

Exploring The gut-Brain Axis: How Microbiome Affects Mental Health

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1. Introduction

There exists the concept of the gut-brain axis, a relation that is considered to be intricate since the alimentary canal and the brain are involved. Therefore, its investigation in the sphere of mental health has been further developed. The bidirectional communication system (Figure 1) through neural, hormonal, and immunological signals, referred to as the gut-brain axis, ensures continuous two-way communication between the gastrointestinal tract (GI) and central nervous system (CNS) (Montagnani et al., 2023). This dialogue remains active throughout life and impacts nearly all of the body's physiological and psychological functions, such as digestion, metabolism, immune response, mood, and cognition (Jugran, 2024). The enteric nervous system is the second brain a combination of neurons that exists in the muscular layers of the gastrointestinal tract. This suborder controls peristalsis, secretion, and blood flow in GIT and can be regulated by the non-central nervous system (Pencheva et al., 2015).

However, the enteric nervous system (ENS) is also in consistent conversation with the CNS through the vagus nerve, which is mostly engaged in transmitting messages from the stomach to the head. The human gastrointestinal tract is abode to trillions of microorganisms that are familiar as the gut microbiome and hence act as a moderator in the gut-brain axis (Massaquoi, 2022). These microorganisms release several neuroactive substances like serotonin, dopamine, and gamma-aminobutyric acid (GABA) that, in a way, influence the brain and behavior (Wiley et al., 2021). Moreover, gut microbial communities are known to be closely associated with the immune system during life development and become the chief actor of immune-regulating and stress modulation through the HPA axis during adulthood (Stadler, 2018). The concept of the gut-brain axis is not that novel in scientific circles. This was only when disturbing sensations were identified as butterflies in the stomach gut feeling corresponded to the outlook of the first civilizations where proper functioning of the stomach was perceived necessary for the well-being of the spirit. However, it was at the dawn of the twentieth century that realistic research was focused on the link between gut bacteria, behavior, and the brain (Logan et al., 2016). The human microbiome, a complex, diverse community of microorganisms inhabiting the human body, is considered a novel immune effector and a compelling factor in the occurrence of both health and diseases (Anwar et al., 2019). These bacteria and other single-celled microorganisms that live in humans' digestive systems are mostly involved in metabolism, digestion, immune regulation, and pathogen defense mechanisms. The gut microbiome is not an inactive organ composed of bacteria that waits for an opportunity to invade the host's tissues it communicates with them through a complex method of the gut-brain axis. It influences the functioning of the body and behaviors in humans. Dysbiosis can be defined as alterations in the composition or the function of microbiota. It is linked to various diseases, including inflammatory bowel diseases, obesity, type-2 diabetes mellitus, cardiovascular diseases, Parkinson's disease, multiple sclerosis, and others (Kurowska et al., 2023).

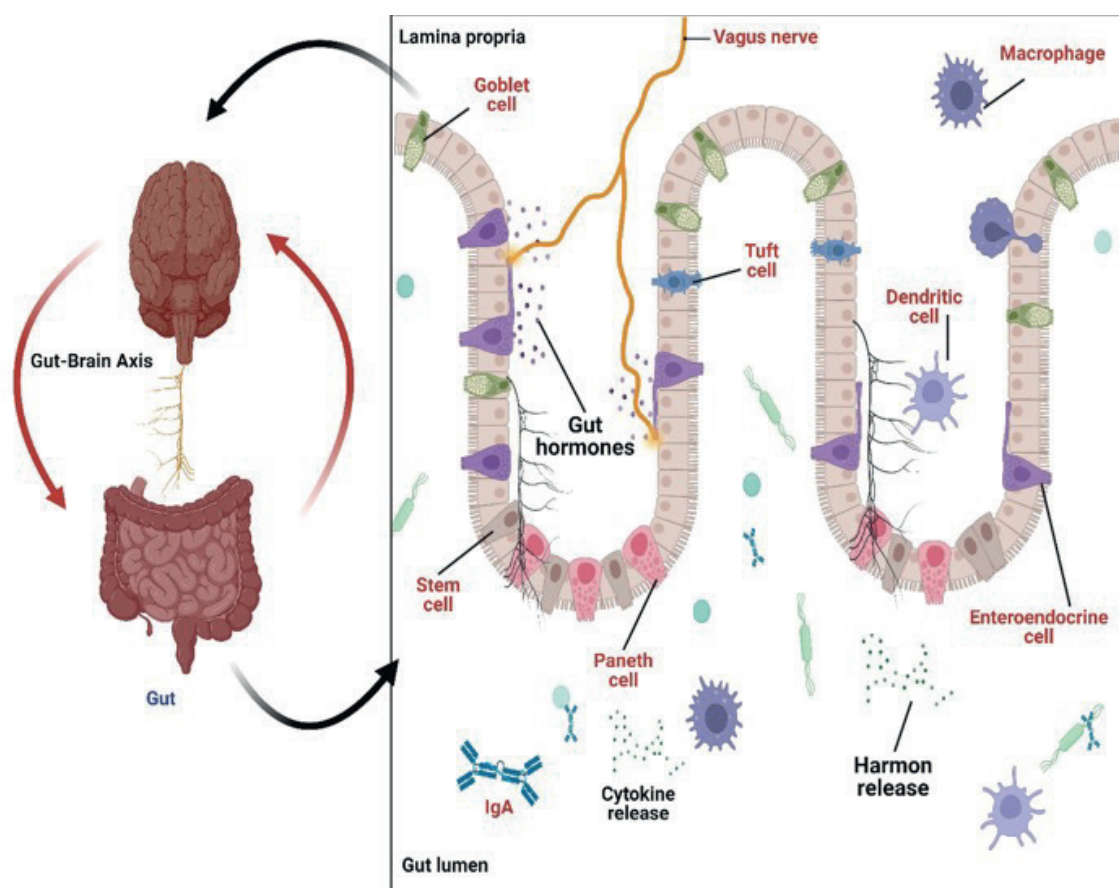


Figure 1. The Gut-Brain Axis: Unveiling the Bidirectional Communication Pathways Between the Gut and Brain

2. Anatomy and Physiology of the Gut-Brain Axis

The Gut-Brain axis can be explained as a very long bidirectional neuroscience line connecting CNS and ENS placed in the digestive system tract. These are the neural, hormonal, and immunological connections whereby all these are involved in bidirectional communication to ensure that at any one time, there is unrestricted flow of information between the gut and the brain (Kazempour, 2022).

2.1 Structure of the Gut-Brain Axis

Gut (Gastrointestinal Tract): Alimentary canal or gastrointestinal tract a long muscular tube from the mouth to the anus itself is the primary organ for the digestion and absorption of foods as well as the excretion of waste products (Maynard & Downes, 2019). But is not just an organ with the tasks of digestion in the limited sense of the term. Coated within the walls of the gastrointestinal tract is the enteric mammalian forebrain like, composed of neurons, neurotransmitters, and glial cells, known as the enteric nervous system (ENS). Also known as the intestinal brain, ENS has evolved and possesses most of the architectural features that can function independently of the CNS. Among these include motor function, secretion, blood flow, and immune responses of the mucosa in the gastrointestinal tract (You et al., 2021).

Brain: Some stimuli from body organs, such as the gut go to the head or the headquarters of the body organ system, which is the brain (Swanson, 2012). It is transported through various networks to the brain, and it is relayed through the vagus nerve, which, in effect, establishes most of the cross-talk between the gut and the brain. Such signs can influence the mood control regions within the brain: the hypothalamus, amygdala, and the prefrontal cortex (Bao & Swaab, 2019).

Communication Pathways

1. Neural Pathways: The vagus nerve, which is the tenth cranial nerve, is the longest in the human body and has bidirectional communication between the gut and the brain (Rangon & Niezgoda, 2022). Sensing in the gut concerns the functional state of the gut, its nutrient status, as well as the reported levels of microbial metabolites, all of which are conveyed to the brain via efferent fibers within the vagal nerve. Efferent fibers transmit information to the latter parts of the body and figure in the motility and secretion of the gut as well as its immune response (Bernardazzi et al., 2016).

2. Hormonal Pathways: These include peptide YY, coicotensin releasing factor and cholecystokinin, and glucagon-like peptide-1 that aids in controlling appetite, satiety, and glucose levels. These gut hormones also act directly on the brain regions the centers for mood regulation, the reward pathways of the brain, and the stress pathway. Conversely, hormones produced by the brain will affect the movements, health, and immune system response of the gut through cortisol, as observed (Makris et al., 2021).

3. Immune Pathways: Based on the congruent distribution of immune cells with the microbes, a definite gut arrangement is made as a premier immunological organ. Available findings prove that microbiota is involved in the formation and maintenance of immunity (Maranduba et al., 2015). However, it should be pointed out that any deviation in the balance of the gut microbial population provokes an immune response, which affects the state of both the gut and the brain. Molecules produced by immune cells are cytokines that are chondroitin and can cross the blood-brain barrier, influencing the brain, which is related to mood disorders and neuroinflammation (Liberman et al., 2019). Therefore, more must be understood about the variety of this relationship to explicate the link between gut microbiota and the mind's condition. Once this relationship is understood, it leads to the implication of treatment methods that will enhance the functioning of this particular axis, improving the methods of treating mental illnesses.

2.2 Key Components and Their Functions

Enteric Nervous System (ENS): The ENS, also referred to as the second brain, is a widespread connection of nerve cells, glial cells located in the submucosa and muscular layers of the gut ranging from the esophagus to rectum (El Munshid, 2000). This Little Brain, a roughly 500 million neuron formation, is quite similar to the neurons located in the spinal cord and is entirely separate from CNS (Sem). The ENS is responsible for a wide array of crucial functions that ensure the smooth operation of the gastrointestinal system: The ENS is in charge of numerous significant functions of the proper functioning of the gastrointestinal tract:

1. Motility: The ENS synchronizes the attenuation and contraction of the muscular layers of the gastrointestinal tract to push food along the tract (peristalsis) and mix it with the digestive juices (segmentation). This rhythmic movement is essential in digestion and the absorption of substances in the GI tracts (Tobias & Sadiq, 2019).

