Research Progress: Relationship Between Gut Microbiome and Mental Health

Jiani Yao *

Faculty of Agricultural and Environmental Sciences, McGill University, Sainte-Anne-de-Bellevue, Quebec, H9X 3V9, Canada

* Corresponding Author Email: jiani.yao@mail.mcgill.ca

Abstract. The relationship between the gut microbiome and mental health has received much attention recently. Recent studies have demonstrated a dual crosstalk relationship within the gut-brain axis (GBA), but some specific mechanisms of their relationship still need to be further explored. Based on recent GBA-related research, this article summarizes and analyzes the intricate connections within GBA and analyzes the potential of probiotic treatment for mental health (especially depression and anxiety). Through analysis, this paper found that a variety of indicators can be used to monitor the effectiveness of treatment processes, including questionnaires and DNA sequencing of stool samples. The clinical application of probiotics can also help relieve symptoms such as anxiety and insomnia, providing patients with a relatively safe treatment option. The conclusions of this article help to provide a reference for the research progress related to GBA and provide new ideas for further exploring the intrinsic mechanism of GBA.

Keywords: Gut microbiome, mental health, probiotic treatments, gut-brain axis.

1. Introduction

The gut microbiome is a complex ecosystem of trillions of microorganisms residing in a human's lower digestive tract. Although it is not a part of any organs, a balanced gut microbiome contributes significantly to maintaining good health by regulating metabolism, aiding nutrient absorption, and boosting the immune system. On the contrary, an imbalanced gut microbiome is related to undesirable health conditions like inflammatory bowel disease (IBD) and irritable bowel syndrome (IBS). It also increases the risk of atopy, type II diabetes, and obesity [1]. Recently, scientific inquiries have uncovered a profound and bidirectional relationship between the gut microbiome and mental health. A well-balanced and diverse gut microbiome would promote a healthier mental status. In contrast, an unbalanced or disrupted gut microbiome would link to bad moods or more severe cases of mental illnesses like depression and anxiety. Simultaneously, mental functions can also have a positive or negative impact on the gut microbiome through stress hormones and neural signalling, as researchers have shown that depressed individuals typically show a decreased microbial diversity or dysbiosis in comparison to healthy individuals [2].

As there is a dramatic advance in technology globally, the working structure has changed significantly over the past twenty years. People are more likely to live or work in a fast-paced environment. Therefore, the people who experience mental issues generally showed an increasing trend, primarily depression and anxiety. According to research by the White House, prior to the pandemic, the depression rate in adolescents (12-17 years) in the United States increased from 8.3 percent to 15.7 percent from 2008 to 2019—almost 90 percent of rate increase. For young adults (18-23 years) in the United States, the depression rate was also increasing, with an 81 percent increase [3]. Furthermore, the pandemic has had immeasurable negative impacts on people's mental status. Raising awareness and conducting research on mental health is vital in modern societies. The traditional treatments for mental disorders include psychotherapy and pharmacological treatments. Researching and understanding the mechanisms of the interactions between gut microbiome and emotional wellness pave new ways for potential interventions, such as probiotic treatments and dietary changes, to impact mental well-being positively.

This intricate interplay between the gut and human emotions is often referred to as the GBA. The GBA is a complex communication network between the nervous systems and the gastrointestinal tract. It involves a dynamic and bidirectional interaction involving the gut microbiome, the enteric nervous system, the autonomic nervous system, and the central nervous system — the brain and the spinal cord. Through these tight linkages with several parts of the nervous system, the GBA is able to monitor and combine gut activities, connecting emotional and cognitive centers. This includes mechanisms like immune activation, intestinal permeability, enteric reflex, and entero-endocrine signalling. The communication within the GBA is facilitated by mediators encompassing the realms of neurology, immunology, and endocrinology [4].

When it comes to the gut microbiome, diet plays an important role. According to the Encyclopedia of Nutrition Science, a diet rich in indigestible carbohydrates like dietary fibers and resistant starches can increase the abundance of beneficial bacteria like bifidobacterium, lactobacillus, ruminococcus, eubacterium rectale, and rothia. At the same time, it decreases the number of disruptive bacteria like clostridium and enterococcus. Nonetheless, a high-fat or high animal-based protein diet, as well as an excess intake of artificial sweeteners, might have the opposite effect [5]. Hence, maintaining a healthy diet is crucial to maintaining a diverse gut microbiome, thus contributing to a healthier mental state.

In summary, although many studies have focused on the relationship between GBA and microorganisms with mental health, the study of this topic is still a relatively new field due to the complex mechanisms of action and intricate interferences naturally presented. This article will analyze the effects of probiotics on mental issues, specifically depression and anxiety, as well as their interactions and underlying mechanisms, with the aim of providing recommendations for future research.

