Microbiota and depression an update

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Author contributions
Lester Domínguez conceived this study, carried out this study, and drafted the manuscript. Maria Domínguez Ríos designed the study, collected, and analyzed the data. Both authors were responsible for this manuscript and reviewed the article critically. All authors read and approved the final manuscript.

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Abbreviations
MGBA, microbiota-gut-brain axis; ASD, autism spectrum disorder; COVID-19, CNS, central nervous system; CDS, chronic social beat stress; LH, learned helplessness; SCFAs, short-chain fatty acids; MDD, major depressive disorder; TST, tail suspension test; FST, forced-swim test; BDNF, brain-derived neurotrophic factor; EECs, enteroeccrine cells; GABA, gamma-aminobutyric acid.

Citation

Abstract
The highest rates of morbidity and impairment related to gastrointestinal difficulties are associated with depression, which is associated with the highest rates of all mental disorders. It has been demonstrated that the composition of an individual’s gut microbiome plays a significant part in determining that person’s risk of developing depression. According to the hypothesis known as the gut-brain axis, there may be a connection between the intestinal microbial system and the brain. In recent years, it has been common practice to treat disorders by concentrating on the bacteria that are found in the digestive tract (for instance, by making use of probiotics) and incorporating the gut-brain axis mechanism. Our research revealed a remarkable association between the composition of the bacteria in the stomach and the incidence of depression. Alterations in the structure of the microbiota system in the gut could possibly have direct and special impacts on the rise in the prevalence of depression. This study investigated the mechanisms underlying the two-way communication in the gut-brain axis, including the current techniques of relieving symptoms and antidepressant medicines that are related to gut microbiota. An increase in the amount of research into the medical potential of probiotics has led to a rapid expansion of the field of probiotics over the past few decades. Numerous preclinical and clinical studies have established that the therapeutic effects of probiotics-mediated microbiota remodeling near the microbiota-gut-brain axis (MGBA) are present. These studies were conducted near one another. However, the potential effects of probiotics on numerous mental illnesses, which have been proved in vivo and in vitro research, have set the ground for the translation of preclinical models to humans, which is still in its infancy.

Keywords: depression; probiotics; gut-brain axis; gut microbiota

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Introduction

The process of neurodevelopment is a complicated one that is controlled by a variety of stimuli, both endogenous and exogenous. Even though the brain has traditionally been the primary focus of research, peripheral factors have been shown to influence several neurological illnesses. Recent research on autism spectrum disorder (ASD) and the link between the stomach and the brain, as well as the emotions and thoughts associated with ASD, lend credence to this theory [1]. The development of a healthy brain that can perform all its functions depends on several essential prenatal and postnatal processes, including conservational shows and chemical signals coming from the stomach. A significant source of these cues comes from the microbiome, which is the colony of beneficial bacteria that is found naturally within all mammals. The gut microbiota has recently been shown to influence a wide variety of characteristics of animal behavior as well as fundamental neurogenerative processes such as the creation of the blood-brain barrier, myelination, neurogenesis, and microglia maturation. In this article, we investigate the theory that the bacteria that live in one’s digestive tract play a significant part in the formation of the nervous system as well as the preservation of a healthy equilibrium between mental sickness and mental well-being [1].

It is common knowledge that mood disorders such as sadness and anxiety have garnered a significant amount of attention over the course of the past several years, particularly since the beginning of the pandemic. The direct connection with suicide is the reason for this attention that has been linked to it. According to this estimate, only five percent of all cases of depression are found in adults, but there are approximately 280 million people around the world who suffer from it. This condition has a direct influence on the limitations of opportunities, which can have repercussions for the individuals who suffer from it as well as their families [2–4].

As was noted before, both conditions have been the primary focus of the COVID-19 pandemic. This emphasis is backed by 5683 separate information bases from the global burden of illness research in the year 2020. There has been significant development in terms of therapies for this condition. For instance, it has been determined that the condition is brought on by a chemical imbalance in the brain. These are examples of the progress that has been made [2, 3]. However, there is one aspect that has not been resolved yet, and that is the fact that the specific processes that are behind the pathophysiology of depression are yet unclear. This is the part that has not been solved yet. The physiological mechanisms that underlie depression are poorly understood to this day. Because of this, recent discoveries on the interaction between the brain, the digestive system, and the microbiome could be able to better capture the complexity of depression and inspire the development of successful novel treatments [1, 2, 4].

