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Association Between Gastrointestinal Microbiome and Anxiety: A Systematic Review

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Abstract

Recently in numerous studies , a significant association between the gastrointestinal microbiome and anxiety has been proven, so it can be said that this makes the important role of the gut-brain axis more prominent in aspects related to mental health. Gut microbiome is a type of complex ecosystem including microorganisms in the gastrointestinal tract that influence brain function through neural, hormonal and immune pathways. Research shows that people with anxiety disorders often have an imbalance in their intestinal microbiota. This is usually associated with the reduction of beneficial bacteria such as *Lactobacillus* and *Bifidobacterium* as well as the increase of harmful species such as *Escherichia coli*. In fact, this microbial imbalance may aggravate anxiety symptoms by disrupting active nerve compounds that include neurotransmitters such as GABA. On the other hand, clinical trials have shown that probiotics and prebiotics can help restore the microbial balance and reduce anxiety, but their effectiveness can differ depending on individual and microbial variations. Although there are promising findings in this field so far, but still more clinical trials are needed to gain a better and more understanding of the unknown mechanisms that exist in the gut-brain connection, so as to control the resulting anxiety. Future research needs to focus on the long-term impact of diet, lifestyle, and medication on the gut microbiome, as well as its role in anxiety.

Keywords: anxiety, microbiome, gut-brain, intestinal

Introduction

Anxiety is a very common mental disorder that can have a great impact on the quality of human life[1]. Regarding the symptoms of anxiety, we can mention matters like constant worry, fear and restlessness without a known cause. The effects of anxiety are so destructive that it can even affect a person's performance in his daily affairs[2].

Anxiety disorders in general constitute 18% of the cases of mental disorders. Meanwhile, the global prevalence of anxiety disorders is about 7.3%. The research even found that people with SAD earn an average of 10% less than the general population and typically have fewer friends. They marry even less and divorce more. This disorder is often associated with other mental disorders such as panic disorder (PD), agoraphobia, atypical depression, and body dysmorphic disorder. Women also suffer from anxiety disorders 1.5 to 2 times more than men[3].

Regarding the causes of anxiety, many cases have been discovered so far, but recently several researches have reached the results that have highlighted the role of the microbiome of the gastrointestinal tract in this regard, in such a way that these microbes not only play a role in the occurrence but also in the exacerbation of anxiety[4].

The human gut microbiome is a complex collection of microorganisms that actually live in the digestive tract. These microbes, which play a role in human health, help in food digestion, produce vitamins, strengthen the immune system and protect against infections. It should be noted that the composition of the gut microbiome is different in different people and can be influenced by factors such as diet, antibiotics, lifestyle and genetic factors. If there is a disturbance in the balance of the intestinal microbiome, diseases such as inflammatory bowel diseases, obesity, diabetes, cardiovascular diseases and mental illnesses may develop in humans. Some of the important bacteria in the human gut microbiome include *Lactobacillus*, *Bifidobacterium*, and *Bacteroidetes*[5,6].

During the last decade, a significant association was found between the gut microbiome and the brain, which is also referred to as the gut-brain axis, which includes neural, hormonal and immune pathways. In fact this axis connects the gut microbiome to the brain, in which the modification in the composition of the gut microbiome can lead to changes in human behavior, cognition, and mood. During the research conducted on mice, scientists found that the transfer of gut microbiome from anxious mice to non-anxious mice caused anxiety-like behaviors in the recipient mice[7].

In this regard, various studies have been conducted in humans that show a significant association between gut microbiome and anxiety. During a study that examined people with generalized anxiety disorder (GAD), it was found that the composition of the gut microbiome in these people is very different from people who do not have this disorder. In fact, species of beneficial bacteria such as *Lactobacillus*, *Bifidobacterium* and the increase of inflammatory species such as *Escherichia coli* were observed with increasing levels of anxiety. Such results indicate the alignment of the modification in the composition of the gut microbiome along with the effective factors in the occurrence as well as exacerbation of anxiety[8,9].

Anxiety can actually reduce the quality of life, social performance, work, and also could lead to the risk of physical diseases. Therefore, scientists come to know that it is very important to accurately and fundamentally identify any factors that can play a role in suffering from this disorder[10].

Recently, through various studies, it was found that the use of probiotics and prebiotics as food supplements have been able to improve and optimize the composition of the gut microbiome, and subsequently, reduce anxiety symptoms[11]. In the research that addressed the effect of probiotics on the treatment of anxiety and depression, it was

found that when intestinal health was improved by using probiotics, in fact, the gut-brain axis was able to reduce the symptoms of anxiety and depression, especially in cases of mild to moderate. The results of studies in this field are different and depend on various factors such as the type of probiotic, duration of treatment and individual differences in the gut microbiome. The results of this research were very promising and showed that regulating the gut microbiome can improve anxiety in humans as a useful and new solution[12].