2. Secretion: It regulates the secretion of powerful acids, enzymes, mucus, and other substances that aid in the digestion of foods and the protection of the GI tracts. Other functions include secreting gastric acid, with the aid of parietal cells in the stomach for protein digestion or secreting bicarbonate ions from ducts in the small intestine to neutralize the acids from the stomach (HERE'S).

3. Blood Flow: It assisted in the control of blood flow to the gut, thus participating in oxygen and nutrient delivery to the tissue as well as the elimination process of waste products by using the ENS (Muto, 1988). This regulation is necessary for the health's sake of the gastrointestinal system and the metabolic anticipation of digestion.

4. Immune Response: The ENS interacts with different cells and substances of the intestinal immune system, which consists of definite cells and substances that are involved in the immune response against pathogens and the regulation of the function of the intestine (Giuffrè et al., 2020). It can thus modulate firsthand the synthesis of pro-inflammatory cytokines, the infiltration of immune cells, and the barrier function of the mucosa of the intestinal tract (Yin et al., 2018).

Vagus Nerve: In this subhead, one can develop what is referred to as the 10th cranial nerve, commonly known as the vagus nerve, which connects the gut to the brain in two ways based on its function. It has also been described as the two-way communicative nerve because it sends or transmits signals to or from the body; hence, it has an afferent nerve, which is the sensory function, and an efferent nerve, which is the motor function (Banerjee et al., 2023).

1. Afferent Fibers: These fibers notify the brain about the gut condition and get feedback that it is stretched or has changed its portfolio of chemicals or microbial products (Lipski, 2020). This implies that the head has to control many activities that are considered innate in any human being, for example, hunger and fullness, feelings, and stress.

2. Efferent Fibers: information between the brain and the gut regarding movement, secretion, and immunity (Dinan & Cryan, 2017). The vagus nerve is important in triggering the work of the parasympathetic system referred to as the ‘rest and digest’.

Neurotransmitters and Hormones: This molecular communication path from the gut to the brain utilizes many chemicals inherent in the body, including neurotransmitters and hormones (Fatima-Shad, 2024).

1. Neurotransmitters: It generates a vast number of neurotransmitters (Table 1) which are serotonin, dopamine, GABA, non-epinephrine, and acetylcholine involved with mood, emotion, cognition, and the regulation of the stomach (Kuma, 2019).

Table 1: Neurotransmitters and Hormones Involved in Gut-Brain Communication

Neurotransmitter and Hormone	Source (Gut/Brain)	Effects on Gut	Effects on Brain	References
Serotonin	Gut (95%)	Motility, secretion	Mood regulation, sleep, appetite	(Fatima-Shad, 2024)
Dopamine	Gut/Brain	Motility	Reward, motivation, motor control	(García-Cabreri- zo et al., 2021)
GABA (Gamma-aminobutyric acid)	Gut/Brain	Inhibits nerve activity	Reduces anxiety, promotes relaxation	(Mazzoli & Pessione, 2016)
Norepinephrine	Brain	Inhibits gut function	Arousal, stress response, vigilance	(Bonaz et al., 2012)
Cortisol	Brain	Alters gut permeability	Stress response, metabolism, immune function	(Brzozowski et al., 2016)
Ghrelin	Gut	Stimulates appetite	Reward, motivation, learning	(García-Cabreri- zo et al., 2021)
Leptin	Gut	Suppresses appetite	Energy balance, metabolism	(Bauer et al., 2016)
Peptide YY	Gut	Inhibits appetite	Satiety	(Pizarroso et al., 2021)

2. Hormones: This organ secretes several hormones that are involved in appetite, satiety, energy status, and glucose regulation, and they are ghrelin, leptin, peptide YY, and cholecystokinin (Geary, 2004). It can also signal the brain to affect the mood, the brain reward system, and the stress system. Instead, stress hormones produced in the brain, for example, cortisol, influence the function and permeability of the gastrointestinal tract as well as the immune system alternative relationship between the gastrointestinal tract and the brain known as the gut-brain axis.

2.3 Interaction Between Gut Microbiota and the Brain

Fears of microbes exist in the global population's human gastrointestinal tracts, and the one that is particularly relevant to the Gut-brain axis is called the Gut microbiome.

Microbial Composition and Diversity: Previous studies have shown that many of the factors inside an individual's microbiome concerns include diet, genetics, and other features of the environment. Probiotics thus acknowledge the value of the different types of favorable gut bacteria as crucially viable to the gut as well as the overall well-being of an individual (Binns, 2013). However, glycome shift or other forms of dysbiosis in the friendly bacteria are out-competed or suppressed, and the pathogenic bacteria that overgrow frank impact the operations of the gut-brain axis and other health issues, including mental health (Mills et al., 2019).

Mechanisms of Communication

1. Metabolites: They also produce metabolites, which are short-chain fatty acids, tryptophan metabolites, and the neurotransmitters GABA and serotonin. These metabolites can enter circulation and penetrate the blood/brain barrier, and this allows them to have a direct effect on the brain and the animal's behavior (Banks, 2019).

2. Immune System: They state that these microorganisms in the gut affect the immune system and, by extension, the brain functions (Sherman et al., 2015). The smaller intestine bacteria can synthesize cytokines that are inflammatory burdens that affect mood and the brain apart from neuroinflammation.

3. Vagus Nerve: It also has the function of the line by which the body of the organism and the brain information, as well as the signal from the gut microbiota, are transmitted (Hooks et al., 2019) mention that the unpredictable aspect of the communications between digestive microbiota and the brain is perceived through vagal afferent neurons, which control moods, emotions, and cognition.

3. Microbiome and Mental Health

3.1 Microbial profile and Mental health

Anxiety: As for anxious patients, especially those with high cortisol levels, it is possible to use probiotics, but they are not a universal remedy and can have several side effects recalling the connection between the current literature and the gut microbiome and anxiety one can hardly explain that these two are the only means that are linked but have an extremely extensive interaction. Some studies about the correlation between anxiety disorders and the bacterial population in the gut indicate that the patients are comparatively much more deprived of diversity and display certain distinct shifts in the features (Mitrea et al., 2022). Numerous experiments with rats have shown that GM can be changed with probiotics or FMT by decreasing the anxious phenotypes (Vasiliu, 2023b).

Depression: It also mentioned that gut microbiota is before the severity of depression and its parts and drivers. It has been postulated several times that there is a difference in the gastrointestinal microbiota between depressed and normal persons, and it has been noted that slightly there is a correlation between bacterial species and depression. As stated in some articles, constipation is said to be industrialized, and the administration of probiotics or FMT may enhance depressive-like

phenotypes in animals (Gao et al., 2023).

Autism Spectrum Disorders (ASD): For the mentioned disturbances in the composition of the resident microorganisms of the gut the development of ASD is presumed. Some of the researchers stated that there was a change in the proportions of the gastrointestinal microbiome profile in ASD children compared to children without the disorder. In the same regard, defining that SCFA can induce the alteration of microbiota by diet and probiotics can help some behavioral symptoms of ASD (Mintál et al., 2022).

Other Neuropsychiatric Conditions: However, the effects of gut microbiome reach other systems that are involved in disorders to the nervous system as well. It has also been established that Schizophrenia and Bipolar disorder patients also present changed gut microbiota patterns of the same type as was identified in the depression group, obsessive-compulsive disorder, and post-traumatic stress disorder (Offor et al., 2021). There is no information regarding how these activities are affected by the gut microbiome. Still, it is posited that it has the potential to modulate neuroinflammation, generate neurotransmitters, and give feedback to stress, which are relevant in these states.

3.2 Investigations and Research Conducted

Animal Studies: Mice have, therefore, been useful in addressing issues to do with the interaction of the gut microbiota and psychological functions as systems. Animal studies in rats reveal that if mice devoid of bacteria are elevated in a germ-free environment, they have behavioral alterations, such as higher levels of anxiety and inability to survive with stressors properly than the normal gut bacteria. However, this type of manipulation may not always be possible. However, anxiety-like signs could be transmitted by having stressed and anxious mice's gut microbiota transferred to germ-free mice (Yixin, 2019).

Human Clinical Trials: As mentioned, most of the earlier research on the gut-brain axis has been carried out in animals. However, several latest clinical trials in humans exist. These have focused on the effects of probiotics, prebiotics, and diet on the mental health of different populations (Sivamaruthi et al., 2019). For example, a meta-RCT systematic examination was conducted about control trials of probiotics, and it was found that probiotics could have a small effect on reducing depressive symptoms. However, there is still some necessity to define specific randomized strains of probiotics and their doses and the administration period in certain types of mental disorders.

Correlation vs. Causation: According to numerous studies, there is an association between the changes in the strains of the excavated bacterial population and various forms of mental illnesses; however, one should not confuse correlation and causation (Khan, 2015). The reader needs to be told that many of the things explored at the moment are comparative, which means that the studied things can only show some associations but not history. Therefore, considering the interest and the outcomes presented in the present research signifying the role of the gut microbiome in mental health, additional studies are called to identify how much the changes in gut microbiota help to develop a mental disease. In RCTs, individuals are randomly assigned to microbiome-targeted interventions such as probiotics, prebiotics, or diet modifications regarding the composition of mental health outcomes, and these are done over time (Peckmezian et al., 2022). Attempts for such an approach persist, and the results will reveal lots of information on the prospective prospects of tuning the gut microbiota to boost mental health.

