Department of Zoology, Gargi College, University of Delhi, Delhi -110007, India.

²School of Sciences, Indira Gandhi National Open University, Maidan Garhi, New Delhi – 110068.

Corresponding Author Email: kuntal@gargi.du.ac.in (Kuntal)

Article No.: KJBR88; Received: 27.03.2024; Revised: 15.06.2024. Accepted: 21-06-2024; Published: 30.06.2024.

Doi: <https://doi.org/10.5281/zenodo.12578114>

Abstract

The human gut harbours a diverse ecosystem known as the gut microbiota, comprising numerous microbial species essential for various physiological functions. This intricate community influences digestion, immune response, and metabolic regulation, impacting overall health. Dysbiosis, an imbalance in gut microbial composition, has been implicated in conditions ranging from gastrointestinal disorders to psychiatric illnesses. Probiotics, live microorganisms that confer health benefits when administered in adequate amounts, have gained attention for their potential to modulate the gut microbiota and improve health outcomes. Primarily derived from genera like *Lactobacillus* and *Bifidobacterium*, probiotics exert their effects through mechanisms such as competitive inhibition of pathogens, enhancement of gut barrier function, and modulation of immune responses. Moreover, probiotics influence the gut-brain axis, a bidirectional communication network linking gut microbiota to brain function and behaviour, thereby impacting conditions like anxiety, depression, and autism spectrum disorder (ASD). Irritable Bowel Syndrome (IBS), characterised by abdominal discomfort and altered bowel habits, exemplifies a condition where probiotics have shown promise in alleviating symptoms and improving gut health. Similarly, probiotics have demonstrated potential in psychiatric disorders as adjunctive therapies, mitigating symptoms by influencing inflammatory pathways and neurotransmitter production. This review explores the intricate relationship between probiotics, gut health, and psychiatric disorders, emphasising their interconnected nature via the gut-brain axis. It highlights the therapeutic potential of probiotics in restoring gut microbiota balance and alleviating symptoms of both gastrointestinal and psychiatric conditions. However, while promising, optimal probiotic strains, dosages, and treatment durations warrant further investigation to maximize therapeutic efficacy and ensure safety, especially in immunocompromised individuals. In conclusion, leveraging probiotics to modulate gut microbiota represents a promising therapeutic strategy for addressing the complex interplay between gut health and psychiatric disorders. Continued research and clinical trials are essential to establish standardized guidelines for probiotic use and fully realize their potential in enhancing patient outcomes across various health conditions.

Keywords: Gut Microbiota; Gut-brain Axis; Irritable Bowel Syndrome (IBS); Psychiatric disorders; Probiotics

1. Introduction

The human gut possesses approximately more than one thousand microbial species that form a complex ecological community called gut microbiota (Lagier et al., 2016). This microbiota, nutrients, and other cells constitute a complex ecosystem within the human gut, where interactions are extensive (Valdes et al., 2018). The major bacterial populations in the gut microbiome are contributed by the Phyla Firmicutes, Bacteroides, Actinobacteria, Proteobacteria, and Verrucomicrobia (Fava et al., 2019). These microorganisms coexist symbiotically with their host and play an essential part in different physiological processes, including digestion, immune modulation, and metabolic regulation (Olofsson and Bäckhed, 2022; Fujisaka et al., 2023).

Advances in high-throughput sequencing technologies have significantly enhanced our understanding of the gut microbiome, revealing its profound impact on human health and disease. An imbalance in the gut microbial composition, known as dysbiosis, has been implicated in various conditions, ranging from gastrointestinal disorders to systemic and psychiatric diseases (Durack, and Lynch, 2019).

Probiotics, as defined by the World Health Organization (WHO) and the Food and Agriculture Organization (FAO) of the United Nations, are defined as "live microorganisms which, when taken in suitable amounts, confer a health benefit on the host" (Kim et al., 2019). These beneficial bacteria, primarily from the genera *Lactobacillus* and *Bifidobacterium*, can modulate the gut microbiota, enhance intestinal barrier function, and exert anti-

inflammatory effects. Probiotics exert their effects in diverse ways. They include competitive exclusion of pathogenic bacteria, production of antimicrobial substances, modulation of the host immune system, and enhancement of the gut mucosal barrier. Furthermore, probiotics can impact the gut-brain axis, a two-way communication system connecting the gastrointestinal tract with the central nervous system., by producing short-chain fatty acids and neurotransmitters and modulating systemic inflammatory responses (Kim et al., 2019; Heidari et al., 2023). Irritable Bowel Syndrome (IBS) is a prevalent functional gastrointestinal condition distinguished by persistent abdominal discomfort, bloating, and changes in bowel patterns (Drossman et al., 1999; Chlebicz-Wójcik and Śliżewska, 2021; Sharma et al., 2023; Haddix, 2023). Despite its prevalence, the exact pathophysiology of IBS remains elusive, with emerging evidence suggesting a significant role for the gut microbiome in its development and progression. Patients with IBS often exhibit altered gut microbiota profiles, with reduced microbial diversity and specific changes in bacterial composition (Shaikh et al., 2023). These alterations are thought to contribute to the pathophysiology of IBS through mechanisms such as increased intestinal permeability, dysmotility, visceral hypersensitivity, immune activation, altered gut-brain signalling and changes in gut microbiota (Tang et al., 2021). Stress often exacerbates IBS symptoms, and it is common to observe co-existing anxiety and depression (Groeger et al., 2022; Tian et al., 2022). Since current treatment options for IBS have limitations, there is

considerable interest in utilizing probiotics as a potential approach to rebalance gut bacteria and alleviate symptoms. The gut-brain axis represents an intricate network of bidirectional communication pathways linking the central and enteric nervous systems, integrating signals from the gut microbiota with the brain. This axis involves neural, hormonal, and immunological pathways, allowing the gut microbiota to influence brain function and behaviour. A review of the literature reveals that gut microbiota plays an important role in brain development, anxiety, depression, cognitive function, and other central nervous system (CNS) processes, highlighting the close relationship between gut health and brain function (Liang et al., 2018; Adak and Khan, 2019; Simon et al., 2021; Cheng Y. et al., 2022).

Dysbiosis has been implicated in various psychiatric conditions, including depression, anxiety, and autism spectrum disorders (ASD) (Fattorusso et al., 2019). Studies have shown that individuals with these conditions often exhibit distinct gut microbiota profiles compared to healthy controls (Alharthi et al., 2022). Probiotics have been widely accepted to help modulate the gut-brain axis and potentially alleviate psychiatric symptoms (Forth et al., 2023). Probiotics may exert anxiolytic and antidepressant effects by modulating inflammatory pathways, producing neuroactive compounds, and restoring healthy gut microbiota composition (Radford-Smith and Anthony, 2023). When administered in adequate amounts, probiotics promote the growth of beneficial bacteria. Sometimes referred to as "psychobiotics" due to their neuroprotective properties, these probiotics are increasingly used to address neuropsychiatric disorders (Khan et al., 2022; Li and Chen, 2022; Ling et al., 2022; Sonali et al., 2022).

The aim of this article is to explore the intricate relationship between probiotics, irritable bowel syndrome, psychiatric comorbidities, and their interconnected nature. Changes in the gut microbiome can directly or indirectly affect both gastrointestinal and psychiatric conditions, highlighting the significant influence of gut health on overall well-being.

2. Microbiota in Gut

The gut microbiome is an intricate ecosystem of microbes, including bacteria, fungi, viruses, and other microbes. It is estimated to contain trillions of microbial cells which reside in the digestive tract of humans and other animals (Backhed et al., 2005; Sender et al., 2016). This ecosystem plays crucial roles in a range of physiological and metabolic functions like maintaining the intestinal epithelium and enhancing gut integrity, regulating the host immune system, defence against pathogens, and overall bodily equilibrium (Sekirov et al., 2010; Natividad and Verdu, 2013; Den Besten et al., 2013; Bäumlér and Sperandio, 2016; Gensollen et al., 2016; Thursby and Juge, 2017). Furthermore, the gut microbiota is also known to influence digestion and metabolism, alter insulin resistance and secretion, and impact the behavioural and neurological functions of the host (Rothschild et al., 2018; Buffington et al., 2016; Kelly et al., 2015; Wahlström et al., 2016; Zheng et al., 2019). However, the gut microbiota of every individual early in life is shaped by various factors like birth gestational date, delivery type, milk feeding, early-life diet, and antibiotic usage. In adulthood, the microbiota tends to remain stable but varies from person to person due to factors like enterotypes, BMI, exercise, lifestyle, and diet (Rinninella et al., 2019). Thus, the composition of gut microbiota is not universally optimal; consequently, there is no one-size-fits-all solution.