2. The Bidirectional Impacts of Gut Microbiota and Mental Wellness

2.1. The Impact of Gut Microbiota on Mood

2.1.1 Indicators

As mental state or emotions are relatively more subjective concepts, when studying the relationship between gut microbiota and emotions, researchers focus on some indicators that can reflect the state of gut microbiota and its potential impact on emotions.

A very commonly used method to determine the participants mental states is to use questionnaires. There are a variety of questionnaires available to determine different mental issues such as depression, anxiety, and insomnia. These types of questionnaires list the symptoms observed in these mental issues and ask the participants to rate the symptoms based on a numbered scale. Therefore, by adding up numbers the participants rates for themselves, the severity of the mental issue can be quantified. These questionnaires also provide a score range for the examiner to categorize the issue from not present to severe [6].

While the questionnaires primarily based on the participants on judgement that might lead to potential bias or false reports, DNA extraction and 16S rRNA sequencing can be used to detect the diversity index or the abundance of one or multiple specific microbiological organisms in the faecal sample of the participants. The diversity index reflects the richness and balance of different types of microorganisms in microbial communities. A higher diversity intex is often considered a characteristic of a healthy microbial community, and a poor or decreased microbial diversity in the gut would correspond to mental disorders. DNA test kits specifically designed for extracting DNA from bacterial samples are available on the market, and the 16S rRNA sequencing can be done by polymerase chain reaction at the laboratories in biotechnology companies. The alpha diversity index can be then calculated using the results from the tests [6]. When it comes to mental health, according to multiple studies, the ones with higher alpha diversity generally have lower chances of getting mental disorders. However, there is not a specific number or range that indicates a healthy or unhealthy gut microbiota, it is varied between individuals.

2.1.2 The possible impact of bacterial metabolites on mood

Microbiotas reside inside the intestines can metabolize residues from the ingested food and produce metabolites like short-chain fatty acids (SCFA). These metabolites have the possibility to affect brain function and emotions through multiple pathways. Some can pass through the blood-brain barrier thus directly reach the brain and affect the activity of neurons. This effect would impact the release of neurotransmitters and neuronal excitability regulation. Therefore, an analyzation of metabolites from faecal samples of the participants in the study can also be an effective way to determine the mental wellness [6]. The impact of gut microbiota on mood is usually dependent on the chemicals or metabolites of the bacteria that would affect the brain or the GBA, most often, Gamma aminobutyric acid (GABA) and SCFAs. GABA is a neurotransmitter that primarily exerts inhibitory effects in the central nervous system. When it comes to anxiety and depression in mammals, GABA have the ability to regulate these emotions as it regulates the excitability of neurons, lessens the signals sent between nerve cells and brain, thus reaching a calming and relaxing effect. GABA can also modulate gut–brain axis response [7]. Recent studies have shown that some gut microbiotas have been found to synthesize GABA too. These microorganisms include certain types of lactic acid bacteria and other bacteria in the intestine. They produce GABA by fermenting amino acids in the diet. According to the research by Duranti et al., among many different types of probiotics, there is a close relationship between Bifidobacterium and the production of GABA. Their research studied more than 1000 strains of Bifidobacterium and revealed that Bifidobacterium adolescentis could be a typical GABA producer in human's gastrointestinal tract. The specific mechanisms by which Bifidobacteria produce GABA are not fully understood, and research in this area is still ongoing, but there are some possible mechanisms. Bifidobacteria may utilize precursor molecules present in their environment, such as glutamate or monosodium glutamate, to synthesize GABA. As GABA is often synthesized through the decarboxylation of glutamate, Bifidobacteria may possess the enzyme glutamate decarboxylase, which would utilize the precursors as building blocks, and catalyze the conversion of glutamate to GABA.[7] Other studies also suggest that some lactobacillus strains like Lactobacillus rhamnosus can impact the emotion and central GABA receptor in mammals too [8].

As mentioned in the previous paragraphs, the SCFA produced by the fermentation process of many gut bacteria may also be involved in modulating mental wellness, predominately acetic acid, propionic acid, and butyric acid. These SCFAs have been found to affect the metabolism of glutamate, an important neurotransmitter that has an impact on emotional regulation. Furthermore, some studies suggest that butyric acid, in particular, have the ability to influence the serotonin production in mammals. Serotonin is known for its important role in mood regulation, and any alteration in its levels in humans or other mammals would be associated with mental state and behavioural alterations. Certain types of gut bacteria are proved to have associations with SCFA productions, including butyric acid like some strains of Bifidobacteria such as Bifidobacterium bifidum and Bifidobacterium longum. Some strains of Lactobacillus like Lactobacillus plantarum and Lactobacillus rhamnosus are also reported to contribute to the production of SCFA [9].