3.3 Mechanisms of Action

There are now indications of its implication in mental health through mediating the following mechanisms in the brain and behavior (Figure 2). Information concerning these processes is crucial

in devising the right interventions that could, in one way or another, have a positive impact on the population's mental health.

Inflammation and Immune Response: Gut microbiota impacts the immune system since it is the police of the bacterial movement in the gut. Gut dysbiosis results in the alteration of the microbiota population in the gut and results in locally as well as systematically sustained low-grade inflammation (Vetrani et al., 2022). This inflammation can begin to activate the immune cells and set off a cascade of activation of the production of pro-inflammatory cytokines that can even penetrate the blood-brain sort of thing and, therefore, disrupt normal brain functions. Neuroinflammation is believed to be one of the pathophysiologic mechanisms of multiple mental disorders, including depressive and anxious disorders and schizophrenia (P. G. Almeida et al., 2020).

Neurotransmitter Production: The gut bacteria have been observed to directly produce or else regulate the production of many neuroactive substances, including neurotransmitters that are associated with brain operations and mood alteration (Gupta et al., 2024). For example, some of these gut bacteria produce gamma-aminobutyric acid or GABA, which is the major anti-anxiety neurotransmitter in the brain. Other bacteria influence the synthesis of serotonin, which is a neurotransmitter associated with mood, appetite, and sleep patterns (LaGreca et al., 2021). Hence, any variations to the composition of microbiota should have implications on the synthesis and operation of these neurotransmitters and, therefore, impact mental disease.

Stress Response and HPA Axis: The concept is that the gut microbiome controls the stress regulation system of the body, the HPA axis. Stress impacts the content of gut microbiota, and as such, the changes in homeostasis affecting the microbiota impact the HPA axis stress response (Zhang et al., 2023). This dysregulation can lead to the development of certain mental illnesses, such as depression and other anxiety-related disorders, given that stress is usually related to them. New studies present the above connection between the gut microbiota and mental health as rather intricate. Scientists proved that some alterations in the makeup of people's gut bacteria influence certain diseases, including anxiety, depression, and autism spectrum disorders (C. Almeida et al., 2020). Hence, results obtained from different animal investigations and human clinical trials confirm this relationship; however, most of them are correlational. Among the processes that are fostered in this relationship are immune alteration of the immune system, secretion of neurotransmitters, and stress-responsive system. More efforts are needed to translate the findings on the connection between gut microbiota and mental health into practice and identify which areas require intervention (Swann et al., 2020).

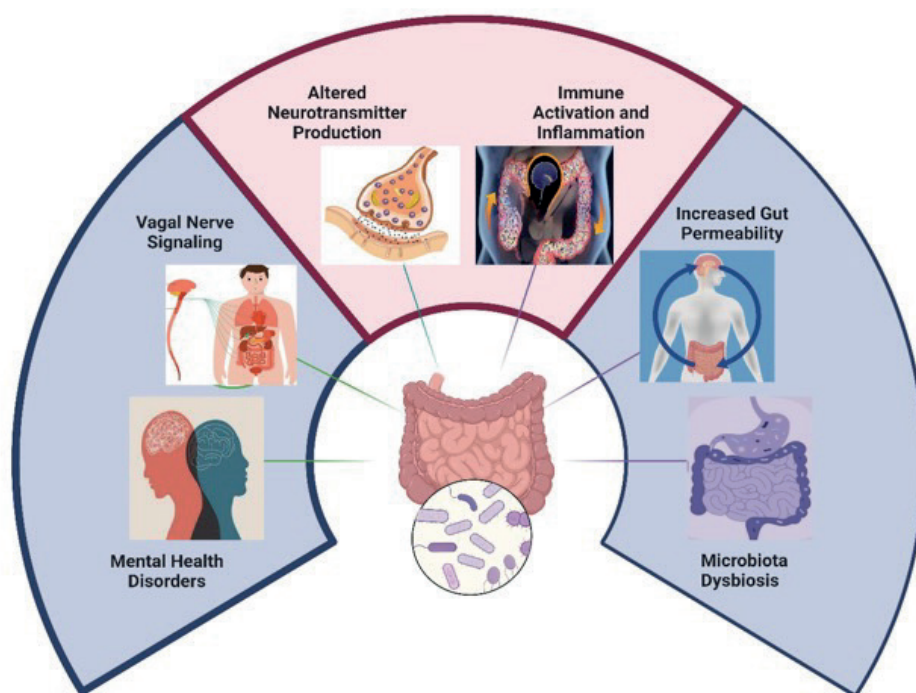


Figure 2. Hypothesized Mechanisms of Gut Microbiota Influence on Mental Health

4. Mechanisms of Microbiome-Gut-Brain Interaction

Collectively referred to as the second brain, the gut microbiome has been established in the current literature as an influential player in regulating the brain and behavior with a focus on the gut-brain axis. This interactive communication system involves a two-way linkage between the aforementioned gut microbes and CNS (Figure 3). It is thanks to such knowledge of the nature of this interaction that one can explain the role of the specific part of the gut microbiome regarding the state of mind and develop new therapeutic approaches.

Neurotransmitter Production: It also notes that the gut microbiome is involved in synthesizing and regulating some of the brain and mood-related neurotransmitters. It is further illustrated that gut bacteria can create neurotransmitters on their own: for instance, gamma-aminobutyric acid (GABA), which is regarded as being one of the major inhibitory transmitters within the brain and relates to depression of neuronal excitation, and lethargy. It has been established that some kinds of *Lactobacillus* and *Bifidobacterium* can produce GABA and, hence, manage anxiety action in animal models (Lalonde & Strazielle, 2022). Also, gut microbes are involved in influencing serotonin since it is synthesized in the gut, and is among the mood, appetite, and sleep regulators known as neurotransmitters. Also, tryptophan, a precursor of serotonin, and the metabolites that the gut bacteria produce directly affect serotonin receptors in the brain and can also be regulated by the gut bacteria (Legan et al., 2022). The composition and performance of the gut microbiome can thus be used to influence the content of neurotransmitters, which may lead to poor mental health.

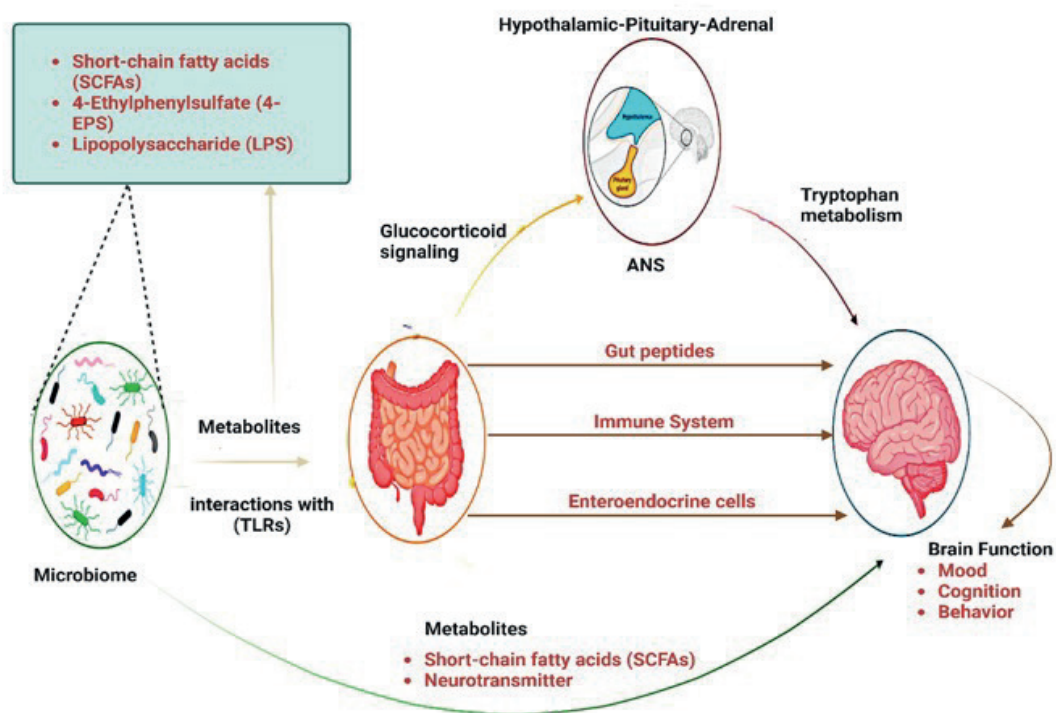


Figure 3. Mechanisms of Microbiome-Gut-Brain Interaction

Short-Chain Fatty Acids (SCFAs) and Inflammation: Butyrate, propionate, and Acetate are referred to as the short-chain fatty acids acting as end products of dietary fibers by gut bacteria (Vinelli et al., 2022). Consequently, SCFAs have more than one role in the gut, including regulation of the integrity of the intestinal barrier, innate immunity, and as an energy substrate for colonocytes. However, besides the regional modulatory effects seen here in the gut region, SCFAs can affect the brain according to the following points. It can cross the blood-brain barrier without restriction and intervene directly with the receptors on neurons and glial cells, hence interfering with neuronal functionality and synaptic plasticity (Zhao et al., 2021). SCFAs have also been described to regulate inflammation as they inhibit the onset of pro-inflammatory signals and enhance the production of anti-inflammatory compounds. Specifically, such an effect can be exerted in the brain, which suggests that it may influence the processes of neuroinflammation and neuroplasticity that occur in connection with various mental disorders (Halaris, 2018).