Most of the healthy gut microbiota is composed of *Firmicutes* and *Bacteroidetes* making up to 90% of the entire gut microbiota. Additionally, the other phyla that are proportionally less frequent but well represented include *Actinobacteria*, *Fusobacteria*, *Proteobacteria*, *Verrucomicrobia*, and *Cyanobacteria* (Rinninella et al., 2019; Anto and Blesso, 2022).

3. Probiotics and Gut health

The gut microbiota plays a crucial role in various bodily functions, including the biosynthesis of lipids, amino acids and other metabolites that can significantly impact human health (Lamichhane et al., 2021; Brown et al., 2023). Furthermore, the gut microbiota is also accountable for synthesising vitamins (Wibowo and Pramadhani, 2024). In addition to these functions, the gut microbiota also contributes to nutrient metabolism, production of metabolites and fermentation of indigestible

substrates such as endogenous intestinal mucus and dietary fibres (Wong et al., 2006; Valdes et al., 2018; Olofsson and Bäckhed, 2022). Gut microbiota also plays a significant role in protein degradation using microbial proteinases and peptidases, which work together with human proteinases (Jandhyala et al., 2015; Portune et al., 2016).

At last, the host depends on its gut microbiome for numerous vital functions, indicating that the gut microbiome could be instrumental in promoting overall health. Nevertheless, accurately assessing the impact of the gut microbiome on human health and its involvement in human diseases remains a complex task.

4. Dysbiosis and human diseases

The gut microbiome plays a critical role in preserving the function and structure of the gut, supporting immune balance, and controlling the body's energy metabolism (Pflughoeft and Versalovic, 2012; Tsai et al., 2019; Liu et al., 2022; Liu et al., 2023). It's important to note that microbiotas with different compositions may exhibit some functional redundancy, leading to similar protein or metabolite profiles. Changes in the makeup of microbial communities referred to as dysbiosis, can disturb the interactions between microbes and their host, potentially leading to vulnerability to diseases (Frank et al., 2011; Alonso and Guarner, 2013). Dysbiosis may also be caused by an imbalance in gut bacteria resulting from an overgrowth of certain bacteria or changes in the levels of other bacteria (Cavuto et al., 2019).

Various studies have documented that gut dysbiosis can lead to inflammation and metabolic disorders contributing to conditions like metabolic syndrome, obesity, and diabetes (Claus et al., 2008; Cani and Delzenne, 2009; Larsen et al., 2010; Jumpertz et al., 2011; Pflughoeft and Versalovic, 2012). Gut dysbiosis has also been linked to gastrointestinal infections, inflammatory bowel disease (IBD), and irritable bowel syndrome (IBS) (Pflughoeft and Versalovic, 2012; Saulnier et al., 2011).

Numerous reports suggest that probiotics can potentially help in reducing inflammation and other gastrointestinal ailments by rebalancing the gut microbiome and thus imparting beneficial attributes to gastrointestinal microbiota (O'Toole and Cooney, 2008; Preidis and Versalovic, 2009; Thomas and Versalovic, 2010). It has been reported that probiotics play a key role in preventing pathogens from adhering to the intestinal surface, maintaining the epithelial barrier, and modulating the immune system (Gou et al., 2022; Mazziotto et al., 2023). This provides a strong rationale for utilising probiotics to support intestinal health.

A recent review of the literature suggests that probiotics work through competitive inhibition. Probiotics limit the adhesion and colonisation of pathogens on mucous membranes. Some probiotics release proteases that aid in the breakdown of toxins. Additionally, probiotics form secondary metabolites capable of protecting the gut epithelial barrier and integrating with antimicrobial peptides, promoting mucus secretion and enhancing the expression of tight junction proteins (Paradis et al., 2021; Gou et al., 2022). They may contribute to restoring the composition of the gut microbiome and introducing beneficial functions to gut microbial communities, thereby ameliorating or preventing gut inflammation and related diseases (Wang et al., 2021; Tang et al., 2021; Hemarajata et al., 2012). The immunomodulatory role of probiotics is particularly significant. They promote the survival of intestinal epithelial cells, enhance barrier function, and stimulate protective responses. These actions enhance an individual's innate immunity and modulate pathogen-induced inflammation (Vanderpool et al., 2008; Yan and Polk, 2011; Yan and Polk, 2020; Yan et al., 2011; Gilad et al., 2011; Errard et al., 2011).

5. Irritable bowel syndrome (Ibs) and probiotics

Irritable bowel syndrome (IBS) is a long-term and sometimes unbearable functional bowel condition of the digestive system, (Mearin et al., 2016) characterised by stomach discomfort and changed bowel patterns, with mostly diarrhoea, constipation, or both (Canavan et al., 2014). According to Rome IV criteria, IBS is categorised into four subtypes based on symptoms, which include IBS with constipation (IBS-C), IBS with diarrhoea (IBS-D), IBS with a mixed pattern (IBS-M) of constipation and

diarrhoea, and unclassified IBS (IBS-U), without any of the previous symptoms (Longstreth et al., 2006; Astegiano et al., 2008; Barandouzi et al., 2021).

The global prevalence of IBS is around 11%, with a range of 9–23%, negatively affecting quality of life and work productivity (Lovell and Ford, 2012; Quigley et al., 2016). The cause of IBS is believed to be complex, with several factors, such as changes in gut movement, excessive bacteria in the small intestine, tiny areas of inflammation, and heightened sensitivity in the gut, potentially playing a role (Aragon et al., 2010). IBS is often associated with psychiatric and psychological conditions, especially anxiety and depression (Mayer et al., 2023). The exact cause of IBS remains unclear, and most drug therapies for IBS have weak evidence for efficacy, leading to unsatisfactory symptom control (Simren et al., 2004; Quartero et al., 2005; Holtmann et al., 2016; Sun et al., 2020), thus alternative approaches are needed.

It has been documented that probiotics can appreciably be used to recuperate the symptoms of IBS by improving the frequency and consistency of stool and, gut transit time (Sun et al., 2020; Gupta and Maity, 2021; Benjak Horvat et al., 2021; Kumar et al., 2022; Goodoory et al., 2023). There are reports that demonstrated that certain microbial strains like *Bacillus*, *Bifidobacterium*, *Clostridium*, *Escherichia*, *Lactobacillus*, and *Streptococcus* have been proven to be effective in relieving the symptoms of IBS, such as abdominal pain, bloating, diarrhoea, nausea, constipation, vomiting, and stomach rumbling (Nobaek et al., 2000; Kim et al., 2005; Dolin, 2009; Aragon et al., 2010; Guglielmetti, et al., 2011; Yoon et al., 2014; Dimidi et al., 2017; Sun et al., 2018; Rodiño-Janeiro et al., 2018; de Sequeira et al., 2021; Kumar et al., 2022). Furthermore, it has been well documented that when probiotics are consumed in sufficient quantities, they have positive effects on the gastrointestinal tract (Tegegne and Kebede, 2022). Probiotics within the gastrointestinal mucosa help in absorbing vital nutrients, eliminating toxins, improving intestinal immunity, inhibiting the spread of harmful microbes and thus aiding in the recovery of the altered gut mucosal barrier (De Vres et al., 2008; Frič, 2002; Salminen et al., 2005; Toma and Pokrotnieks, 2006; Kechagia et al., 2013; Chlebicz-Wójcik and Śliżewska, 2021).