It should be noted that despite this promising research, more studies are still needed for a better understanding. This is in order to better understand the exact mechanisms of this relationship and to better make out factors such as diet, lifestyle, medicine use on the gut microbiome, as well as the consequently in relieving anxiety. Therefore, it can be claimed that future researches need to investigate these factors more comprehensively and how they affect the gut-brain axis and ultimately mental health[13].

Overall, it can be claimed that the association between gut microbiome and anxiety is considered an emerging and even complex issue in science, so that the clearer discovery of this relationship can improve our understanding of mental disorders and provide more effective approaches for prevention and treatment. It is expected that with more research, we will be able to find more effective ways to regulate the microbiome and reduce anxiety, which will lead to the improvement of the quality of life of many people[13,14].

Background

An introduction to gastrointestinal microbiome and anxiety:

In recent years, a complex ecosystem that includes various numbers of micro-organisms which play an important role in human health has attracted the attention of researchers around the world. These microbes are mainly in the human digestive system for various physiological processes that include digestion, vitamin production and immune system function[15]. The presence of these microbes is also considered essential. Due to the fact that the gut microbiome has a significant effect on mental health, especially anxiety disorders, it is referred to as the gut-brain axis[16].

Gut-brain axis and its role in anxiety:

The gut-brain axis is a kind of complex communication pathway that connects the human central nervous system (CNS) with the enteric nervous system (ENS) in the gut. This mentioned axis includes neural, hormonal and immune pathways through which the gut microbiome can affect brain function and behavior, in which anxiety is also very important among them. It is clear that changes in the gut microbiome can significantly alter human mood and anxiety levels. Studies conducted on animal models proved that the transfer of gut microbiota from anxious mice to non-anxious mice causes anxiety-like behaviors in the recipients. Therefore, the role of the microbiome in causing and aggravating anxiety disorders is important[7,17].

Current research limitations:

Most of the existing researches are not clinical and their data from human studies are also limited. So the precise and definitive mechanisms of these microbial changes that affect anxiety are still not fully known, which means that there are speculations about all these mechanisms[18].

Materials and Methods

Literature search:

Literature search was performed mostly in the articles which were published in PubMed. We also reviewed other databases which were relevant including cochrane library, articles which were published in scopus and etc.,

Inclusion criteria:

Studies that were in English language and their focus was mostly on the direction of our article.

Exclusion criteria:

The researches which didn't have the above mentioned criteria.

Any research which did not have enough information for in-depth research.

Results and discussion

Gut microbiome composition and its role in anxiety:

Studies that have been reviewed show a clear difference in the composition of the gut microbiome between those people who have anxiety disorders and those who do not have problems in this regard[19]. But it should be noted that there was a decrease in beneficial bacteria including *Lactobacillus* and *Bifidobacterium* with an increase in harmful bacteria such as *Escherichia coli* at the same time, which means an association between both matters[20]. In fact, it can be hypothesized that microbial imbalance may lead to the creation and even aggravation of anxiety through the gut-brain axis[21].

It can definitely be claimed that the production of neuroactive compounds by intestinal bacteria, including neurotransmitters and short-chain fatty acids (SCFAs), play a role in this process[22]. It has been proven that a decrease in *Lactobacillus* species that produces GABA, which is a key inhibitory neurotransmitter, causes an increase in anxiety levels[23].

Therapeutic potential of probiotics and prebiotics:

During clinical trials, it has been concluded that adjusting the intestinal microbiome through a variety of probiotics, including *Lactobacillus rhamnosus* and *Bifidobacterium longum*, will reduce anxiety symptoms[12]. But it is still not clear whether the effectiveness of these probiotics depends on a specific strain or whether it differs according to racial, gender, etc[24]. Prebiotics promote the growth of beneficial bacteria and also strengthen the connection between the gut and the brain, which ultimately leads to a reduction in anxiety[11].

Mechanisms of gut-brain interaction:

There is a two-way communication between the gut and the brain, which is facilitated through the gut-brain axis[7]. In the animal studies that transferred intestinal microbiota from anxious mice to non-anxious mice, it was observed that the recipient mice showed anxiety-like behaviors, which indicates the significant role of the microbiome in anxiety disorders[8]. It seems that this process is carried out by active nerve compounds, inflammatory pathways, as well as direct nerve communication through the vagus nerve[25].