Immune System Modulation: The construction and familiarization with the immune system rely to a major extent on the gut microbiome (Kuehnast et al., 2022). Many bacteria in the commensal microbiota interact with the immune cells located in the GALT and modulate immune tolerance and the balance of pro-inflammatory and anti-inflammatory reactions. Because dysbiosis pertains to the change in the balance of gut microbiota, any immune response that occurs because of this condition can raise low-grade inflammation locally in the gut and systemically throughout the body (Mundula et al., 2022). It can lead to neuro-inflammation, where there is activation of first responders in the brain, and there is an established connection between inflammation and other psychological afflictions such as depression, anxiety, and schizophrenia, to mention but a few. Furthermore, it is well documented that gut microbes are associated with cytokines, and cytokines are signal proteins that are very imperative in immunity and play a role in regulating the brain and behavior (Caputi et al., 2021).

Endocrine Signaling: The gut microbial communities involve an interaction with the endocrine system, which consists of glands that release hormones to regulate the various operations in the body (Forsythe, 2013). It has been found that the microbiome can change the production rates and release of various hormones, among which is cortisol, which is the main stress hormone. Thus, it has been proposed that stress will manifest an effect on microbiota and that dysbiosis in reciprocation will act on the hypothalamic pituitary adrenal (HPA) axis (Sharma et al., 2022), which is the body's stress response system, leading to hyper-hyperstress, which makes the affected person prone to mental stress to ill-health. Lactobacillus and Bifidobacterium, for instance, have been discovered to reduce cortisol stress hormone and restrain stress-induced behaviors in animal studies in addition to apparently both sexes (Wang, 2018). This is a sign that there is a potential that changing the balance of bacteria in the gut could help in eradicating or at least controlling stress and all the schemes that are bound to affect the mental health of an individual.

5. Factors Influencing the Gut Microbiome

Therefore, the actual combination of microorganisms of gut microbiota regarding bacteria, archaea, fungi, and viruses is thought to be in a constant dynamic state and open that develops under the impact of numerous factors. These attributes include diet, drugs, exercise schedule, and other features of the topic's environment. Some of the factors of interest include. Hence, it is crucial to understand how these factors work in gut microbiome applications in the construct of developing personalized approaches that may improve gut and, by association, mental health.

Table 2: Impact of Dietary Patterns on Gut Microbiome Composition

Dietary Pattern	Effect on Gut Microbiome	References
High-Fiber	Increased diversity, beneficial bacteria (Bifidobacterium, Lactobacillus), SCFAs	(Piccioni et al., 2023)
High-Fat/Sugar	Decreased diversity, harmful bacteria (Bilophila Wadsworth), SCFAs	(Berding & Donovan, 2020)
Plant-Based	Increased beneficial bacteria, decreased harmful bacteria	(Sheflin et al., 2017)
Mediterranean Diet	Diverse, balanced microbiome	(Merra et al., 2020)
Western Diet	Reduced diversity, harmful bacteria	(Zhang et al., 2020)

5.1 Diet and Nutrition

An individual's diet is a key factor of gut microbiota its composition as well as function. For instance, the type of foods that we take contains nutrients (Table 2) entering into our body microenvironments and trillions of microbial passengers in our intestines. These feeding habits are presumed to define the level of complexity in the bacterial strains regarding the batch size with the metabolic parameters and hosts (San Roman & Wagner, 2018).

Probiotics and Prebiotics:

1. Probiotics: They are microorganisms capable of producing a specific function in the body of the host. Each time the consumer takes a particular quality of the microorganisms, the host benefits by experiencing a boost in health. Probiotics can be incorporated in the solid or liquid part of foods that are likely to have passed through some fermentation stage, which includes Yogurt, Kefir, Sauerkraut, and kimchi, and can be taken as nutritional supplements. Certain types of probiotics from the Lactobacillus and Bifidobacterium genera for bettering mental health owing to the management of the gut-brain axis (Sabit et al., 2023). Some of these probiotics also influence the synthesis of neurotransmitters, immunity, and actions against inflammation, leading to psychological health.

2. Prebiotics: Prebiotics can, therefore, be described as food products whose constituents cannot be assimilated, and this brings out the activity and growth of friendly bacteria in the large

intestines (Włodarczyk & Śliżewska, 2021). These fibers nourish the good bacteria as the bad ones do and also give them a better environment to triumph over the latter. Many prebiotic sources are present in foods such as onion, garlic, bananas, salads, asparagus, and wholesome grains. Prebiotics operate by the principle of, and this is the idea that only the positive bacteria are required to restore the balance of the gut microbiome, thus the state of the gut, as well as the moods since they are partners in the stomach (Appanna & Appanna, 2018).

3. Dietary Patterns and Their Impact: It can be distinguished that the researchers did not observe the influence of specific dietary components on the overall microbial population balance but noted the dependency of the location of certain microbes in the gut on the total diet. Plant food, which is rich in fiber and phytochemicals, constitutes a major part of the diet and has a role to play in populating the human gut with healthy bacteria (Sudheer et al., 2022). This is so because fiber varies, and complex carbohydrates get fermented in the presence of specific bacteria, thus producing SCFAs and other useful metabolites that promote the healthy state of the gut and brain. However, a poor diet characterized by taking processed foods high in sugar and unhealthy fats will differentiate the current effect on the microbiome. Thus where microbial diversity is bound to shrink, the gram-negative bacteria have a higher propensity to be inflammatory (Escobar-Salom et al., 2022).

5.2 Antibiotics and Medications

The human gut is known to be a host or a dwelling place for trillions of microorganisms, which are usually referred to as the human microbiota, which plays crucial roles in human health, disregarding the mental health aspect. However, such a balance can change with the assistance of several factors, with the aid of antibiotics and some medications.

Effects of Antibiotics on Gut Flora: Role of Antibiotics on the Experiments on Gut Flora

According to this reasoning, while bacterial infections can be cleared up by antibiotics, the price one pays for this victory is that antibiotics are hostile to the symbiotic flora of the human gastrointestinal tract. However, distinguishing between the pathogenic and the symbiotic bacteria is almost impossible most of the time (Martinson et al., 2020). As a result, antibiotic use can have profound and lasting consequences for the gut microbiome; consequently, the process of antibiotic treatment influences the composition of the gut microbiota, and that effect is quite long-term.

1. Reduced Diversity: Each antibiotic decreases the number of members in the communities living in people's guts, starting with pathogenic germs, which were expected, and continuing with so valuable participants in the digestion process and immune response (Schmidt, 2009). This loss of diversity may offset some of the protective mechanisms of stress and proliferation of vulnerability that keeps the host susceptible to being infected by other diseases.

2. Altered Composition: The primary concern here is that administering antibiotics alters the balance of GM; some types of bacteria decrease in number while others increase (Jiménez-Avalos et al., 2021). This may lead to disruption of the healthy bacterial community, Dysbiosis, which may present or worsen many pathogens' health states, which are inflammatory bowel diseases, obesity, and metabolic disorders.

3. Increased Pathogen Colonization: An example of pathogens that exploit such a break in the maturity of the community include *Clostridium difficile*, which colonizes the gut and causes infections due to disruption by antibiotics (Rosa et al., 2018). *Clostridium difficile* infection (CDI) which ranges from mild diarrhea to severe colitis, is a major observed con in patients who were hospitalized and had a history of using broad-spectrum antibiotics.

4. Long-Term Consequences: In similar regards, there is evidence of how antibiotics affect the population of the microbiota in the human gut as having a persistent even after they have ceased to be administered (Kokou et al., 2020). Abnormal changes in the composition of bacterial microflora in the intestine persist for months or even for several years after taking antibiotics and their consequences, including obesity, autoimmune diseases, allergies, and neurodevelopmental disorders.

Role of Psychobiotics

Because antibiotics trigger negative effects on the composition of gut microbiota, much attention is paid to the application of psychobiotics to reduce the negative influence on the mental condition. Probiotics are defined as the live microbial nutrients that cause a positive effect on the host's condition while psychobiotics appear to have a positive influence on the mental health of the host in the considered gut-brain axis (Ağagündüz et al., 2023). Certain *Lactobacillus* and *Bifidobacterium* species may have the potential to be classified as psychobiotics and positive effects on anxiety and depression were recorded in clinical studies (Ross, 2023). These beneficial bacteria can modulate the gut-brain axis through various mechanisms, including Such beneficial bacterial can influence the gut-brain axis in several ways;

1. Neurotransmitter Production: Psychobiotics may influence the synthesis processes and added activity of other neurotransmitters like GABA and serotonin, agents that have a big role in dictating a person's feelings (Lachmansingh et al., 2023).

2. Immune Modulation: They may enhance tight junctions and decrease the inflammation as well as immune responses that, in general, contribute to the modulation of brain and mental health (Holzer et al., 2017).

3. Stress Response: As for the improvement of the physiological aspect, regarding the psychobiotics' influence on stress as manifested by cortisol decrease and regulation of the HPA axis, the focus flexibility levels are increased, and anxiety levels are moderated (Hernandez Barrueta, 2022). Thus, it can be concluded that the strategies of using psychobiotics in addition to antibiotics or as a single treatment for patients with mental disorders can be viewed as one of the promising fields for further research. However, these studies need to define the combinations of strains, dosages, and time courses of psychobiotic interventions that can be of therapeutic value to the conditions and patients related to these mental health disorders (Vasiliu, 2023a).

5.3 Lifestyle Factors

Diet is the acknowledged and the most influential factor affecting gut microbiota and its functionality; however, some aspects of a person's lifestyle can also noticeably influence gut microbiota. These include:

Stress: In this case, stress has an impact on the nervous system and hormonal changes, leading to changes in the movement of the gut, secretion, and permeability of the lining thus exposing the gut to inflammations and infections (Oroian et al., 2021). Also, stress can activate the HPA axis and further hormones such as cortisol, which can also remove the gut microbiotas and intensify mental illnesses.

