The Correlation Between Anxiety and the Gut-Microbiome

By Kayla Roos

Introduction:

A staggering 6.8 million adults in the U.S suffer from generalized anxiety disorder and the gut might have something to do with it[1]. Research on the human gut-microbiome is beginning to shed light on the complex yet deeply important relationship between the gut-microbiome and mental health disorders. Trillions of organisms such as bacteria, fungi, and viruses are home to the gut and are part of the microbiome[2]. These microbiota continuously interact with the brain via a bi-directional communication pathway known as the gut-brain axis, which is responsible for influencing metabolism, digestion, and even mood[3]. Recent studies suggest that an alteration of the composition of the gut-microbiome (gut dysbiosis) has considerable impact on gut homeostasis, leading to greater experiences of general anxiety disorders[2]. In particular, the depletion of certain beneficial microbiota, such as *Lactobacillus* species, exacerbates these symptoms. This review will examine the correlation between changes in gut composition and anxiety, specifically targeting the role of neurotransmitters and how lifestyle changes such as diet have a positive impact on human guts. It must be recognized that due to the complexity of this topic, only a few factors are reviewed.

Diet:

The gut microbiome is a constantly changing environment. Its health and homeostasis are primarily reliant on diet and foods. Too much or too little of certain food groups can cause gut dysbiosis, which makes nutritional choices important. The saying, “you are what you

eat," is in many ways true. The foods that the body consumes have a direct impact on the overall health of a person. Interestingly, foods that are both rich in *Lactobacillus* and that contribute to an uptick in neurotransmitters, such as GABA and serotonin, seem to have a significant effect in relieving anxiety. In an article by Brianna Elliott[4], yogurt was cited as a good food source to reduce inflammation and increase the production of serotonin, leaving a calming and relieving effect on mood. According to the Cleveland Clinic, many fermented foods - such as yogurt - are also a natural source of many probiotics including *Lactobacillus* species, *L. rhamnosus, and L. plantarum*[5]. Other notable beneficial food sources include turmeric and salmon, both of which are rich in omega-3 (help reduce inflammation) [4,6]. Conversely, consuming foods with modified ingredients such as refined sugar and processed meats have been associated with an altered gut microbiome, leading to inflammation; therefore, increasing the risk of mental health disorders such as anxiety and depression[7].

Foods that cultivate a healthy gut-microbiome[4,5]:

- Yogurt
- Other fermented foods: kimchi, kombucha, sauerkraut
- Turmeric
- Salmon
- Turkey

Foods that harm a healthy gut-microbiome[7]:

- Artificial sweeteners
- Soda
- Processed meats

- Canned foods
- Packaged snacks: chicken or fish nuggets, noodle packets

It is important to remember that eating these foods either too often or not at all can be harmful to the body. The gut microbiome is all about balance.

Neurotransmitters:

The influence of *Lactobacillus* reveals an alteration in serotonin properties and expression that consequently affect mood. 95% of the human body's serotonin is located in the microbiome or 'gut brain', rather than in the central nervous system. Its synthesis is dependent on the essential amino acid called tryptophan, which is primarily absorbed by the large intestine. Serotonin synthesis begins when tryptophan is hydroxylated to form 5-HTP, which then by aromatic L-amino acid decarboxylase is converted to serotonin[6]. Recent research shows that *Lactobacillus* expresses high levels of serotonin-synthesizing properties via tryptophan synthetase mediation[8]. Serotonin transporters have also been shown to have a correlation with gut bacteria levels, like that of *Lactobacillus*. The role of serotonin transporters is to regulate serotonin levels in the brain and regulate mood and emotions. Therefore, low amounts of serotonin transporters have been associated with Generalized Anxiety Disorder. In a study conducted by the University of Missouri, adult zebrafish anxiety levels were assessed by a novel tank diving behavioral test[6]. Two groups of zebrafish were measured in this behavioral test; a control group and a group of zebrafish that received *L. plantarum,* a species of *Lactobacillus.* The zebrafish that was given *L. plantarum* spent more time in the top portions of the tank which correlated with less anxiety. Furthermore, the administration of *L. plantarum* caused an increase

of serotonin transporter expression in the brain and an up-regulation of genes encoding serotonin transporter A *(slc6a4a)*[6]. This shows that the gut bacteria *Lactobacillus* has considerable effect on the uptick of serotonin transporters in the brain. It must be noted that this was tested on an animal model and so there may be limitations when applying this research to humans.

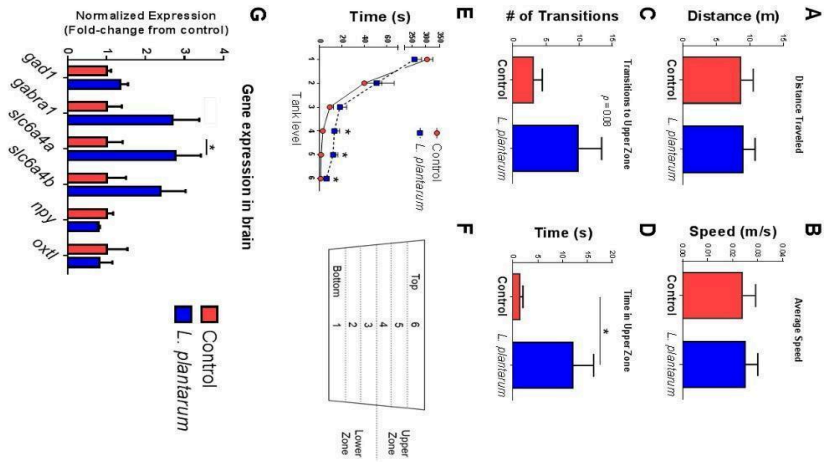

Figure 1. Changes in zebrafish administered with *L. plantarum* measured against a control group. (a) distance, (b) average speed, (c) # of transitions, (d-f) time spent in upper zones of tank, (g) gene expression. This experiment was conducted by Davis, et al[9].