The brain-gut-microbiota system

In addition, there have been studies conducted on the relationships between the gastrointestinal tract’s endocrine system and its hormone communication with the neurons and brain cells that led to the discovery of a gut-brain axis in the year 1980. This is why, over the course of the past few years, a significant number of researchers have expanded on this concept to account for the role that the microbiome plays in the gut-brain axis [4]. In modern times, the phrase ‘brain-gut-microbiota’ refers to not only the axis but also the system of if in hosts. This system includes the central nervous system (CNS), the endocrine chemical signal system, immunological regulation, microbiota and metabolic impacts, and barrier functions of both the brain and the gut (Figure 1). It is essential to emphasize the fact that all these components must cooperate with one another for a person’s health to be preserved. This role is then moved to the explanations of the disorders of sadness and anxiety, indicating that the troubles are simply one of the many that might emerge from an imbalance in this area. The microbiome is comprised of trillions of microorganisms such as bacteria, viruses, archaea, and fungi, and its genetic material contains more than one hundred times as many genes as the human genome does [5]. Therefore, there are as many bacteria in the human body as there are human cells. In addition to this, the microbiota secretes key vitamins such as folic acid and vitamin K for the overall health of the body, assists in digestion and the absorption of nutrients from food, and acts as a defense mechanism against infectious agents. It has been demonstrated that the microbiota in a mother’s gut can have a favorable effect on her child’s brain development and mental health beginning in the earliest stages of embryonic life and extending all the way through the mother-child bond. This serves as an illustration of this concept. Our awareness of the function that the gut plays in mental health and the development of mood disorders like depression has been expanded because of recent research that has thrown light on the intricate ways in which the microbiota in the gut communicates with the central nervous system [1].

Role of the brain-gut-microbiota in depression

Results since rodent models

The gut microbiota is a complex and diverse community of billions of bacteria that dwell in the digestive tracts of humans, animals, and insects [6, 7]. Microbiota is 10 times more plentiful than our body’s somatic and germ line cells [8]. The human gut microbiota is made up of many microbes such as bacteria, archaea, eukarya, viruses, and parasites [9] and is the first line of defense for the gastrointestinal (GI) apparatus. The gut microenvironment promotes the growth of bacteria from seven major divisions (Firmicutes, Bacteroidetes, Actinobacteria, Fusobacteria, Proteobacteria, Verrucomicrobia, and Cyanobacteria) [10]. Bacteroidetes and Firmicutes account for more than 90% of the overall population [9]. The presence of the microbiota varies across the GI tract, ranging from a few microorganisms in the stomach and small intestine to a concentration of around 1012 bacteria in the colon [11, 12]. In humans, the gut microbiota contains the most germs and the most species when compared to other areas of the body [13].

Kelly et al. tested the hypothesis that there is a bidirectional link between depressive states and microbiome composition. Researchers analyzed the saliva, serum, and fecal compositions of 34 depressed patients and 33 healthy controls for the study. Fecal samples from three patients with the most severe depression were mixed and transplanted into 13 adult male rats given antibiotics earlier. In the study material, depressive patients had significantly greater levels of total cortisol production, IL-6, IL-8, TNP-α, and CRP, as well as a higher kynurenine/tryptophan ratio. There was a decrease in the overall number of species found and poor phylogenetic diversity in stool samples from depressed patients. There were no variations in plasma lipopolysaccharide-binding protein or short-chain fatty acid levels, but depressed symptoms were adversely associated with daily dietary fiber intake. In an animal study, rats with “depressed” microbiota transplanted showed anhedonia-like and anxiety-like behaviors when compared to the control group. Plasma kynurenine content and ratio, as well as plasma CRP concentration, were considerably higher in the depressed group. The authors concluded that dysbiosis may play an essential role in the pathophysiology of depression based on these findings [14].