6. Psychiatric conditions and probiotics

The link between the brain and gut, known as the gut-brain axis (Dash et al., 2015), involves a complex network of millions of nerves, neurons, and various chemicals, including neurotransmitters, connecting the two (Collins et al., 2012; Carabotti et al., 2015; Ojeda et al., 2021). It has been well-researched that to control and regulate movement, secretion and sensory signalling, the brain and gastrointestinal tract communicate with each other through hormonal, enzymatic and neuronal signals (Bercik et al., 2011; Liu et al., 2015; Tabrizi et al., 2019; Mörkl et al., 2020; Ojeda et al., 2021).

It is becoming increasingly evident that the gut microbiome is the key part of the gut-brain axis, and any dysregulation of the gut-brain microbiome can lead to disorders including irritable bowel syndrome and neuropsychiatric disorders, depression, Alzheimer's disease, and autism spectrum disorder (Person and Keefer, 2021; Góralczyk-Bińkowska et al., 2022). Changes in the GMB can alter microbial-derived metabolites and peripheral immunity, potentially altering CNS immune response in the context of neurological disease. (Donoso et al., 2022)

Growing evidence suggests that the gut microbiome may influence the gut-brain relationship, impacting mental health, emotional regulation, neuromuscular function, hypothalamic-pituitary-adrenal (HPA) axis and various cognitive functions (Mayer et al., 2014; Carabotti et al., 2015; Appleton, 2018; Nobile et al., 2022; Ansari et al., 2023). It has been shown that various psychological stresses like crowding, heat stress, crowding, separation from loved ones and acoustic stress can impact the gut microbiota (Bailey et al., 2011; De Palma et al., 2014; Foster et al., 2017).

It has been reported that several microbial strains, including *Bifidobacterium* and *Lactobacillus*, show beneficial effects on anxiety and depression, and improve memory dysfunction (Desbonnet et al., 2010; Bercik et al., 2010; Bravo et al., 2011; Bercik et al., 2011; Dinan et al., 2013; Foster et al., 2013; Ohland et al., 2013). Recently, it has also been demonstrated that live *Mycobacterium vaccae* can also reduce anxiety-like behaviours (Matthews and Jenks, 2013). Furthermore, it has

also been noted that a combination of different microbial strains can reverse stress-induced and age-associated memory dysfunctions (Gareau et al., 2011; Distrutti et al., 2014).

Furthermore, altered gut microbiota can also lead to autism spectrum disorder (ASD) (Sanders et al., 2013; Taniya et al., 2022). Numerous pieces of evidence suggest that various factors, including early colonisation of pathogenic microbes, dysbiosis during the gestation period, mode of delivery, overuse of antibiotics, and stress, can impact the CNS function through the production of neurotoxins (Taniya et al., 2022).

In order to understand the mechanism by which the microbiota-gut-brain axis works, numerous studies have been conducted on germ-free rodents or by administering certain bacterial strains (Carabotti et al., 2015; Appleton, 2018; Fülling et al., 2019; Cryan et al., 2019; Hou et al., 2022). In recent years, extensive studies have shown that the gut microbiome can trigger enteroendocrine cells to release peptides and hormones. The gut microbiome is also reported to stimulate the release of chemokines and cytokines, which regulate bacterial concentrations. These factors subsequently affect centrally mediated events upon entering the bloodstream and lymphatic systems (Fülling et al., 2019; Wang et al., 2021).

Moreover, the gut-brain axis is known to be dysregulated and linked to neuroinflammation and altered blood-brain barrier (BBB) permeability during gut microbiota dysbiosis or disturbance in the gut ecosystem (Gong et al., 2019; Kumar et al., 2022; Chaudhry et al., 2023; Yuan et al., 2023).

There is substantial evidence suggesting that stress, depression and anxiety can lead to an increase in gut permeability. Consequently, bacteria can seep into the circulation and cause an inflammatory response through increased levels of cytokines (Valkanova, et al., 2013; Kiecolt-Glaser and Derry, 2015; Liang et al., 2023). Additionally, the inflammatory cytokines alter the activity of neurotransmitters and induce depressive and anxiety symptoms (Dantzer et al., 2011; Ochoa-Repáraz et al., 2011; Vanuytsel et al., 2014). Moreover, Gamma-aminobutyric acid (GABA), secondary bile acids, short-chain fatty acids, and tryptophan metabolites generated from the microbiota also regulate the neuroendocrine and neuroimmune mechanisms, and these mechanisms are responsible for controlling the gut-brain axis (Kumar et al., 2022). According to studies done on germ-free animal models, the gut microbiota also appears to influence the development of emotional behaviour, stress- and pain-modulation systems, and brain neurotransmitter systems (Emeran et al., 2015).

Probiotics could be used in the treatment of mental disorders which involve increased intestinal permeability, like depression, anxiety, autism, and schizophrenia (Bangsgaard et al., 2012; Wilmes et al., 2021). Specific strains differentially impact the brain. A meta-analysis found that probiotics significantly alleviate symptoms of depression (Cryan and O'Mahony, 2011). In healthy volunteers, *Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175 given for 30 days reduced Hospital Anxiety and Depression Scale scores versus placebo (Mörkl et al., 2020). Also, other strains like *Lactococcus lactis*, *B. longum*, *Lactobacillus bulgaricus*, *Bifidobacterium animalis*, *Streptococcus thermophilus*, and *L. helveticus* decrease depression and stress (Wand and Kasper, 2014). Probiotics are also known to decrease inflammation and improve behavioral symptoms in patients with autism spectrum disorder (ASD) (Jiang et al., 2015). In schizophrenia, probiotics with vitamin D given for 12 weeks improved Positive and Negative Syndrome Scale (PANSS) scores, suggesting utility in countering gastrointestinal inflammation (Ait-Belgnaoui et al., 2014). Probiotics may also improve COVID-19-associated mood disturbances by restoring intestinal balance and preventing pathogen overgrowth (Savignac et al., 2014; Maes et al., 2012; Ghannoum et al., 2021). However, limitations exist, like avoiding probiotics in immunocompromised patients on corticosteroids (Savignac et al., 2014).

Probiotics have prospective beneficial usages for mental disorders involving increased intestinal permeability, such as anxiety, depression and ASD. It has been reported that specific probiotic strains, like *Lactobacillus*, *Bifidobacterium* and *Streptococcus*, can differentially impact brain function and significantly reduce symptoms of anxiety and depression (Ahmed et al., 2024).

7. Discussion

The intricate relationship between the gut-brain axis and gut microbiota provides a ray of hope to treat both gastrointestinal

and psychiatric conditions. By rebalancing the microbiota of the intestine and affecting the gut-brain axis, this study demonstrates how probiotics can be used to treat irritable bowel syndrome (IBS) as well as psychiatric comorbidities. The evidence provided here shows that physiological homeostasis is largely controlled by intestinal bacteria in a way that if there is any dysbiosis, it will lead to many diseases, such as IBS and psychiatric disorders, among which are anxiety and depression. Gut health can be positively impacted by live microorganisms like probiotics by enhancing interrupted intestinal barrier, immune modulation and competitive inhibition of pathogenic bacteria. This alteration in the composition of gut microbiota which might lead to improved symptoms of IBS, includes bowel regularity, abdominal pains, bloating, etc. Probiotics-specific strains example *Lactobacillus* and *Bifidobacterium*, have been proven to effectively relieve these symptoms, making it possible for gut-friendly bacteria them a therapeutic option in managing IBS.

Gut-brain axis has a two-way communication network integrating immunological, neuronal and endocrine connections, which enables gut microbiota to affect brain activity and behavior. It is thought that imbalances in the microbial population are connected with psychiatric illnesses such as depression and anxiety, implying that rectifying the composition of gut microbiota would be beneficial to mental health. “Psychobiotics” are alternatively referred to as probiotics which have shown improvement in modulation of inflammatory pathways, production of neuroactive substances and enhancing gut microbiota structure, thereby reducing psychiatric symptoms. Numerous studies highlighted in this review show that probiotics have the capability to decrease anxiety and depression, enhance memory impairment, and produce anxiolytic antidepressant effects in various ways, including modulating the brain axis. On top of that, probiotics have been found useful in lessening symptoms of autism spectrum disorder (ASD) as well as improving outcomes in schizophrenia by modulation of gut microbiota and reducing inflammation. However, it is important to note that there are limitations to the use of probiotics, especially among immune-compromised patients. More research is needed regarding optimal strains, doses and duration of treatment to obtain the maximum therapeutic benefits of using Probiotics in gastrointestinal and psychiatric conditions.