Physical Activity: Motor activity influences the number and density of the beneficial bacteria in the gut; it has been shown that relaxation time physical activity has a positive impact on the density of microbes and the health of the gut (Resende et al., 2021). The movement enhances the motion of the intestines hence improving the composition of the gut microbiome through lessening inflammation while also enhancing the barrier strength. Moreover, exercise assists in the inhibition of stress levels and a myriad of other things that influence the mood thereby creating the bridging of the gut and the brain link.

Sleep Patterns: As illustrated in the literature, sleep plays a crucial role in the health of not only any particular organ but the general health of one's body including the gut. Sleep also has an impact on the gut microbiota and its subsequent functionality; this is because either reduced or disrupted sleep leads to the same outcomes (Han et al., 2022). Individuals who do not sleep can have several health complications due to a changed intestinal barrier, boosted inflammation, and altered balance of the microbiota, which interferes with metabolism and mental well-being.

6. Therapeutic Applications and Directions for Research

A relatively new field of science concerns the relationship between the gut and the brain, where several therapeutic approaches regarding the suppression of mental illnesses have been discovered. Refers to the possible interventions that may be helpful now and those that are currently being tested, proposed to change the focus of mental health disorders.

6.1 Possible Treatments and Action Plan

1. Probiotics and Prebiotics

Probiotics: These live microorganisms, when ingested in adequate quantity, will have positive effects on the host's health (Marco et al., 2020). Some of these probiotics, especially of the *Lactobacillus* and *Bifidobacterium* species, have been useful in reducing signs of anxiety, depression, and stress in experimentations. These mechanisms include the influence on the synthesis of neurotransmitters, the strengthening of the gut barrier, and the control of immune response and inflammation (Sharkey & Savidge, 2014).

Prebiotics: Prebiotics are defined as non-hydrolyzable food ingredients that stimulate the growth and activity of beneficial gut bacteria (Garcia-Alonso et al., 2023). It works as a prebiotic that spurs the fermentation by the gut bacteria, resulting in the formation of SCFAs and other beneficial physiologic metabolites for the gut and brain. Inulin, fructooligosaccharides (FOS), and galactooligosaccharides (GOS) are among the most familiar prebiotics inherent in foods such as onions, garlic, bananas, asparagus, and whole grains. The findings from earlier studies practiced in prebiotics revealed that it positively influences mood, stress levels, and cognitive performance (Karbownik et al., 2022).

2. Dietary Interventions

It is essential to distinguish eating habits that have a critical impact on the gut's microbial composition and, therefore, mental health. Various plant matters, for instance, fruits, vegetables, whole grains, legumes, nuts, and seeds, have been linked to better gut flora and a lesser prevalence of mental illnesses (Shanmugam et al., 2022). These foods produce elaborate baskets of fibers and slowly digestible carbohydrates that are prebiotically metabolized by beneficial gut bacteria. This results in the nourishing production of SCFAS and other beneficial metabolites that promote gut and brain health. On the other hand, the customary diet comprising processed foods, sugars, and unfavorable fats in the Western world deteriorates the gut microbiota. It leads to dysbiosis, which is connected to elevated susceptibility to mental disorders (Choi et al., 2020). Like the Mediterranean diet, a balanced and colorful diet that can favorably affect the composition of gut microbiota has been reported to enhance mood and decrease depressive symptoms.

3. Fecal Microbiota Transplantation (FMT)

FMT directly transfers fecal material from a donor into the patient's gastrointestinal tract. For these reasons, people with dysbiosis or those with a particular disease state can have the typical flora recovered in the gut (Bhutiani et al., 2018). FMT has been quite successful in treating multiple relapses of *C. difficile* infection, and modern research indicates that it may also be useful in managing other diseases, such as inflammatory bowel disease, irritable bowel syndrome, and certain mental disorders. FMT for mental health is a relatively new area under research, and thus,

several studies have documented the amelioration of symptoms of depression, anxiety, and autism spectrum disorder (ASD) (Goo et al., 2020). However, prospective trials must be done to define the level of its sustainable effectiveness for treating mental disorders and the best practices of FMT's application.

6.2 Targeted Strategies in Diseases Related to the Gut-Brain Axis

Precise medicine solutions are applied to GBA, targeting strategies for a person's microbiome and specific disease features. This therapeutic strategy is intended to maximize the potential therapeutic benefit and the least amount of harm from the medications due to the complex interactions between the gut microbiome and the brain, as well as take into consideration the patient's characteristics.

Microbiome Profiling

Metagenomics, the most commonly used holistic approach in personalized therapies in this setting, is the detailed analysis of a human body's microbiome. This can be done using, for instance, 16S rRNA sequencing, metagenomic sequencing, and metabolomic profiling (Han et al., 2020). The above techniques give a clear and detailed depiction of the subsets of microbiota, the items within the subsets, and the functionalities needed to understand dysbiosis that may lead to symptoms of mental disorders.

1. 16S rRNA Sequencing: This technique focuses especially on the 16S rRNA gene sequence of bacteria and allows the identification and determination of the number of bacteria in that sample. It offers information on the bacterial occurrence of gut flora and enables the comparison of the stomach content of the normal and those of the mentally ill (Hooks et al., 2019).

2. Metagenomic Sequencing: This approach is slightly different from the previous one as it includes DNA sequencing of the entire microbial content that was applied to a microbial sample. This provides a clearer picture of the gut microbiome in addition to bacteria, viruses, fungi, and other microorganisms (Pérez, 2021). Some of the basic and advanced properties of the human gut microbiome are as follows: Metagenomic sequencing can help stratify the gut microbiome's metabolic pathways, virulence factors, and antibiotic resistance in the human body.

3. Metabolomic Profiling: This technique estimates the concentrations of metabolites derived from gut bacterial activity and illuminates how the host influences them (Silpe & Balskus, 2020). Using metabolomic analysis, it is possible to define the biomarkers that connect with particular mental disorders and, thus, adjust therapy and treatment.

Customized Treatment Plans

It is possible to design treatment regimens given the microbiome's profile and other characteristics of an individual, clinical symptoms, and other factors influencing the dysbiosis of gut microbiota and mental health. These treatment plans may involve a combination of These treatment plans may involve a combination of:

1. Probiotics and Prebiotics: It is possible to have some specific effects of certain probiotic strains, including *Lactobacillus* and *Bifidobacterium* species, on mental health as supported by clinical studies (Dey & Mookherjee, 2021). These probiotics can thus be used to repopulate the gut with helpful bacteria strains or at least attempt to control the communication between the gut and the brain. Probiotics that feed health-promoting bacteria are also recommended and can be prescribed to the patient to supply additional prebiotics, which will help promote the ideal growth and action of such bacteria (Ranjha et al., 2021).

2. Dietary Interventions: Dietary diets also play a role in determining the complex gut microbiota. Sweeping the concept of microbiome-specific interventions relating to diet can involve a set of specific recommendations for developing beneficial bacteria in the gut and reducing

inflammation levels (Juritsch, 2023). These measures may comprise elevating the consumption of fiber-containing foods, foods that undergo fermentation, and nutrients that are believed to enhance the health of the intestinal lining.

3. Fecal Microbiota Transplantation (FMT): The use of FMT is considered for patients with severe dysbiosis or severe mental illness that has not responded to other forms of treatment. The procedure entails the process where the fecal matter of a healthy individual is placed in the recipient's gut to enhance a healthy bacterial flora (Ademe, 2020). FMT for mental health is a relatively new research area however, it has been observed that some studies carried out in this background show positive trends in the treatment of depression, anxiety, and autism spectrum disorder.

6.3 Future Research Directions

The gut-brain axis and its connection to mental health are unexplored and progressively developing research areas. Therefore, future research directions can provide an even deeper understanding of this reciprocal interaction and offer new avenues of therapy and treatment of mental health disorders.

Emerging Technologies and Methodologies

1. Multi-omics Approaches: The use of genomics, transcriptomics, proteomics, and metabolomics will enhance our understanding of gut microbiota, host, and gene-environment interactions in contributing to mental health (Hayes et al., 2020). This particular approach will help define new biomarkers, therapeutic targets, and personalized treatments for patients.

2. Advanced Bioinformatics and Machine Learning: The internship work in this case will involve various analyses using multi-omics data. Thus, bioinformatics tools and intricate machine learning algorithms in analysis will be central to this project. These tools will allow investigators and clinicians to understand regularly the correlations and cause-and-effect relationships between the microbiome and the subject's health, particularly their mental health (Lange et al., 2020).

3. Organoid Models and Humanized Mice: Organoid models are three-dimensional primary cell cultures that establish the structure and functioning of an organ, and humanized mice, which are mice engrafted with human gut microbiota, bring out the gut-brain axis in more physiological settings (Boylin et al., 2024). Such models can enable the comprehension of how gut bacteria influence the host and evaluate the efficiency of the reported treatments.

Long-Term Studies and Clinical Trials

1. Longitudinal Studies: However, to obtain a more profound understanding of how the gut microbiome would affect the mental health parameter's occurrences, elaborate on the needed cohort studies that would look at the state of the above parameter at different time points. Such studies can indicate time shifts in the participants' GI microbiotic metagenomics and functionality, address the initiating stimuli levels of the condition, and evaluate the interventions' efficacy for the sustainment of mental health (Al Tarraf, 2021).

2. Large-Scale Clinical Trials: Well-controlled trials with large cohorts are required to assess the outcomes of administering microbiome-related products, namely probiotics, prebiotics, diet changes, and Fecal Microbiota Transplant (FMT), for core mental health disorders (Lum, 2023). Such trials should also recruit people from various ethnic backgrounds to generalize results and uncover variations in response to treatment across different groups.