Multiple studies have found that in depressed patients, tryptophan metabolism shifts from the serotonin pathway to the kynurenine pathway [15]. The major precursor of the kynurenine pathway, tryptophan, is transformed into kynurenine and then into other molecules. Anthranilic acid, kynurenic acid, and 3-hydroxykynurenine are a few examples. Tryptophan is converted to 5-hydroxytryptophan, then to serotonin, and finally to 5-hydroxyindoleacetic acid via the serotonin pathway [16]. Tryptophan levels are lower in MDD, which presumably reflects its relevance in the disorder, particularly in terms of serotonin bioavailability. The decreased bioavailability of tryptophan is at least partly responsible for the lower serotonin levels seen in MDD. This drop in tryptophan levels is most likely responsible,
Figure 1 The significance of the axis formed by the brain, the gut, and the microbiome. Reproduced with permission. Chang LJ, Wei Y, Hashimoto K. Brain-gut-microbiota axis in depression: A historical overview and future directions. Brain research bulletin 2022;182: 44-56. Copyright 2022, Elsevier Inc.

Figure 2 Depression and the brain-gut-microbiota axis. Reproduced with permission. Chang LJ, Wei Y, Hashimoto K. Brain-gut-microbiota axis in depression: A historical overview and future directions. Brain research bulletin 2022;182: 44-56. Copyright 2022, Elsevier Inc.
at least in part, for the lower kynurenine bioavailability reported in MDD. Furthermore, we found an increase in the kynurenine to tryptophan ratio in MDD, implying that the decrease in serotonin bioavailability, which was previously thought to be one of the foundations of the monoamine hypothesis, is secondary not only to a decreased pool of tryptophan but also to a shift in tryptophan metabolism away from serotonin and toward kynurenine [15, 16]. All the alterations in various circuits including the spleen, BNDF, and pro-inflammatory cytokines, increase resilience, and stress plays a role in depression. It has been discovered that rodents do not experience the psychological effects of chronic social beat stress (CSDS) or learned helplessness (LH). Our research has shown that mice who are resistant to CSDS have a considerably higher number of Bifidobacterium than control mice and mice that are susceptible to CSDS. In addition, the number of CSDS-resistant mice was significantly higher after oral administration of Bifidobacterium in comparison to the treatment with the vehicle, which suggests that Bifidobacterium promotes resistance to CSDS. When compared to the control and LH-resistant rats, the relative quantities of Lactobacillus, Clostridium cluster III, and Anaerococcus were all considerably higher in the LH-vulnerable rats. There is a growing body of evidence derived from studies conducted on animals that suggests the brain-gut-microbiota axis is essential for the development of depression symptoms in humans. Abnormally high levels of short-chain fatty acids (SCFAs) and amino acids metabolites, including alanine, isoleucine, L-threonine, serine, and tyrosine, corresponded with gut microbiota that has been linked to stress-induced depression and behaviors in rodents. These metabolites, which influence the amounts of 5-HT in the brain, may also have an effect on phenotypes that are similar to those of depression. There is evidence to suggest that the brain-gut-microbiota axis regulates depression in both directions. This means that the supervision of microbiota and their metabolites must have opposing effects on depressive symptoms. On the other hand, research has indicated that administering a combination of SCFAs, such as acetate, butyrate, and propionate, to rats helps reduce the depressive-like behaviors that are brought on by stress. These shifts in the microbiota-determined protein composition lend credence to the hypothesis that the gut-brain axis is potentially involved in the development of depression. It was expected that the modified protein reports would contribute to the inflammation of the immune system and the control of metabolism. Evidence supporting the brain-gut axis in depression can be strengthened by increasing one's understanding of the profound changes that can occur in either the brain or the gut [6]. Look at Figure 2.

It is essential to know the mammalian microbiome is made up of numerous microbial communities that are connected to various organs, tissues, and other parts of the mammalian body. Studies on both animals and humans have been able to confirm a connection between the microorganisms that live in one's digestive tract and the development and functionality of one's immune system. This is because of the reason stated above. The existence of several bacteria, each of which plays a part in either increasing or alleviating the symptoms of immunologic illnesses such as diabetes type 1, asthma, and inflammatory bowel disease, is essential to the microbiome's overall state of health. In addition, because the gut microbiome can have an effect on the immune system, it is difficult to think that it would not also have an effect on the nervous system. For instance, in comparison to standard (specific-pathogen-free [SPF]) mice, germ-free (GF) mice, which do not contain any microorganisms, are more prone to engage in risky behavior, be hyperactive, and have cognitive deficits. GF mice exhibit altered expression of the 5-hydroxytryptamine receptor (5-HT1A), neurotrophic factor (such as BNDF), and NMDA receptor subunit in the hippocampus. This is in addition to a decreased blood-brain barrier function and amplified myelination in the prefrontal cortex. There is evidence, while preliminary and primarily derived from animal models, that the microbiome may play a role in neuropsychiatric disorders like melancholy and autism, anxiety spectrum disorder (ASD) [6], schizophrenia, Parkinson's disease (PD), and Alzheimer's disease. These illnesses include Alzheimer's disease and Parkinson's disease [7].