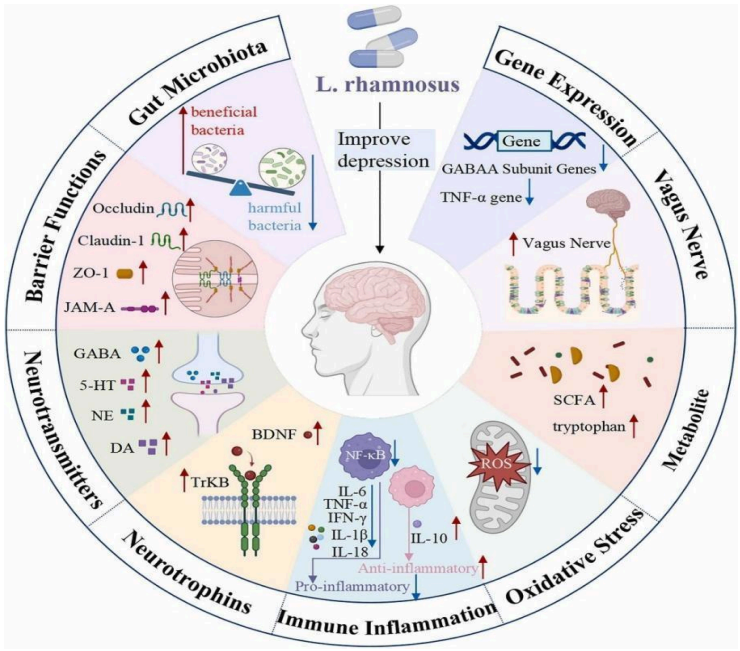

Figure 2. Biological methods of *L. rhamnosus* in treating depression[10].

Gamma-aminobutyric acid (GABA) is an amino acid that is the primary inhibitory neurotransmitter in the brain. Its role in blocking stimulation of neurotransmitters and chemical messages in the brain is key in relieving symptoms of stress[11]. Patients experiencing anxiety and depression are shown to have decreased levels of GABA in the brain. According to a study conducted by Feng, et al, the *Lactobacillus* species, *L. rhamnosus JB-1* has been seen to restore neurochemical balance in the glutamate+glutamine (Glx)/GABA cycle, as displayed in relieving depressive symptoms in CUMS rats[10]. It was also shown to promote increases of GABA and Glx levels in healthy mice. Furthermore, another experiment conducted in 2011[12], discovered that *JB-1* decreased $GABA_{Aa2}$ mRNA expression in the amygdala but elevated expression in the hippocampus. Typically, anxiety is associated with increased $GABA_{Aa2}$ expression in the amygdala and decreased $GABA_{Aa2}$ expression in the hippocampus. These discoveries of *Lactobacillus* are interesting because of its supplementation possibilities; however, it is worth noting that the applications of this study to humans must still be researched. To conclude, *Lactobacillus* species support the expression and secretion of various neurotransmitters and have the potential to relieve anxiety and depressive symptoms.

The Vagus Nerve:

The relationship between various microbiota and neurotransmitters is highly dependent on the functionality of the vagus nerve. The vagus nerve is one of the 12 cranial nerves and is a vital part of the parasympathetic nervous system. It is responsible for regulating digestion and conveying sensory information straight from the gut to the brain[13]. In other words, it is a large component of the gut-brain axis. An experiment conducted by Bravo, et al, studied the effects of

Lactobacillus when the vagus nerve was cut. In an open field test, mice that received lactobacillus but had their vagus nerve cut did not spend any more time in the open field than mice who did not receive lactobacillus treatment. Furthermore, the previous connections discussed between the amygdala and hippocampus were not shown in mice that had their vagus nerve cut[12]. This demonstrates that the effects of lactobacillus on the brain are reliant on signaling through the vagus nerve, and that the signals are unable to reach the brian unless the vagus nerve is intact. There are still questions to be asked regarding vagus nerve signaling, such as, what cells are responsive to the bacterial signals?

Conclusion:

Generalized Anxiety Disorders are one of the most common mental health disorders worldwide, affecting the livelihood and health of millions globally. Research is beginning to show that mental disorders are closely linked to both diet and therefore the composition of the gut microbiome. Foods rich in beneficial bacteria, such as *Lactobacillus*, have the potential to strengthen the important connection between neurotransmitters in the nervous system and bacteria in the digestive system. These discoveries are indicative of a possible future where anxiety, (and other adjacent health disorders), may be treated through more natural methods such as diet and supplementation. The role of bacteria within the gut-brain axis is still under heavy research and essential questions remain unanswered such as; the effectiveness of all *Lactobacillus* species or just certain species; long term effects of supplementation; specifics of communication within the gut-brain axis; and the application of experimental results on humans. This review hopes to examine only the surface of the role of specific microbiota and provide insight into the groundbreaking discoveries of the human gut and brain.

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