8. Conclusion

The findings of this review underline the noteworthy role of gut microbiota in both gastrointestinal and psychiatric health, underscoring the probable of probiotics as a therapeutic intervention. The gut-brain axis acts as a critical pathway through which gut microbiota can affect brain function and behaviour, and dysbiosis in this axis relates to numerous disorders. Probiotics offer a promising approach to re-establishing gut microbiota balance, thereby alleviating indicators of IBS and psychiatric conditions like anxiety and depression. While the existing data supports the use of probiotics in dealing with these conditions, further clinical trials and mechanistic studies are indispensable to ascertain uniform standards for probiotic use. The intricacy of the gut microbiota and its interactions with the host necessitates a nuanced approach to probiotic therapy, tailored to individual patient needs and conditions. In summary, the potential therapeutic advantages of probiotics in tackling IBS and psychiatric comorbidities signify an encouraging future in medical research. By exploiting the multifaceted relationship between gut health and overall well-being, probiotics have the prospective to considerably improve the quality of life for individuals coping with these conditions. Ongoing research and clinical implementation will be vital in fully harnessing the advantages of probiotics in healthcare.

9. Future Perspectives

The subsequent studies on probiotics should thus find out the impact of these biological agents on the gut-brain axis, by focusing on neurotransmitters, endocrine or immune system. This could make better patient outcomes and reduce toxicity for treating with tailored probiotic products based on a person's unique microbiome. They also need to be followed by longitudinal studies to assess probiotics' long-term effects on mental health disorders and establish standard protocols.

Another research priority is determining which IBS patients will benefit from a given strain of probiotics, as well as how these strains influence disease symptoms and quality of life. Also, there is a need to investigate how probiotics influence gastrointestinal microbiota diversity and stability over time and how they interact with other microbial communities within the gut. Understanding the impact of dietary patterns and lifestyle on probiotic efficacy is essential for enhancing interventions. Although some evidence supports the benefits of probiotics, how these compounds work remains unclear. This knowledge is critical to develop more appropriate therapies. Furthermore, lack of standardisation in probiotic research hampers reproducibility and comparability between studies. Therefore, guidelines will help in converting research findings into clinical practice faster. Besides, more long-term safety data are required, especially among immunocompromised individuals. Additionally, a broader exploration of non-GI microbiota effects by probiotics would improve their health benefit understanding.

Conflict of Interest

The authors declare that there is no conflict of interest, financial or otherwise.

Funding

This work did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Acknowledgements

Kuntal, MY, BC and AA would like to thank Gargi College, University of Delhi, for providing the resources to the authors to complete this work. SK is thankful to the School of Sciences, IGNOU, for their help in completing this review article.

Author's contributions

Kuntal, MY and SK conceptualized the review article. BC and AA wrote the initial draft. Kuntal and SK assisted in the literature search while Kuntal and MY revised the manuscript. All authors read and approved the final manuscript.

Conflict of interests

The authors declare that they have no conflict of interest.

References

- Adak A and Khan MR. 2019. An insight into gut microbiota and its functionalities. *Cellular and Molecular Life Sciences* 76 (3): 473-493.
- Ahmed GK, Ramadan HKA, Elbeh K and Haridy NA. 2024. Bridging the gap: associations between gut microbiota and psychiatric disorders. *Middle East Current Psychiatry* 31 (2): 1-14.
- Ait-Belgnaoui A, Colom A, Braniste V, Ramalho L, Marrot A, Cartier C, Houdeau E, Theodorou V and Tompkins T. 2014. Probiotic gut effect prevents the chronic psychological stress-induced brain activity abnormality in mice. *Neurogastroenterology and Motility* 26 (4): 510–520.
- Alharthi A, Alhazmi S, Alburae N, and Bahieldin A. 2022. The Human Gut Microbiome as a Potential Factor in Autism Spectrum Disorder. *International Journal of Molecular Sciences* 23(3):1363.
- Alonso VR and Guarner F. 2013. Linking the gut microbiota to human health. *British Journal of Nutrition* 109(S2): S21-S26.
- Ansari F, Neshat M, Pourjafar H, Jafari SM, Samakkhah SA, and Mirzakhani E. 2023. The role of probiotics and prebiotics in modulating of the gut-brain axis. *Frontiers in Nutrition* 10: 1173660.
- Anto L and Blesso CN. 2022. Interplay between diet, the gut microbiome, and atherosclerosis: Role of dysbiosis and microbial metabolites on inflammation and disordered lipid metabolism. *The Journal of Nutritional Biochemistry* 105: 108991.
- Appleton J. 2018. The Gut-Brain Axis: Influence of Microbiota on Mood and Mental Health. *Integrative medicine Encinitas, Calif* 17(4): 28–32.
- Aragon G, Graham DB, Borum M and Doman DB. 2010. Probiotic therapy for irritable bowel syndrome. *Gastroenterology & Hepatology* 6(1): 39–44.
- Astegiano M, Pellicano R, Sguazzini C, Berrutti M, Simondi D, Reggiani S, and Rizzetto M. 2008 Clinical approach to irritable bowel syndrome. *Minerva Gastroenterologica e Dietologica* 54(3): 251-257.