3. Mechanistic Studies: Several research works have highlighted the interconnection between the gut microbiota and mental health; however, the processes involved are not well explored. Future investigations should concentrate on how gut bacteria directly affect the brain and behavior in more detail, especially regarding neurotransmitter, cytokine, and metabolite levels (Ignatova, 2019).

4. Personalized Medicine Approaches: Precision medicine is an appropriate trend in developing gut microbiome interventions, hence a call for more personalization in approaches (De Filippis et al., 2018). This includes defining personal microbial signatures, selecting therapy based on the patient's characteristics, and assessing therapeutic outcomes using objective markers. Through these future research directions, it is possible to realize the full potential of the gut-brain axis for transforming the future of mental health. Understanding how the gut microbiome and the brain interact will create new treatment approaches for mental disorders, positively affecting the treatment process and patients' quality of life.

7. Conclusion

Different, more recent discoveries, such as the gut-brain axis and the communication network between the microbiome in the gut and the central nervous system, have proven significant to this aspect of human health. This complex interplay affects, among other things, mood, nutrient absorption, and learning capabilities, and its dysregulation is associated with a plethora of mental ailments. Understanding how gut microbiota interacts with the brain is noteworthy; this involves neurotransmitters, short-chain fatty acids, microbe-derived tokens, cytokines, and endocrine signaling. Such understanding has given rise to a novel therapy that seeks to address the microbiome in the gut to enhance patients' mental well-being. Clinical trials and in vitro studies have shown the effectiveness of probiotics, prebiotics, diets, and FMT in improving symptoms of anxiety, depression, and related issues. Microbiome profiling for tailoring individualized treatment programs also seems more effective and responsive to patients' needs in selecting the most appropriate treatment methods. Despite the growing interest, knowledge concerning the so-called gut-brain axis is still rather limited. There is a lot of potential for future work to investigate this intricate association, and new technologies like single-cell sequencing and better bioinformatics tools help in this endeavor. More large-scale and long-term investigations and clinical trials are necessary to prove and confirm the causal benefits of microbiome-based therapies and determine the exact place of such approaches in treating mental diseases. Therefore, the gut-brain axis concept offers a revolutionary standpoint in understanding the causes and cures for psychological disorders. These findings revealed the vast potential of staking a direct claim on the human body's gut-master microbiome to create unique, long-lasting, and more productive treatment mechanisms for many mental health issues that impact millions globally.

References

- Ademe, M. (2020). Benefits of fecal microbiota transplantation: a comprehensive review. *The Journal of Infection in Developing Countries*, 14(10), 1074-1080.
- Ağagündüz, D., Çelik, E., Cemali, Ö., Bingöl, F. G., Özenir, Ç., Özoğul, F., & Capasso, R. (2023). Probiotics, live biotherapeutic products (LBPs), and gut-brain axis related psychological conditions: implications for research and dietetics. *Probiotics and Antimicrobial Proteins*, 15(4), 1014-1031.
- Al Tarraf, A. (2021). Impact of polyphenols and feeding rhythms on the immunomodulation properties of the probiotic bacteria in the gastro-intestinal tract [Université Bourgogne Franche-Comté].
- Almeida, C., Oliveira, R., Soares, R., & Barata, P. (2020). Influence of gut microbiota dysbiosis on brain function: a systematic review. *Porto biomedical journal*, 5(2), 1.
- Almeida, P. G., Nani, J. V., Oses, J. P., Brietzke, E., & Hayashi, M. A. (2020). Neuroinflammation and glial cell activation in mental disorders. *Brain, Behavior, & Immunity-Health*, 2, 100034.
- Anwar, H., Irfan, S., Hussain, G., Faisal, M. N., Muzaffar, H., Mustafa, I., Mukhtar, I., Malik, S., & Ullah, M. I. (2019). Gut microbiome: A new organ system in body. *Parasitol Microbiol Res*,

1, 17-21.

Appanna, V. D., & Appanna, V. D. (2018). Dysbiosis, probiotics, and prebiotics: in diseases and health. *Human microbes-The power within: Health, healing and beyond*, 81-122.

Banerjee, D., Das, P. K., & Mukherjee, J. (2023). Nervous System. In *Textbook of Veterinary Physiology* (pp. 265-293). Springer.

Banks, W. A. (2019). The blood–brain barrier as an endocrine tissue. *Nature Reviews Endocrinology*, 15(8), 444-455.

Bao, A.-M., & Swaab, D. F. (2019). The human hypothalamus in mood disorders: the HPA axis in the center. *IBRO reports*, 6, 45-53.

Bauer, P. V., Hamr, S. C., & Duca, F. A. (2016). Regulation of energy balance by a gut–brain axis and involvement of the gut microbiota. *Cellular and Molecular Life Sciences*, 73, 737-755.

Berding, K., & Donovan, S. M. (2020). Dietary patterns impact temporal dynamics of fecal microbiota composition in children with autism spectrum disorder. *Frontiers in Nutrition*, 6, 193.

Bernardazzi, C., Pêgo, B., & de Souza, H. S. P. (2016). Neuroimmunomodulation in the gut: focus on inflammatory bowel disease. *Mediators of inflammation*, 2016(1), 1363818.

Bhutiani, N., Schucht, J., Miller, K., & McClave, S. A. (2018). Technical aspects of fecal microbial transplantation (FMT). *Current gastroenterology reports*, 20, 1-6.

Binns, N. (2013). Probiotics, prebiotics and the gut microbiota.

Bonaz, B., Pellissier, S., Sinniger, V., Clarençon, D., Peinnequin, A., & Canini, F. (2012). The irritable bowel syndrome: how stress can affect the amygdala activity and the brain-gut axis. The amygdala-A discrete multitasking manager.

Boylin, K., Aquino, G. V., Purdon, M., Abedi, K., Kasendra, M., & Barrile, R. (2024). Basic models to advanced systems: harnessing the power of organoids-based microphysiological models of the human brain. *Biofabrication*, 16(3), 032007.

Brzozowski, B., Mazur-Bialy, A., Pajdo, R., Kwiecien, S., Bilski, J., Zwolinska-Wcislo, M., Mach, T., & Brzozowski, T. (2016). Mechanisms by which stress affects the experimental and clinical inflammatory bowel disease (IBD): role of brain-gut axis. *Current Neuropharmacology*, 14(8), 892-900.

Caputi, V., Popov, J., Giron, M. C., & O'Mahony, S. (2021). Gut microbiota as a mediator of host neuro-immune interactions: implications in neuroinflammatory disorders. *Microbes and the Mind*, 32, 40-57.

Choi, T.-Y., Choi, Y. P., & Koo, J. W. (2020). Mental disorders linked to crosstalk between the gut microbiome and the brain. *Experimental Neurobiology*, 29(6), 403.

De Filippis, F., Vitaglione, P., Cuomo, R., Berni Canani, R., & Ercolini, D. (2018). Dietary interventions to modulate the gut microbiome—how far away are we from precision medicine. *Inflammatory Bowel Diseases*, 24(10), 2142-2154.

Dey, G., & Mookherjee, S. (2021). Probiotics-targeting new milestones from gut health to mental health. *FEMS Microbiology Letters*, 368(15), fnab096.

Dinan, T. G., & Cryan, J. F. (2017). Microbes, immunity, and behavior: psychoneuroimmunology meets the microbiome. *Neuropsychopharmacology*, 42(1), 178-192.

El Munshid, H. A. (2000). The brain of the gut. *Saudi Journal of Gastroenterology*, 6(1), 18-26.

Escobar-Salom, M., Torrens, G., Jordana-Lluch, E., Oliver, A., & Juan, C. (2022). Mammals' humoral immune proteins and peptides targeting the bacterial envelope: from natural protection to therapeutic applications against multidrug-resistant Gram-negatives. *Biological Reviews*, 97(3), 1005-1037.

Fatima-Shad, K. (2024). Serotonin-Neurotransmitter and Hormone of Brain, Bowels and Blood: Neurotransmitter and Hormone of Brain, Bowels and Blood. BoD–Books on Demand.

Forsythe, P. (2013). Gut microbes as modulators of the neuro-immuno-endocrine system. *PharmaNutrition*, 1(4), 115-122.

Gao, J., Zhao, L., Cheng, Y., Lei, W., Wang, Y., Liu, X., Zheng, N., Shao, L., Chen, X., & Sun, Y. (2023). Probiotics for the treatment of depression and its comorbidities: A systemic review. *Frontiers in cellular and infection microbiology*, 13, 1167116.

Garcia-Alonso, A., Sanchez-Paniagua Lopez, M., Manzanares-Palenzuela, C. L., Redondo-Cuenca, A., & López-Ruiz, B. (2023). Edible plant by-products as source of polyphenols: Prebiotic effect and analytical methods. *Critical reviews in food science and nutrition*, 63(31), 10814-10835.

García-Cabrerizo, R., Carbia, C., O' Riordan, K. J., Schellekens, H., & Cryan, J. F. (2021). Microbiota-gut-brain axis as a regulator of reward processes. *Journal of neurochemistry*, 157(5), 1495-1524.

Geary, N. (2004). Endocrine controls of eating: CCK, leptin, and ghrelin. *Physiology & behavior*, 81(5), 719-733.

Giuffrè, M., Moretti, R., Campisciano, G., da Silveira, A. B. M., Monda, V. M., Comar, M., Di Bella, S., Antonello, R. M., Luzzati, R., & Crocè, L. S. (2020). You talking to me? Says the enteric nervous system (ENS) to the microbe. How intestinal microbes interact with the ENS. *Journal of Clinical Medicine*, 9(11), 3705.

Goo, N., Bae, H. J., Park, K., Kim, J., Jeong, Y., Cai, M., Cho, K., Jung, S. Y., Kim, D.-H., & Ryu, J. H. (2020). The effect of fecal microbiota transplantation on autistic-like behaviors in *Fmr1* KO mice. *Life sciences*, 262, 118497.