Future directions:

In order to have a better understanding of the long-term effects of the gut microbiome on anxiety, we need to conduct larger scale clinical trials as well as more in-depth clinical research[8].

Table 1: Aspects, key findings and implementations

Aspect	Key findings	Implications
Gut Microbiome Composition	- Significant difference in gut microbiome between individuals with and without anxiety. - Decrease in beneficial bacteria (e.g., Lactobacillus, Bifidobacterium), increase in harmful bacteria (Escherichia coli).	- Imbalance in gut microbiome may contribute to onset and exacerbation of anxiety. - Beneficial bacteria play a protective role, while harmful bacteria may promote anxiety through the gut-brain axis.
Neuroactive Compound Production	- Intestinal bacteria produce neurotransmitters and SCFAs, which influence anxiety levels. - Decrease in Lactobacillus (GABA producer) linked to higher anxiety.	- Neuroactive compounds produced by gut bacteria are critical in mood regulation. - Restoring beneficial bacteria may lower anxiety by normalizing GABA levels and other neurotransmitters.
Probiotics and Prebiotics	- Clinical trials show reduction in anxiety symptoms with probiotics like Lactobacillus rhamnosus and Bifidobacterium longum. - Effectiveness varies with strains and individual factors.	- Probiotics and prebiotics can be used to manage anxiety, but optimal strains and treatment durations need further research. - Prebiotics enhance beneficial bacteria growth, potentially reducing anxiety via gut-brain communication.
Gut-Brain Axis Interaction	- Two-way communication via neural, hormonal, and immune pathways. - Anxiety-like behaviors observed in animal models receiving gut microbiota from anxious donors.	- Gut microbiome has a profound effect on brain function and behavior, highlighting the potential of microbiome-targeted therapies in anxiety treatment.

Future Research Directions	- Need for larger-scale clinical trials to explore long-term effects. - Investigation of diet, lifestyle, and medication on gut-brain axis and anxiety.	- Understanding the complex interactions and long-term effects could lead to more personalized and effective treatments for anxiety through microbiome modulation.
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Preventive and management instructions

1. Assessment of nutritional needs and its relationship with intestinal microbiome and elimination of problematic factors in this regard[9].
2. Consuming as much dietary fibers as possible, including beta-glucans and arabinoxylans, in order to strengthen the growth of beneficial intestinal bacteria and the subsequent production of short-chain fatty acids (SCFAs), which thus help to improve mental health[26]. It should be noted that these fatty acids such as omega-3 polyunsaturated play a significant role in regulating inflammation and strengthening the integrity of the blood-brain barrier and play a role in managing anxiety[27].
3. Diets rich in polyphenols include berries, green tea, and dark chocolate which can help the growth of beneficial bacteria such as *Akkermansia muciniphila* and *Faecalibacterium prausnitzii*, and since they have anti-inflammatory properties and the ability to produce SCFAs, will be effective in reducing inflammatory responses and improving anxiety symptoms[28,29].
4. Adding new generation probiotics including *Akkermansia muciniphila* and *Faecalibacterium prausnitzii* are very effective because they both strengthen the intestinal barrier and are able to produce neuroactive metabolites. Therefore, they have therapeutic effects in reducing anxiety[29,30].
5. Discovering drug therapies that directly affect the gut microbiome offers new strategies for treating anxiety[31].

6. Promoting and improving the gut-brain axis and turning to techniques that can help regulate physiological responses such as heart rate variability and bowel movements. In this way, it is possible to create a positive effect on the intestinal microbiome, which results in a decrease in anxiety levels[32,33].

Conclusion

There is a complex association between the gastrointestinal microbiome and anxiety , and in fact, evidence suggests that the gut-brain axis plays a critical role in regulating anxiety. Disturbance of the balance in the gut microbiome may lead to the onset and even exacerbation of anxiety symptoms. This relationship is made through neuroactive pathways, immune responses, and also the direct neural connection between the brain and gut, which also affect brain function and behavior.

There is a possibility of therapeutic measures by regulating the intestinal microbiome, which is possible by using probiotics, prebiotics and dietary interventions. Although the current researches have not been able to provide a fully decisive and definitive convincing results in this field, and there is still a need for more researches, but the basic interventions based on nutrition modification, relying on the use of probiotics, etc., are very effective in improving the related problems.

Also, large-scale clinical trials are considered necessary in the future, which will not only improve our understanding of the association between gastrointestinal microbiome and anxiety, but also improve the quality of life of people who suffer from the related complications.

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