- Backhed F, Ley RE, Sonnenburg JL, Peterson DA and Gordon JI. 2005.. Host-bacterial mutualism in the human intestine. *Science* 307(5717): 1915-1920.
- Bailey MT, Dowd SE, Galley JD, Hufnagle AR, Allen RG, and Lyte M. 2011. Exposure to a social stressor alters the structure of the intestinal microbiota: implications for stressor-induced immunomodulation. *Brain, Behavior, and Immunity* 25(3): 397-407.
- Bangsgaard BKM, Krych L, Sørensen DB, Pang W, Nielsen DS, Josefsen K, Hansen LH, Sørensen SJ, and Hansen AK. 2012. Gut Microbiota Composition Is Correlated to Grid Floor Induced Stress and Behavior in the BALB/c Mouse. *Aziz RK, ed. PLoS ONE* 7(10): e46231.
- Barandouzi ZA, Lee J, Maas K, Starkweather AR, and Cong XS. 2021. Altered gut microbiota in irritable bowel syndrome and its association with food components. *Journal of Personalized Medicine* 11(1): 35.
- Bäumler AJ and Sperandio V. 2016. Interactions between the microbiota and pathogenic bacteria in the gut. *Nature* 535 (7610): 85-93.
- Benjak HI, Gobin I, Kresović A, and Hauser G. 2021 How can probiotic improve irritable bowel syndrome symptoms? *World Journal of Gastrointestinal Surgery*. 13(9): 923-940.
- Bercik P, Elena FV, Jane AF, Joseph M, Murray P, Xiaxing H, Paul M, Wendy J, Patricia B, Karen AN, Jun Lu, Waliul IK, Irene CT, Christine C, Gabriela EB and Stephen MC. 2010. Chronic gastrointestinal inflammation induces anxiety-like behavior and alters central nervous system biochemistry in mice. *Gastroenterology* 139(6): 2102-2112.
- Bercik P, Emmanuel D, Josh C, Wendy J, Jun Lu, Jennifer J, Yikang D, Patricia B, Joseph M, Kathy D. McCoy EF, Verdu SMC. 2011. The intestinal microbiota affect central levels of brain-derived neurotropic factor and behavior in mice. *Gastroenterology*, 141(2): 599-609.
- Bravo JA, Forsythe P, Chew MV, Escaravage E, Savignac HM, Dinan TG and Cryan JF. 2011. Ingestion of *Lactobacillus* strain regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve. *Proceedings of the National Academy of Sciences*, 108(38): 16050-16055.
- Brown EM, Clardy J, and Xavier RJ. 2023. Gut microbiome lipid metabolism and its impact on host physiology. *Cell Host & Microbe* 31(2): 173–186.
- Buffington SA, Di Prisco GV, Auchtung TA, Ajami NJ, Petrosino JF, Costa-Mattioli M. 2016. Microbial reconstitution reverses maternal diet-induced social and synaptic deficits in offspring. *Cell* 165 (7) :1762–1775.
- Canavan C, West J, and Card T. 2014. The epidemiology of irritable bowel syndrome. *Clinical Epidemiology* 6: 71–80.
- Cani P, and Delzenne N. 2009. Interplay between obesity and associated metabolic disorders: new insights into the gut microbiota. *Current Opinion in Pharmacology* 9: 737–743.
- Carabotti M, Scirocco A, Maselli MA, and Severi C. 2015. The gut-brain axis: interactions between enteric microbiota, central and enteric nervous systems. *Annals of Gastroenterology* 28(2): 203–209.
- Cavuoto KM, Banerjee S, and Galor A. 2019. Relationship between the microbiome and ocular health. *Ocular Surface* 17(3): 384-392.
- Chaudhry TS, Senapati SG, Gadam S, Mannam HPSS, Voruganti HV, Abbasi Z, Abhinav T, Challa AB, Pallipamu N, Bhemisetty N, and Arunachalam SP. 2023. The Impact of Microbiota on the Gut-Brain Axis: Examining the Complex Interplay and Implications. *Journal of Clinical Medicine* 12(16): 5231.
- Cheng Y, Shen Z, Gao Y, Chen F, Xu H, Mo Q, Chu X, Peng CL, McKenzie TT, Palacios BE, Hu J, Zhou H, and Long J. 2022. Phase transition and remodeling complex assembly are important for SS18-SSX oncogenic activity in synovial sarcomas. *Nature Communications* 13(1): 2724
- Chlebicz WA and Śliżewska K. 2021. Probiotics, prebiotics, and synbiotics in the irritable bowel syndrome treatment: a review. *Biomolecules* 11 (8):1154.
- Claus S, Tsang T, Wang Y, Cloarec O, Skordi E, Martin F, et al. 2008. Systemic multicompartmental effects of the gut microbiome on mouse metabolic phenotypes. *Molecular Systems Biology* 4: 219.
- Collins SM., Surette M. and Bercik, P. 2012. The interplay between the intestinal microbiota and the brain. *Nature Reviews Microbiology* 10(11): 735-742.
- Cryan JF, and O'Mahony SM. 2011. The microbiome-gut-brain axis: from bowel to behavior. *Neurogastroenterology & Motility* 23(3): 187-192.
- Cryan JF, Kenneth J. O'R, Caitlin SMC, Kiran VS, Thomaz FSB, Marcus B, Martin GC, Sofia C, Christine F, Anna VG, Katherine EG, Minal J, Caitriona M. Long-Smith, Joshua ML, Jason A. Martin, Alicia MP, Gerard ME, Morelli Enrique K, Rory O'Connor, Joanna SCP, Veronica LP, Kieran R, Nathaniel LR, Eoin Sherwin, Simon Spichak Emily MT, Marcel VDW, Ana Paula VS, Shauna E. Wallace F, Niall Hyland GC and Timothy GD. 2019. The microbiota gut brain axis. *Physiological Reviews* 99(4): 1877-2013
- Dantzer R, O'Connor JC, Lawson MA and Kelley KW. 2011. Inflammation-associated depression: from serotonin to kynurenine. *Psychoneuroendocrinology* 36(3): 426-436.
- Dash S, Clarke G, Berk M, et al. 2015. The gut microbiome and diet in psychiatry: focus on depression. *Current Opinion Psychiatry* 28:1–6
- De Palma G, Collins SM, Bercik P and Verdu EF. 2014. The microbiota-gut-brain axis in gastrointestinal disorders: stressed bugs, stressed brain or both? *Journal of Physiology* 592(14): 2989-2997.
- De Sequeira CLM, Kaeber M, Cekin SE, Enck P and Mack I. 2021. The effect of probiotics on quality of life, depression and anxiety in patients with irritable bowel syndrome: a systematic review and meta-analysis. *Journal of Clinical Medicine* 10(16):3497
- Den BG, Van E K, Groen AK., Venema K., Reijngoud DJ and Bakker BM. 2013. The role of short-chain fatty acids in the interplay between diet, gut microbiota, and host energy metabolism. *Journal of Lipid Research* 54(9): 2325-2340.
- Desbonnet L, Garrett L, Clarke G, Kiely B, Cryan JF, Dinan T 2010. Effects of the probiotic *Bifidobacterium infantis* in the maternal separation model of depression. *Neuroscience* 170(4):1179-1188.
- Dimidi E, Christodoulides S, Scott SM, and Whelan K. 2017. Mechanisms of action of probiotics and the gastrointestinal microbiota on gut motility and constipation. *Advances in Nutrition* 8(3): 484-494.
- Dinan TG, Stanton C, Cryan JF. 2013. Psychobiotics: a novel class of psychotropic. *Biological Psychiatry* 74: 720-726
- Distrutti E, O'Reilly JA, McDonald C, Cipriani S, Renga B, Lynch MA and Fiorucci S. 2014. Modulation of intestinal microbiota by the probiotic VSL# 3 resets brain gene expression and ameliorates the age-related deficit in LTP. *PLoS one* 9(9): e106503.
- Dolin BJ. 2009. Effects of a proprietary *Bacillus coagulans* preparation on symptoms of diarrhea-predominant irritable bowel syndrome. Methods and findings in experimental and clinical pharmacology 31(10): 655-659.
- Donoso F, Cryan JF, Olavarría-Ramírez L, Nolan YM, Clarke G. 2022. Inflammation, lifestyle factors, and the microbiome-gut-brain axis: relevance to depression and antidepressant action. *Clinical Pharmacology & Therapeutics* 113(2): 246-259. doi:10.1002/cpt.2581
- Drossman DA, Creed FH, Olden KW, Svedlund J, Toner BB, Whitehead WE. 1999. Psychosocial aspects of the functional gastrointestinal disorders. *Gut* 45 (Suppl 2): II25–II30.
- Durack, J., & Lynch, S. V. 2019. The gut microbiome: Relationships with disease and opportunities for therapy. *The Journal of Experimental Medicine* 216(1): 20–40.
- Emeran AM, Rob K, Sarkis KM, John F. Cryan and Kirsten T. 2014. Gut microbes and the brain: paradigm shift in neuroscience. *Journal of Neuroscience* 34: 15490–15496
- Evrard B, Coudeyras S, Dosgibert A, Charbonnel N., Alamé J, Tridon A, and Forestier C. 2011. Dose-dependent immunomodulation of human dendritic cells by the probiotic *Lactobacillus rhamnosus* Lcr35. *PLoS one* 6(4): e18735.
- Fattorusso A, Di Genova L, Dell'Isola G B, Mencaroni E and Esposito S. 2019. Autism spectrum disorders and the gut microbiota. *Nutrients* 11(3): 521.
- Fava F, Rizzetto L, and Tuohy K. 2019. Gut microbiota and health: Connecting actors across the metabolic system. *Proceedings of the Nutrition Society* 78: 177–188.
- Forth E, Buehner B, Storer A, Sgarbossa C, Milev R and Chinn Meyyappan A. 2023. Systematic review of probiotics as an adjuvant treatment for psychiatric disorders. *Frontiers in Behavioral Neuroscience* 17: 1111349.
- Foster JA, McVey Neufeld KA. 2013. Gut-brain axis: how the microbiome influences anxiety and depression. *Trends in Neurosciences* 36(5): 305-312.
- Foster JA, Rinaman L, and Cryan JF. 2017. Stress & the gut-brain axis: regulation by the microbiome. *Neurobiology of Stress* 7: 124-136.
- Frank D., Zhu W, Sartor R., Li E. 2011. Investigating the biological and clinical significance of human dysbioses. *Trends in Microbiology* 19: 427–434
- Frič P 2002. Probiotics in gastroenterology. *Zeitschrift für Gastroenterologie* 40(03): 197-201.