Gupta, S., Dinesh, S., & Sharma, S. (2024). Bridging the Mind and Gut: Uncovering the Intricacies of Neurotransmitters, Neuropeptides, and their Influence on Neuropsychiatric Disorders. *Central Nervous System Agents in Medicinal Chemistry (Formerly Current Medicinal Chemistry-Central Nervous System Agents)*, 24(1), 2-21.

Halaris, A. (2018). Neuroinflammation and neurotoxicity contribute to neuroprogression in neurological and psychiatric disorders. *Future Neurology*, 13(2), 59-69.

Han, D., Gao, P., Li, R., Tan, P., Xie, J., Zhang, R., & Li, J. (2020). Multicenter assessment of microbial community profiling using 16S rRNA gene sequencing and shotgun metagenomic sequencing. *Journal of Advanced Research*, 26, 111-121.

Han, M., Yuan, S., & Zhang, J. (2022). The interplay between sleep and gut microbiota. *Brain research bulletin*, 180, 131-146.

Hayes, C. L., Peters, B. J., & Foster, J. A. (2020). Microbes and mental health: Can the microbiome help explain clinical heterogeneity in psychiatry? *Frontiers in Neuroendocrinology*, 58, 100849.

HERE'S, W. Y. H. B. Digestion and Absorption.

Hernandez-Barrueta, T. (2022). Psychobiotics, a special type of probiotics, and their potential molecular mechanisms to ameliorate symptoms of stress and anxiety. *Molecular Mechanisms of*

Functional Food, 28-56.

Holzer, P., Farzi, A., Hassan, A. M., Zenz, G., Jačan, A., & Reichmann, F. (2017). Visceral inflammation and immune activation stress the brain. *Frontiers in immunology*, 8, 1613.

Hooks, K. B., Konsman, J. P., & O'Malley, M. A. (2019). Microbiota-gut-brain research: a critical analysis. *Behavioral and Brain Sciences*, 42, e60.

Ignatova, V. (2019). Influence of gut microbiota on behavior and its disturbances. *Behavioral Neuroscience*, 17-43.

Jiménez-Avalos, J. A., Arrevillaga-Boni, G., González-López, L., García-Carvajal, Z. Y., & González-Avila, M. (2021). Classical methods and perspectives for manipulating the human gut microbial ecosystem. *Critical reviews in food science and nutrition*, 61(2), 234-258.

Jugran, D. (2024). *The Healing Mindset: Understanding Psychology of Wellness: The Synthesis: Unleashing the power of Body & Mindset*. Shashwat Publication.

Juritsch, A. F. (2023). Utilizing Human Microbiota Associated Mice to Understand the Gut Microbiome-Dependent Effects of Dietary Fiber from Sorghum on Experimental Intestinal Inflammation.

Karbownik, M. S., Mokros, Ł., Dobielska, M., Kowalczyk, M., & Kowalczyk, E. (2022). Association between consumption of fermented food and food-derived prebiotics with cognitive performance, depressive, and anxiety symptoms in psychiatrically healthy medical students under psychological stress: a prospective cohort study. *Frontiers in Nutrition*, 9, 850249.

Kazempour, A. (2022). Large Association of GI Tract Microbial Community with Immune and Nervous Systems. In *Immunology of the GI Tract-Recent Advances*. IntechOpen.

Khan, S. (2015). *Health and disease according to Darwinian evolution*. Shahriar Khan.

Kokou, F., Sasson, G., Mizrahi, I., & Cnaani, A. (2020). Antibiotic effect and microbiome persistence vary along the European seabass gut. *Scientific reports*, 10(1), 10003.

Kuehnast, T., Abbott, C., Pausan, M. R., Pearce, D. A., Moissl-Eichinger, C., & Mahnert, A. (2022). The crewed journey to Mars and its implications for the human microbiome. *Microbiome*, 10(1), 26.

Kuma, S. S. (2019). Clinical Study on the Effectiveness of Jatipatri Ksheerapaka in Anidra (Primary Insomnia) Rajiv Gandhi University of Health Sciences (India)].

Kurowska, A., Ziemichód, W., Herbet, M., & Piątkowska-Chmiel, I. (2023). The role of diet as a modulator of the inflammatory process in the neurological diseases. *Nutrients*, 15(6), 1436.

Lachmansingh, D. A., Lavelle, A., Cryan, J. F., & Clarke, G. (2023). Microbiota-Gut-Brain Axis and Antidepressant Treatment. In: Springer.

LaGreca, M., Hutchinson, D. R., & Skehan, L. (2021). The microbiome and neurotransmitter activity. *The Journal of Science and Medicine*, 3(2).

Lalonde, R., & Strazielle, C. (2022). Probiotic effects on anxiety-like behavior in animal models. *Reviews in the Neurosciences*, 33(6), 691-701.

Lange, K. W., Lange, K. M., Nakamura, Y., & Kanaya, S. (2020). Is there a role of gut microbiota in mental health? *Journal of Food Bioactives*, 9.

Legan, T. B., Lavoie, B., & Mawe, G. M. (2022). Direct and indirect mechanisms by which the gut microbiota influence host serotonin systems. *Neurogastroenterology & Motility*, 34(10),

e14346.

Liberman, A. C., Trias, E., da Silva Chagas, L., Trindade, P., dos Santos Pereira, M., Refojo, D., Hedin-Pereira, C., & Serfaty, C. A. (2019). Neuroimmune and inflammatory signals in complex disorders of the central nervous system. *Neuroimmunomodulation*, 25(5-6), 246-270.

Lipski, E. (2020). The GUT-immune system. *Integrative and Functional Medical Nutrition Therapy: Principles and Practices*, 367-377.

Logan, A. C., Jacka, F. N., Craig, J. M., & Prescott, S. L. (2016). The microbiome and mental health: looking back, moving forward with lessons from allergic diseases. *Clinical Psychopharmacology and Neuroscience*, 14(2), 131.

Lum, G. R. T. (2023). Effects of clinical ketogenic diet therapy for pediatric epilepsy on the gut microbiota and seizure resistance. University of California, Los Angeles.

Makris, A. P., Karianaki, M., Tsamis, K. I., & Paschou, S. A. (2021). The role of the gut-brain axis in depression: endocrine, neural, and immune pathways. *Hormones*, 20(1), 1-12.

Maranduba, C. M. d. C., De Castro, S. B. R., Souza, G. T. d., Rossato, C., da Guia, F. C., Valente, M. A. S., Rettore, J. V. P., Maranduba, C. P., Souza, C. M. d., & Carmo, A. M. R. d. (2015). Intestinal microbiota as modulators of the immune system and neuroimmune system: impact on the host health and homeostasis. *Journal of immunology research*, 2015(1), 931574.

Marco, M. L., Hill, C., Hutkins, R., Slavin, J., Tancredi, D. J., Merenstein, D., & Sanders, M. E. (2020). Should there be a recommended daily intake of microbes? *The Journal of Nutrition*, 150(12), 3061-3067.

Martinson, V. G., Gawryluk, R. M., Gowen, B. E., Curtis, C. I., Jaenike, J., & Perlman, S. J. (2020). Multiple origins of obligate nematode and insect symbionts by a clade of bacteria closely related to plant pathogens. *Proceedings of the National Academy of Sciences*, 117(50), 31979-31986.

Massaquoi, M. S. (2022). Cell Specific Responses to Microbiota Play Global Roles in Host Development & Homeostasis University of Oregon].

Maynard, R. L., & Downes, N. (2019). Alimentary canal or gastrointestinal tract. *Anatomy and Histology of the Laboratory Rat in Toxicology and Biomedical Research*, 147-158.

Mazzoli, R., & Pessione, E. (2016). The neuro-endocrinological role of microbial glutamate and GABA signaling. *Frontiers in microbiology*, 7, 1934.

Merra, G., Noce, A., Marrone, G., Cintoni, M., Tarsitano, M. G., Capacci, A., & De Lorenzo, A. (2020). Influence of mediterranean diet on human gut microbiota. *Nutrients*, 13(1), 7.

Mills, S., Stanton, C., Lane, J. A., Smith, G. J., & Ross, R. P. (2019). Precision nutrition and the microbiome, part I: current state of the science. *Nutrients*, 11(4), 923.

Mintál, K., Tóth, A., Hormay, E., Kovács, A., László, K., Bufa, A., Marosvölgyi, T., Kocsis, B., Varga, A., & Vizvári, Z. (2022). Novel probiotic treatment of autism spectrum disorder associated social behavioral symptoms in two rodent models. *Scientific reports*, 12(1), 5399.

Mitreá, L., Nemeş, S.-A., Szabo, K., Teleky, B.-E., & Vodnar, D.-C. (2022). Guts imbalance imbalances the brain: a review of gut microbiota association with neurological and psychiatric disorders. *Frontiers in medicine*, 9, 813204.

Montagnani, M., Bottalico, L., Potenza, M. A., Charitos, I. A., Topi, S., Colella, M., & Santacroce, L. (2023). The crosstalk between gut microbiota and nervous system: a bidirectional interaction between microorganisms and metabolome. *International journal of molecular sciences*,

24(12), 10322.

Mundula, T., Russo, E., Curini, L., Giudici, F., Piccioni, A., Franceschi, F., & Amedei, A. (2022). Chronic systemic low-grade inflammation and modern lifestyle: The dark role of gut microbiota on related diseases with a focus on COVID-19 pandemic. *Current medicinal chemistry*, 29(33), 5370-5396.

Muto, T. (1988). *Digestion and absorption*. Tokyo: Daiichishuppan Co., Ltd, 228.