2.1.3 Microglia cells

Microglia are a type of cells that exist between the central nervous system (CNS) and the peripheral nervous system (PNS), playing an important role in regulating neuroimmune responses. Studies have shown that gut microbiota may regulate the function of microglia by influencing the immune system and inflammatory processes.

In short, intestinal microbiota affects brain function and emotions by synthesizing neuromodulatory compounds such as GABA and SCFAs, as well as regulating the immune system. The metabolites produced by these microorganisms can affect neuronal activity through various pathways, providing a potential biological basis for emotional regulation.

2.2. The Impact of Mood on Gut Microbiota

2.2.1 Stress hormons

The relationship between mood and the gut microbiome is complex and bidirectional. While an unbalanced gut microbiota might negatively impact mental health, a poor gut microbiota balance may also be caused by emotional instability. However, studies focusing on the impact of mood on gut microbiota are relatively limited contrast to the other direction as individual differences, lifestyle differences, and environmental factors may also affect the complexity of this interaction. But still, the research supporting that negative emotions or unstable mental states might have negative impact on the general health of the gut microbiota through various pathways. This might lead to changes in both the compositions of the microbiota and the metabolites of those bacteria.

Firstly, mental issues like depression and anxiety may lead to increased release of stress hormones such as ACTH, catecholamines, and cortisol. The changes in these hormones may directly or indirectly affect the gut microbiota ecosystem through their impact on the gut environment [10]. Most of these hormones can enter the gut through circulation, and some of these hormones like CRF and cortisol can be produced in smaller amounts by the gut enteric neurons, enterochromaffin cells, and epithelial cells. According to studies, the direct interaction of cortisol with gut microbiota negatively impacts the alpha and beta diversity inside intestines [10]. ACTH, catecholamines, and cortisol can increase the adherence of bacterial to the mucosa on the gut. They also increase the uptake of bacteria into Peyer's patches [11]. With these changes, the abundance and composition of gut microbiota would be drastically influenced.

2.2.2 Neurotransmitters

Depression and anxiety are also related to changes in neurotransmitters in the central nervous system. This change may affect the growth and metabolism of gut microbiota through the influence of neurotransmitters such as serotonin. Alteration of serotonin levels can be observed in multiple psychiatric disorders [12]. This may lead to excessive or insufficient generation of certain products [10]. Although the specific mechanism of how serotonin and gut microbiota affect each other is still unclear, the connection of some neurotransmitters and the gut microbiota can still be suggested [12].

2.2.3 Lifestyle and behavioural changes

Furthermore, negative emotions would alter the regular habits of the individuals. Changes in diet or lifestyle are commonly observed in people with depression or anxiety. For example, anxiety and depression may lead to changes in appetite, and shifting resting schedules. Choosing unhealthy diets or having irregular sleeping schedules may affect the structure and function of the microbial community. Changing to an unhealthy lifestyle would also shift the regulation of the immune system in a negative way. Chronic inflammation might occur, and this abnormal immune system activity may affect the health of gut microbiota. This may lead to the production of metabolites related to inflammation, such as inflammatory mediators.

3. Researches and Applications

In the field of research, how gut microbiota and mental health affect each other have been a growing area of interest. Although this field was still relatively new to many researchers, pioneers are starting to study and explore the potential clinical treatments using probiotics to treat or alleviate mental disorders like depression and anxiety.

Students, especially those who are preparing for important exams are especially vulnerable to mental illnesses from all the stress from intense workloads from school and life. Anxiety is very common among college students. According to the research by Zhu et al. [6], Lactobacillus plantarum JYLP-326 was given to thirty anxious students, and placebo was given to other thirty anxious students. Thirty unanxious students with no treatments were monitored as controlled group. The study used 14-item of Hamilton Anxiety Scale (HAMA-14), 8-item of the 8-item Athens

Insomnia Scale (AIS-8) and the 17-item Hamilton Depression Rating Scale (HDRS-17) to let the students evaluate their mental status themselves while use the 16S rRNA sequencing to analyze the gut microbiota, and untargeted metabolomics to analyze the fecal metabolism from the attendees' faecal samples before and at the end of the trial. The treatment was applied twice a day for three weeks. The questionnaire results have shown that supplementation of Lactobacillus plantarum JYLP-326 can decrease the symptoms of anxiety, insomnia, and depression in stressful students, thus improve their mental wellness. The analysis of faecal samples also suggested a success of the experiment, as the abundance of Prevotella and Bifidobacterium were found decreased in the placebo group but can be partially restored in the treatment group. The anxious students were also found to have higher Ethyl sulfate and lower Cyclohexylamine in their faecal metabolites but could be reversed after the treatment. To sum up, Lactobacillus plantarum JYLP-326 is a possible treatment method for people suffering from anxiety, insomnia, and depression.