- Fujisaka S, Watanabe Y, and Tobe K. 2023. The gut microbiome: a core regulator of metabolism. *Journal of Endocrinology* 256(3): e220111.
- Fülling C, Dinan TG, and Cryan JF. 2019. Gut microbe to brain signaling: what happens in vagus. *Neuron* 101(6): 998–1002.
- Gareau MG, Wine E, Rodrigues DM, Cho JH, Whary MT, Philpott DJ, Macqueen G, Sherman PM. 2011. Bacterial infection causes stress-induced memory dysfunction in mice. *Gut* 60: 307–317
- Gensollen T., Iyer SS, Kasper DL, and Blumberg RS. 2016. How colonization by microbiota in early life shapes the immune system. *Science* 352: 539–544.
- Ghannoum MA, Ford M, Bonomo RA, Gamal A, and McCormick TS. 2021. A microbiome-driven approach to combating depression during the COVID-19 pandemic. *Frontiers in Nutrition* 8: 672390
- Gilad O, Svensson B, Viborg A.H, Stuer-Lauridsen B, and Jacobsen S. 2011. The extracellular proteome of *Bifidobacterium animalis* subsp. *lactis* BB-12 reveals proteins with putative roles in probiotic effects. *Proteomics* 11(12): 2503–2514.
- Gong X, Liu X, Li C, Chen C, Lin J, Li A, An D, Zhou D, and Hong Z. 2019. Alterations in the human gut microbiome in anti-N-methyl-D-aspartate receptor encephalitis. *Annals of Clinical and Translational Neurology* 6(9): 1771–1781.
- Goodoory VC, Khasawneh M, Black CJ, Quigley EMM, Moayyedi P. and Ford AC. 2023. Efficacy of probiotics in irritable bowel syndrome: systematic review and meta-analysis. *Gastroenterology* 165(5): 1206–1218.
- Góralczyk-Bińkowska A, Szmajda-Krygier D, Kozłowska E. 2022. The microbiota–gut–brain axis in psychiatric disorders. *International Journal of Molecular Sciences* 23(19): 11245.
- Gou HZ, Zhang YL, Ren LF, Li ZJ, and Zhang L. 2022. How do intestinal probiotics restore the intestinal barrier? *Frontiers in Microbiology* 13: 929346.
- Groeger D, Murphy EF, Tan HTT, Larsen IS, O'Neill I, and Quigley EMM 2022. Interactions between symptoms and psychological status in irritable bowel syndrome: An exploratory study of the impact of a probiotic combination. *Neurogastroenterology & Motility* 35(1): e14477.
- Guglielmetti S, Mora D, Gschwendner M, and Popp K. 2011. Randomised clinical trial: *Bifidobacterium bifidum* MIMBb75 significantly alleviates irritable bowel syndrome and improves quality of life—a double-blind, placebo-controlled study. *Alimentary Pharmacology & Therapeutics* 33(10): 1123–1132
- Gupta AK. and Maity C. 2021. Efficacy and safety of *Bacillus coagulans* LBSC in irritable bowel syndrome: A prospective, interventional, randomized, double-blind, placebo-controlled clinical study [CONSORT Compliant]. *Medicine* 100(3): e23641.
- Haddix H. 2023. Irritable Bowel Syndrome: Proposed Mechanisms of Pathophysiology and the Underlying Dysregulation of Brain-Gut Interaction. Senior Honors Theses submitted to Liberty University. Spring, pp 1–31.
- Heidari M, Khodadadi JY, Madani S, Shahi S, Shahi MS and Goli M. 2023. Influence of Food Type on Human Psychological–Behavioral Responses and Crime Reduction. *Nutrients* 15: 3715.
- Hemarajata P, Versalovic J. 2012 Effects of probiotics on gut microbiota: mechanisms of intestinal immunomodulation and neuromodulation. *Therapeutic Advances in Gastroenterology* 6(1): 39–51.
- Holtmann GJ, Ford AC and Talley NJ. 2016. Pathophysiology of irritable bowel syndrome. *Lancet Gastroenterology & Hepatology* 1:133–46.
- Hou K, Wu ZX, Chen, XY. et al. 2022. Microbiota in health and diseases. *Signal Transduction and Targeted Therapy* 7: 135.
- Jandhyala SM, Talukdar R, Subramanyam C, Vuyyuru H., Sasikala M and Nageshwar RD. 2015. Role of the normal gut microbiota. *World Journal of Gastroenterology* 21(29): 8787–8803.
- Jiang H, Ling Z, Zhang Y, et al. 2015. Altered fecal microbiota composition in patients with major depressive disorder. *Brain, Behavior, and Immunity* 48: 186–194.
- Jumpertz R, Le DS, Turnbaugh PJ, Trinidad C, Bogardus C, Gordon JI, and Krakoff J. 2011. Energy-balance studies reveal associations between gut microbes, caloric load, and nutrient absorption in humans. *American Journal of Clinical Nutrition* 94(1): 58–65.
- Kechagia M, Basoulis D, Konstantopoulou S, Dimitriadi D, Gyftopoulou K, Skarmoutsou N, and Fakiri EM. 2013. Health benefits of probiotics: a review. *ISRN Nutrition*: 481651.
- Kelly CJ, Zheng L, Campbell EL, Saeedi B, Scholz CC, Bayless AJ, Wilson KE, Glover LE, Kominsky DJ, Magnuson A, Weir TL, Ehrentauf SF, Pickel C, Kuhn KA, Lanis JM, Nguyen V, Taylor CT, Colgan SP. 2015. Crosstalk between microbiota-derived short-chain fatty acids and intestinal epithelial HIF augments tissue barrier function. *Cell Host & Microbe* 17(5): 662–671
- Khan A, Ali H, Rehman UU, Belduz AO, Bibi A, Abdurahman MA, Shah AA, Badshah M, Hasan F, Kilic AO, Ullah A, Jahan S, Rehman MMU, Mansoor R, and Khan S. 2022. Prebiotic potential of enzymatically prepared resistant starch in reshaping gut microbiota and their respond to body physiology. *PLOS ONE*: 17(5): e0267318
- Kiecolt-Glaser JK, Derry HM, Fagundes CP. 2015. Inflammation: depression fans the flames and feasts on the heat. *American Journal of Psychiatry* 172: 1075–1091.
- Kim HJ, Vazquez Roque MI, Camilleri M, Stephens D, Burton DD, Baxter K and Zinsmeister AR. 2005. A randomized controlled trial of a probiotic combination VSL# 3 and placebo in irritable bowel syndrome with bloating. *Neurogastroenterology & Motility* 17(5): 687–696.
- Kim SK, Guevarra RB, Kim YT, Kwon J, Kim H, Cho JH, Kim HB, and Lee JH. 2019 Gut Microbiome-Associated Diseases. *Microbial Biotechnology* 29(9): 1335–1340.
- Kumar A, Pramanik J, Goyal N, et al. Gut Microbiota in Anxiety and Depression: Unveiling the Relationships and Management Options. *Pharmaceuticals* 16(4): 565.
- Kumar SL, Pugalenthi LS, Ahmad M, Reddy S, Barkhane Z and Elmadi J. 2022. Probiotics in Irritable Bowel Syndrome: A Review of Their Therapeutic Role. *Cureus* 14(4): e24240.
- Lagier JC, Edouard S, Pagnier I, Mediannikov O, Drancourt M, and Raoult D. 2015. Current and past strategies for bacterial culture in clinical microbiology. *Clinical Microbiology Reviews* 28: 208–236.
- Lamichhane S., Sen P, Alves MA, Ribeiro HC, Raunioinen P, Hyötyläinen T, and Orešič M. 2021. Linking gut microbiome and lipid metabolism: moving beyond associations. *Metabolites* 11(1): 55.
- Larsen N, Vogensen F, Van Den BF, Nielsen D, Andreasen A, Pedersen BK, Al Soud WA, Sørensen SJ, Hansen LH, Jakobsen M 2010. Gut microbiota in human adults with type 2 diabetes differs from non-diabetic adults. *PLoS One* 5(2): e9085.
- Li W and Chen T. 2022. An Insight into the Clinical Application of Gut Microbiota during anticancer therapy. *Advanced Gut & Microbiome Research*. 2022: 8183993.
- Liang L, Saunders C. and Sanossian N. 2023. Food, gut barrier dysfunction, and related diseases: A new target for future individualized disease prevention and management. *Food Science & Nutrition* 11(4): 1671–1704.
- Liang S, Wu X, and Jin F. 2018. Gut-Brain Psychology: Rethinking Psychology from the Microbiota-Gut-Brain Axis. *Frontiers in Integrative Neuroscience* 12: 33.
- Ling Z, Xiao H and Chen W. 2022. Gut microbiome: the cornerstone of life and health. *Advanced Gut & Microbiome Research* 2022: 1–3. doi:10.1155/2022/9894812
- Liu B, Ye D, Yang H, Song J, Sun X, He Z, Mao Y, and Hao G. 2023. Assessing the relationship between gut microbiota and irritable bowel syndrome: a two-sample Mendelian randomization analysis. *BMC Gastroenterology* 23(1): 150.
- Liu X., Cao S., and Zhang X. 2015. Modulation of gut microbiota–brain axis by probiotics, prebiotics, and diet. *Journal of Agricultural and Food Chemistry* 63(36): 7885–7895.
- Liu Y, Wang J, Wu C. 2022. Modulation of Gut Microbiota and Immune System by Probiotics, Pre-biotics, and Post-biotics. *Frontiers in Nutrition*. 8:634897.
- Longstreth GF, Thompson WG, Chey WD, Houghton La, Mearin F, Spiller RC. 2006.. Functional bowel disorders. *Gastroenterology* 130: 1480–91.
- Lovell RM, Ford AC. 2012. Global prevalence of and risk factors for irritable bowel syndrome: A meta-analysis. *Clinical Gastroenterology and Hepatology* 10: 7:12–21.e4.
- Maes M, Kubera M, Leunis JC and Berk M 2012. Increased IgA and IgM responses against gut commensals in chronic depression: Further evidence for increased bacterial translocation or leaky gut. *Journal of Affective Disorders* 141(1): 55–62.
- Matthews, DM, and Jenks SM. 2013. Ingestion of *Mycobacterium vaccae* decreases anxiety-related behavior and improves learning in mice. *Behavioural Processes* 96: 27–35.