Offor, S. J., Orish, C. N., Frazzoli, C., & Orisakwe, O. E. (2021). Augmenting clinical interventions in psychiatric disorders: systematic review and update on nutrition. *Frontiers in psychiatry*, 12, 565583.

Oroian, B. A., Ciobica, A., Timofte, D., Stefanescu, C., & Serban, I. L. (2021). New Metabolic, Digestive, and Oxidative Stress-Related Manifestations Associated with Posttraumatic Stress Disorder. *Oxidative Medicine and Cellular Longevity*, 2021(1), 5599265.

Peckmezian, T., Garcia-Larsen, V., Wilkins, K., Mosli, R. H., BinDhim, N. F., John, G. K., Yasir, M., Azhar, E. I., Mullin, G. E., & Alqahtani, S. A. (2022). Microbiome-targeted therapies as an adjunct to traditional weight loss interventions: A systematic review and meta-analysis. *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy*, 3777-3798.

Pencheva, M., Darmonska, P., Aleksandrov, A., & Milkov, D. (2015). BM SPERM ANALYSIS OF MEN WITH A HISTORY OF INFERTILITY. *Folia Medica*, 57, 1.

Pérez, J. C. (2021). Fungi of the human gut microbiota: Roles and significance. *International Journal of Medical Microbiology*, 311(3), 151490.

Piccioni, A., Covino, M., Candelli, M., Ojetto, V., Capacci, A., Gasbarrini, A., Franceschi, F., & Merra, G. (2023). How do diet patterns, single foods, prebiotics and probiotics impact gut microbiota? *Microbiology Research*, 14(1), 390-408.

Pizarroso, N. A., Fuciños, P., Gonçalves, C., Pastrana, L., & Amado, I. R. (2021). A review on the role of food-derived bioactive molecules and the microbiota–gut–brain axis in satiety regulation. *Nutrients*, 13(2), 632.

Rangon, C.-M., & Niezgoda, A. (2022). Understanding the pivotal role of the vagus nerve in Health from pandemics. *Bioengineering*, 9(8), 352.

Ranjha, M. M. A. N., Shafique, B., Batool, M., Kowalczewski, P. L., Shehzad, Q., Usman, M., Manzoor, M. F., Zahra, S. M., Yaqub, S., & Aadil, R. M. (2021). Nutritional and health potential of probiotics: a review. *Applied sciences*, 11(23), 11204.

Resende, A. S., Leite, G. S., & Lancha Junior, A. H. (2021). Changes in the gut bacteria composition of healthy men with the same nutritional profile undergoing 10-week aerobic exercise training: a randomized controlled trial. *Nutrients*, 13(8), 2839.

Rosa, R., Donskey, C. J., & Munoz-Price, L. S. (2018). The intersection between colonization resistance, antimicrobial stewardship, and *Clostridium difficile*. *Current infectious disease reports*, 20, 1-6.

Ross, K. (2023). Psychobiotics: Are they the future intervention for managing depression and anxiety? A literature review. *Explore*, 19(5), 669-680.

Sabit, H., Kassab, A., Alaa, D., Mohamed, S., Abdel-Ghany, S., Mansy, M., Said, O. A., Khalifa, M. A., Hafiz, H., & Abushady, A. M. (2023). The effect of probiotic supplementation on the gut–brain axis in psychiatric patients. *Current Issues in Molecular Biology*, 45(5), 4080-4099.

- San Roman, M., & Wagner, A. (2018). An enormous potential for niche construction through bacterial cross-feeding in a homogeneous environment. *PLoS computational biology*, 14(7), e1006340.
- Schmidt, M. A. (2009). *Beyond antibiotics: Strategies for living in a world of emerging infections and antibiotic-resistant bacteria*. North Atlantic Books.
- Sem, I. UNIVERSITY OF C SCHOOL OF DISTANC.
- Shanmugam, H., Ganguly, S., & Priya, B. (2022). Plant food bioactives and its effects on gut microbiota profile modulation for better brain health and functioning in Autism Spectrum Disorder individuals: A review. *Food frontiers*, 3(1), 124-141.
- Sharkey, K. A., & Savidge, T. C. (2014). Role of enteric neurotransmission in host defense and protection of the gastrointestinal tract. *Autonomic Neuroscience*, 181, 94-106.
- Sharma, A., Singh, A. K., Kumar, V., & Prakash, H. (2022). Interferon and HPA Axis: Impact on Neuroimmunological Perturbations. In *Basic and Clinical Aspects of Interferon Gamma*. IntechOpen.
- Sheflin, A. M., Melby, C. L., Carbonero, F., & Weir, T. L. (2017). Linking dietary patterns with gut microbial composition and function. *Gut microbes*, 8(2), 113-129.
- Sherman, M. P., Zaghouani, H., & Niklas, V. (2015). Gut microbiota, the immune system, and diet influence the neonatal gut–brain axis. *Pediatric research*, 77(1), 127-135.
- Silpe, J. E., & Balskus, E. P. (2020). Deciphering human microbiota–host chemical interactions. *ACS Central Science*, 7(1), 20-29.
- Sivamaruthi, B. S., Prasanth, M. I., Kesika, P., & Chaiyasut, C. (2019). Probiotics in human mental health and diseases-A minireview. *Tropical Journal of Pharmaceutical Research*, 18(4), 889-895.
- Stadler, C. (2018). *NUTRITIONAL DETERMINANTS IN THE DEVELOPMENTAL PROGRAMMING OF AUTOIMMUNE DISEASES—FACTS AND HYPOTHESES*.
- Sudheer, S., Gangwar, P., Usmani, Z., Sharma, M., Sharma, V. K., Sana, S. S., Almeida, F., Dubey, N. K., Singh, D. P., & Dilbaghi, N. (2022). Shaping the gut microbiota by bioactive phytochemicals: An emerging approach for the prevention and treatment of human diseases. *Biochimie*, 193, 38-63.
- Swann, J., Rajilic-Stojanovic, M., Salonen, A., Sakwinska, O., Gill, C., Meynier, A., Fança-Berthon, P., Schelkle, B., Segata, N., & Shortt, C. (2020). Considerations for the design and conduct of human gut microbiota intervention studies relating to foods. *European journal of nutrition*, 59, 3347-3368.
- Swanson, L. W. (2012). *Brain architecture: understanding the basic plan*. Oxford University Press, USA.
- Tobias, A., & Sadiq, N. M. (2019). *Physiology, gastrointestinal nervous control*.
- Vasiliu, O. (2023a). The current state of research for psychobiotics use in the management of psychiatric disorders—A systematic literature review. *Frontiers in psychiatry*, 14, 1074736.
- Vasiliu, O. (2023b). Is fecal microbiota transplantation a useful therapeutic intervention for psychiatric disorders? A narrative review of clinical and preclinical evidence. *Current Medical Research and Opinion*, 39(1), 161-177.
- Vetrani, C., Di Nisio, A., Paschou, S. A., Barrea, L., Muscogiuri, G., Graziadio, C., Savastano, S., Colao, A., Obesity Programs of Nutrition, E., Research, & Group, A. (2022). From gut microbiota through low-grade inflammation to obesity: key players and potential targets. *Nutrients*, 14(10), 2103.

Vinelli, V., Biscotti, P., Martini, D., Del Bo', C., Marino, M., Meroño, T., Nikoloudaki, O., Calabrese, F. M., Turrone, S., & Taverniti, V. (2022). Effects of dietary fibers on short-chain fatty acids and gut microbiota composition in healthy adults: a systematic review. *Nutrients*, 14(13), 2559.

Wang, H. (2018). Effects of probiotics on central nervous system functions in humans [Universität Tübingen].

Wiley, N. C., Cryan, J. F., Dinan, T. G., Ross, R. P., & Stanton, C. (2021). Production of psychoactive metabolites by gut bacteria. *Microbes and the Mind*, 32, 74-99.

Włodarczyk, M., & Śliżewska, K. (2021). Obesity as the 21st Century's major disease: The role of probiotics and prebiotics in prevention and treatment. *Food Bioscience*, 42, 101115.

Yin, M., Yan, X., Weng, W., Yang, Y., Gao, R., Liu, M., Pan, C., Zhu, Q., Li, H., & Wei, Q. (2018). Micro integral membrane protein (MIMP), a newly discovered anti-inflammatory protein of *Lactobacillus plantarum*, enhances the gut barrier and modulates microbiota and inflammatory cytokines. *Cellular Physiology and Biochemistry*, 45(2), 474-490.

Yixin, X. (2019). Absence of Gut Microbiota Causes Stress-Induced Anxiety via Amygdala Hyperexcitability in Mice [National University of Singapore (Singapore)].

You, X.-y., Zhang, H.-y., Han, X., Wang, F., Zhuang, P.-w., & Zhang, Y.-j. (2021). Intestinal mucosal barrier is regulated by intestinal tract neuro-immune interplay. *Frontiers in Pharmacology*, 12, 659716.

Zhang, H., Wang, Z., Wang, G., Song, X., Qian, Y., Liao, Z., Sui, L., Ai, L., & Xia, Y. (2023). Understanding the connection between gut homeostasis and psychological stress. *The Journal of Nutrition*, 153(4), 924-939.

Zhang, Q.-S., Tian, F.-W., Zhao, J.-X., Zhang, H., Zhai, Q.-X., & Chen, W. (2020). The influence of dietary patterns on gut microbiome and its consequences for nonalcoholic fatty liver disease. *Trends in Food Science & Technology*, 96, 135-144.

Zhao, M., Jiang, X.-F., Zhang, H.-Q., Sun, J.-H., Pei, H., Ma, L.-N., Cao, Y., & Li, H. (2021). Interactions between glial cells and the blood-brain barrier and their role in Alzheimer's disease. *Ageing research reviews*, 72, 101483.

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