Pregnant and postpartum women are another vulnerable group prone to suffer from depression and anxiety. Due to the special nature of their identity, many medications cannot be used to treat their mental disorders. In the research by Slykerman et al. [13], Lactobacillus rhamnosus HN001was given to 212 women in pregnancy and postpartum who cannot take medication, and placebo was given to 211 women from enrolment until six months after delivering. The rate of depression and anxiety was recorded using Edinburgh Postnatal Depression Scale and State Trait Anxiety Inventory asking the participants to evaluate for themselves. Among these participants, 193 from the treatment groups and 187 from the placebo groups completed filling the questionnaires. The result showed that the mothers who were treated with Lactobacillus rhamnosus HN001 have significantly lower depression and anxiety scores than the placebo group. Although the research lacked the analysis of faecal samples of the attendees to study the specific composition of the gut microbiota of both groups, this study still showed that Lactobacillus rhamnosus HN001 has the potential for the prevention and treatment of postpartum depression and anxiety.

4. Conclusion

In summary, this article analyzes the interaction between the gut microbiome and mental health. Through the analysis of this article, it is found that multiple studies have shown that there is two-way communication within GBA. On the one hand, the richness of the intestinal microbiome can affect a person's health. Emotional state. Probiotics, especially bifidobacteria and lactobacilli, have received attention for their potential positive effects on mental health. On the other hand, emotions are also intuitively important in influencing the health of the gut microbiota. Alterations in stress hormone and neurotransmitter secretion alter the composition of the gut microbiome. In addition, changes in lifestyle and habits associated with mental illness can also lead to changes in the composition of the gut microbiome. However, the formation mechanism of this association is currently unclear, so future research should focus more on changes in related pathways and related mechanisms. By reviewing previous reports, this article found that GBA-related applications have been confirmed in two clinical studies. Both studies showed that the probiotics given to the treatment group alleviated or partially alleviated the psychiatric problems they suffered, demonstrating the potential of probiotic treatment in relieving symptoms of anxiety, insomnia and depression, providing an alternative treatment option for vulnerable groups. Therefore, based on the analysis results of this article, we can provide additional evidence for further exploring the relevant mechanisms in future research.

References

[1] Bull, M. J., & Plummer, N. T. Part 1: The Human Gut Microbiome in Health and Disease. Integrative Medicine (Encinitas, Calif.), 2014, 13(6), 17–22.

[2] Clapp, M., Aurora, N., Herrera, L., Bhatia, M., Wilen, E., & Wakefield, S. Gut microbiota's effect on mental health: the gut-brain axis. Clinics and Practice, 2014, 7(4).

[3] The White House. Reducing the economic burden of unmet mental health needs. The White House. https://www.whitehouse.gov/cea/written-materials/2022/05/31/reducing-the-economic-burden-of-unmet-mental-health-needs/. 2022.

[4] Carabotti, M., Scirocco, A., Maselli, M. A., & Severi, C. The gut-brain axis: interactions between enteric microbiota, central and enteric nervous systems. Annals of Gastroenterology, 28(2), 203–209. 2015.

[5] Yang, Y., Ge, K., & Chinese Nutrition Society. Encyclopedia of Nutrition Science (2nd ed., pp. 403–410). People's Medical Publishing House. 2019.

[6] Zhu, R., Fang, Y., Li, H., et al. Psychobiotic Lactobacillus plantarum JYLP-326 relieves anxiety, depression, and insomnia symptoms in test anxious college via modulating the gut microbiota and its metabolism. Frontiers in Immunology, 2023, 14.

[7] Duranti, S., Ruiz, L., Lugli, G. A., T et al. Bifidobacterium adolescentis as a key member of the human gut microbiota in the production of GABA. Scientific Reports, 2020, 10.

[8] Bravo, J. A., Forsythe, P., Chew, M. V., Escaravage, E., et al. 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), 2011, 16050–16055.

[9] Markowiak-Kopeć, P., & Śliżewska, K. The Effect of Probiotics on the Production of Short-Chain Fatty Acids by Human Intestinal Microbiome. Nutrients, 2020, 12(4), 1107.

[10] Paudel, D., Uehara, O., Giri, S., Yoshida, K., et al. Effect of psychological stress on the oral-gut microbiota and the potential oral-gut-brain axis. The Japanese Dental Science Review, 2022, 58, 365–375.

[11] Keskitalo, A., Aatsinki, A.-K., Kortesluoma, S., et al. Gut microbiota diversity but not composition is related to saliva cortisol stress response at the age of 2.5 months. Stress, 2021, 24(5), 551–560.

[12] Stasi, C., Sadalla, S., & Milani, S. The Relationship Between the Serotonin Metabolism, Gut-Microbiota and the Gut-Brain Axis. Current Drug Metabolism, 2019, 20(8), 646–655.

[13] Slykerman, R. F., Hood, F., Wickens, K., 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.