- Mayer EA, Ryu HJ, and Bhatt RR. 2023 The neurobiology of irritable bowel syndrome. *Molecular Psychiatry* 28(4): 1451-1465
- Mayer EA, Savidge T, and Shulman RJ. 2014. Brain-gut microbiome interactions and functional bowel disorders. *Gastroenterology* 146(6): 1500-1512.
- Mazziotta C, Tognon M, Martini F, Torreggiani E, and Rotondo JC. 2023. Probiotics mechanism of action on immune cells and beneficial effects on human health. *Cells* 12(1): 184.
- Mearin F, Lacy BE, Chang L, Chey WD, Lembo AJ, Simren M, et al 2016. Bowel disorders. *Gastroenterology* 150:1393–407.
- Mörkl S, Butler MI, Holl A, Cryan JF, Dinan TG. 2020.. Probiotics and the microbiota-gut-brain axis: focus on psychiatry. *Current Nutrition Reports* 9(3): 171-182.
- Natividad JMM and Verdu EF 2013. Modulation of intestinal barrier by intestinal microbiota: Pathological and therapeutic implications. *Pharmacology Research* 69: 42–51.
- Nobaek S, Johansson ML, Molin G, Ahrné S, and Jeppsson B. 2000. Alteration of intestinal microflora is associated with reduction in abdominal bloating and pain in patients with irritable bowel syndrome. *Official journal of the American College of Gastroenterology* 95(5): 1231-1238.
- Nobile V, Giardina S and Puoci F. 2022. The Effect of a Probiotic Complex on the Gut-Brain Axis: A Translational Study. *Neuropsychobiology* 81(2): 116–126.
- O'Toole P and Cooney J. 2008. Probiotic bacteria influence the composition and function of the intestinal microbiota. *Interdisciplinary Perspectives in Infectious Diseases* 2008: 175–285
- Ochoa-Repáraz J, Mielcarz D W, Begum-Haque S, and Kasper H. 2011. Gut, bugs, and brain: role of commensal bacteria in the control of central nervous system disease. *Annals of Neurology*, 69(2): 240-247.
- Ohland CL, Kish L, Bell H, Thiesen A, Hotte N, Pankiv E, and Madsen K L. 2013. Effects of *Lactobacillus helveticus* on murine behavior are dependent on diet and genotype and correlate with alterations in the gut microbiome. *Psychoneuroendocrinology* 38(9): 1738-1747.
- Ojeda J, Ávila A, Vidal PM. 2021. Gut microbiota interaction with the central nervous system throughout life. *Journal of Clinical Medicine* 10: 1299.
- Olofsson, LE, and Bäckhed, F. 2022. The metabolic role and therapeutic potential of the microbiome. *Endocrine Reviews*, 43(5): 907–926.
- Paradis T, Bègue H, Basmacıyan L, Dalle F, Bon F. 2021. Tight junctions as a key for pathogens invasion in intestinal epithelial cells. *International Journal of Molecular Sciences* 22: 2506–2525.
- Person H, Keefer L. 2021. Psychological comorbidity in gastrointestinal diseases: Update on the brain-gut-microbiome axis. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 107: 110209.
- Pflughoeft K and Versalovic J. 2012. Human microbiome in health and disease. *Annual Review Pathology* 7: 99–122.
- Portune KJ, Beaumont MDAM, Tomé D, Blachier F, and Sanz Y. 2016. Gut microbiota role in dietary protein metabolism and health-related outcomes: the two sides of the coin. *Trends in Food Science & Technology* 57: 213–232.
- Preidis G. and Versalovic J. 2009. Targeting the human microbiome with antibiotics, probiotics, and prebiotics: gastroenterology enters the metagenomics era. *Gastroenterology* 136: 2015–2031
- Quartero AO, Meineche-Schmidt V, Muris J, Rubin G, de Wit N. 2005. Bulking agents, antispasmodic and antidepressant medication for the treatment of irritable bowel syndrome. *Cochrane Database Systematic Review* 18(2): CD003460.
- Quigley EM, Fried M, Gwee KA, Khalif I, Hungin AP, Lindberg G, Abbas Z, Fernandez LB, Bhatia SJ, Schmulson M, Olano C, LeMair A, and Review Team. 2016. World Gastroenterology Organisation Global Guidelines Irritable Bowel Syndrome: A Global Perspective. *Journal of Clinical Gastroenterology* 50(9): 704–713.
- Radford-Smith DE and Anthony DC. 2023. Prebiotic and probiotic modulation of the microbiota-gut-brain axis in depression. *Nutrients* 15(8): 1880.
- Rinninella E, Raoul P, Cintoni M, Franceschi F, Miggiaro GA D, Gasbarrini A, Mele MC 2019. What is the healthy gut microbiota composition? A changing ecosystem across age, environment, diet, and diseases. *Microorganisms* 7(1): 14.
- Rodiño-Janeiro BK., Vicario M, Alonso-Cotoner C, Pascua-García R, Santos J. 2018. A review of microbiota and irritable bowel syndrome: future in therapies. *Advances in Therapy* 35: 289-310.
- Rothschild D, Weissbrod O, Barkan E, Kurilshikov A, Korem T, Zeevi D, Costea PI, Godneva A, Kalka IN, Bar N, and Shilo S. 2018. Environment dominates over host genetics in shaping human gut microbiota. *Nature* 555(7695): 210-215.
- Salminen SJ, Gueimonde M, Isolauri E. 2005. Probiotics that modify disease risk. *The Journal of Nutrition* 135(5): 1294-1298.
- Sanders M, Guarner F, Guerrant R, Holt P, Quigley E, Sartor R, et al. 2013. An update on the use and investigation of probiotics in health and disease. *Gut* 62 (5):787–796.
- Saulnier DM, Santos F, Roos S, Mistretta T, Spinler J, Molenaar D, Teusink B, James Versalovic J. 2011. Exploring metabolic pathway reconstruction and genome-wide expression profiling in *Lactobacillus reuteri* to define functional probiotic features. *PLoS One* 6(4): e18783.
- Savignac HM, Kiely B, Dinan TG, Cryan JF. 2014. Bifidobacteria exert strain-specific effects on stress-related behavior and physiology in BALB/c mice. *Neurogastroenterology & Motility* 26(11): 1615-1627.
- Sekirov I, Russell SL, Antunes LCM, Finlay BB. 2010. Gut microbiota in health and disease. *Physiological Reviews* 90 (3): 859–904.
- Sender R, Fuchs S, Milo R. 2016. Revised estimates for the number of human and bacteria cells in the body. *PLoS biology* 14(8): e1002533.
- Shaikh, S. D., Sun, N., Canakis, A., Park, W. Y., & Weber, H. C. (2023). Irritable Bowel Syndrome and the Gut Microbiome: A Comprehensive Review. *Journal of Clinical Medicine*, 12(7): 2558.
- Sharma S, Kumar S, Sajjad S, Sharma S. 2023. Probiotics in irritable bowel syndrome: a review article. *Cureus*, 15(3): e36565.
- Simon E, Călinoiu LF, Mitrea L, Vodnar DC. 2021. Probiotics, prebiotics, and synbiotics: implications and beneficial effects against irritable bowel syndrome. *Nutrients* 13(6): 2112.
- Simren M, Brazier J, Coremans G, Dapoigny M, Müller-Lissner SA, Pace F, Smout AJ, Stockbrügger RW, Vatn MH, Whorwell PJ. 2004. Quality of life and illness costs in irritable bowel syndrome. *Digestion* 69:254–61.
- Sonali S, Ray B, Ahmed Tousif H, Rathipriya AG, Sunanda T, Mahalakshmi AM, Rungratanawanich W, Essa MM, Qoronfleh MW, Chidambaram SB, and Song BJ. 2022. Mechanistic insights into the link between gut dysbiosis and major depression: an extensive review. *Cells* 11(8): 1362.
- Sun JR, Kong CF, Qu XK, Deng C, Lou YN, and Jia LQ. 2020. Efficacy and safety of probiotics in irritable bowel syndrome: A systematic review and meta-analysis. *Saudi Journal of Gastroenterology* 26(2): 66–77.
- Sun YY, Li M, Li YY, Li LX, Zhai WZ, Wang P and Li YQ. 2018. The effect of *Clostridium butyricum* on symptoms and fecal microbiota in diarrhea-dominant irritable bowel syndrome: a randomized, double-blind, placebo-controlled trial. *Scientific Reports* 8(1): 1-11.
- Tabrizi A, Khalil L, Homayouni-Rad A., Pourjafar, H, Dehghan P. and Ansari, F. 2019. Prebiotics, as promising functional food to patients with psychological disorders: a review on mood disorders, sleep, and cognition. *NeuroQuantology* 17(6): 1-9.
- Tang, H. Y., Jiang, A. J., Wang, X. Y., Wang, H., Guan, Y. Y., Li, F., & Shen, G. M. 2021. Uncovering the pathophysiology of irritable bowel syndrome by exploring the gut-brain axis: a narrative review. *Annals of Translational Medicine* 9(14): 1187.
- Taniya MA., Chung HJ., Al Mamun A., Alam S., Aziz MA., Emon N U., Islam MM., Hong SS., Podder BR., Ara Mimi A., Aktar Suchi S, Xiao J. 2022. Role of Gut Microbiome in Autism Spectrum Disorder and Its Therapeutic Regulation. *Frontiers in Cellular and Infection Microbiology* 12: 915701.
- Tegegne BA. and Kebede B. 2022. Probiotics, their prophylactic and therapeutic applications in human health development: a review of the literature. *Heliyon* 8(6): e09725.
- Thomas C and Versalovic J. 2010. Probiotics-host communication: modulation of signaling pathways in the intestine. *Gut Microbes* 1: 148–163
- Thursby E., and Juge N. 2017. Introduction to the human gut microbiota. *The Biochemical Journal* 474(11): 1823–1836.
- Tian H, Hu Z, Xu J, Wang C. 2022. The molecular pathophysiology of depression and the new therapeutics. *MedComm* 3(3): e156.
- Toma MM and Pokrotnieks J. 2006. Probiotics as functional food: microbiological and medical aspects. *Acta Universitatis Latviensis* 710: 117-129.

- Valdes AM, Walter J, Segal E, Spector TD. 2018. Role of the gut microbiota in nutrition and health. *The BMJ* 2018: 361
- Valkanova, V, Ebmeier KP, and Allan CL. 2013. CRP, IL-6 and depression: a systematic review and meta-analysis of longitudinal studies. *Journal of Affective Disorders* 150(3): 736-744.
- Vanderpool C, Yan F, and Polk BD. 2008. Mechanisms of probiotic action: implications for therapeutic applications in inflammatory bowel diseases. *Inflammatory bowel diseases* 14(11): 1585-1596.
- Vanuytsel T., Van Wanrooy S., Vanheel H, Vanormelingen C, Verschuere S, Houben E. and Tack J. 2014. Psychological stress and corticotropin-releasing hormone increase intestinal permeability in humans by a mast cell-dependent mechanism. *Gut* 63(8): 1293-1299.
- Wahlström A, Sayin SI, Marschall H-U, Bäckhed F. 2016. Intestinal crosstalk between bile acids and microbiota and its impact on host metabolism. *Cell Metabolism* 24 (1): 41–50.
- Wang X, Zhang P, and Zhang X. 2021. Probiotics Regulate Gut Microbiota: An Effective Method to Improve Immunity. *Molecules* 26(19): 6076.
- Wang Y, Kasper LH. 2014. The role of microbiome in central nervous system disorders. *Brain, Behavior and Immunity* 38: 1-12.
- Wibowo S and Pramadhani A. 2024. Vitamin B, role of gut microbiota and gut health. In *Vitamin B and Vitamin E - Pleiotropic and Nutritional Benefits* Eds Juber Akhtar, Mohammad Ahmad, Mohammad Irfan Khan and Badruddeen IntechOpen. Pp 101-168.
- Wilmes L, Collins JM, O’Riordan KJ, O’Mahony SM, Cryan JF, Clarke G. 2021. Of bowels, brain and behavior: a role for the gut microbiota in psychiatric comorbidities in irritable bowel syndrome. *Neurogastroenterology & Motility* 33(3): e14095.
- Wong JM, De Souza R, Kendall CW, Emam A and Jenkins DJ. 2006. Colonic health: fermentation and short chain fatty acids. *Journal of Clinical Gastroenterology* 40: 235-43.
- Yan F, and Polk DB. 2011. Probiotics and immune health. *Current Opinion in Gastroenterology* 27(6): 496–501.
- Yan F, and Polk DB. 2020. Probiotics and probiotic-derived functional factors—mechanistic insights into applications for intestinal homeostasis. *Frontiers in Immunology* 11: 1428.
- Yan F, Cao H, Cover TL, Washington MK, Shi Y, Liu L and Polk DB. 2011. Colon-specific delivery of a probiotic-derived soluble protein ameliorates intestinal inflammation in mice through an EGFR-dependent mechanism. *The Journal of Clinical Investigation* 121(6): 2242-2253.
- Yoon JS, Sohn W, Lee OY, Lee SP, Lee KN, Jun DW and Seo JG. 2014. Effect of multispecies probiotics on irritable bowel syndrome: a randomized, double-blind, placebo-controlled trial. *Journal of Gastroenterology and Hepatology* 29(1): 52-59.
- Yuan C, He Y, Xie K, Feng L, Gao S, and Cai L. 2023. Review of microbiota gut brain axis and innate immunity in inflammatory and infective diseases. *Frontiers in Cellular and Infection Microbiology* 13: 1282431.
- Zheng P, Zeng B, Liu M, Chen J, Pan J, Han Y, Liu Y, Cheng K, Zhou C, Wang H, Zhou X, Gui S, Perry SW, Wong M-L, Licinio J, Wei H, Xie P. 2019. The gut microbiome from patients with schizophrenia modulates the glutamate-glutamine-GABA cycle and schizophrenia-relevant behaviours in mice. *Science Advances* 5(2): eaau8317