The microbiome, also known as the "Steady-State" microbiome, reaches a state of relational stability known as "Steady-State" in terms of the diversity and abundance of bacteria in adults when environmental and health conditions remain unchanged. Because of this, it is recognized that the microbiome can be influenced by a variety of factors, including genetics, diet, lifestyle, and even location. The phrase "the absence of any overt sickness" is insufficient to serve as a definition of health. Recent research published by Lloyd-Price et al. (2016) provides extensive evaluations of the human microbiome in healthy states. However, the diversity and quantity of microorganisms in the human microbiome are largely reliant on the setting in which they are found. In addition to this, there is a certain bacterium that lives in the intestinal tract, and its name is phylum. The most prevalent bacterium is a species of Streptococcus, followed by Bacteroides and Firmicutes in that order. For the basis of the derived high pool of SCFAs, tyrosine, tryptophan, and minocycline is able to amplify the brain-gut axis thereby affecting the development of depression. The research reveals that depression is associated with abnormalities in the anatomy and function of the hippocampus and the prefrontal cortex. The hypothesis that stress is a risk factor for depression is supported by the...
observation that the HPA axis is dysfunctional in depressed people and animal models of the condition. Animal models of depression [14] frequently incorporate stress as an etiological factor. Anxiety can be a co-occurring or predominant component of a person's health when they have MD illness, which affects around two-thirds of those who have MD illness. In animal studies, the presence of both anxious and depressive signs is usually seen together. The function that the gut microbiota may play in conditions that are triggered by stress is garnering a lot of attention. Alterations in the composition of the microbiota in the gut have been linked to a few mental diseases connected to stress, including anxiety and depression. Most of the information regarding the potential for the gut microbiota to ameliorate stress-induced abnormalities in behavior and brain function has been gleaned from preclinical research. In this part of our post, we will be discussing the significance of the composition of intestinal microbiota in relation to the etiology, pathophysiology, and therapy of mood and anxiety disorders, both preclinically and clinically.

Antibiotic-induced dysbiosis provoked anxiety- and/or depression-like behaviors

Because antibiotic treatment removes significant parts of the physiological microbiota and makes it easier for pathogens to spread, this can result in dysbiosis of the intestinal microbiota. Recent preclinical studies have established a relationship between antibiotic-induced dysbiosis in mice and behavior like anxiety and depression. This notion has been validated by the findings of clinical trials that were conducted to test the idea. Similar rates of mental events, such as anxiety and depression, were detected in mice and humans exposed to fluoroquinolones, according to the research carried out by Kaur and her colleagues. The rates were 72% and 62%, respectively. On the other hand, these findings run counter to both the preclinical evidence that was gathered by Dubonnet et al. and the clinical research that was conducted by Murphy et al. [15].

Effect of probiotic administration on the anxiety- and depressive-like behavior

Probiotic supplementation has been proven to lessen anxious and depressive-like behaviors in mice, rats, zebras, and people, according to both preclinical and clinical investigations. In this study, the GF mouse model was used to evaluate the effects of long-term treatment with Lactobacillus plantarum PSI28 (PS128) on anxiety-like behaviors and depression-like behaviors, as well as on monoamine neurotransmitter levels in the striatum, prefrontal cortex, and hippocampus. After administering live PSI28 over a longer period, unfortunately, we did not find any negative effects. In addition, mice that were given live PSI28 spent a noticeably longer amount of time in the open arms and traveled a noticeably greater distance in the elevated plus maze test; however, this treatment had no influence on the depressive-like behavior of GF mice when they were subjected to the forced swim. Serotonin and dopamine concentrations in the striatum were dramatically increased, according to the results of an examination of monoamine neurotransmitter levels that was performed after chronic injection of live PSI28. The prefrontal cortex and the hippocampi showed no discernible changes at any time during the experiment. In mice with a chronic infection of the gut parasite Trichuris muris, Lactobacillus rhamnosus JB-1 and Bifidobacterium longum NCCL3001 caused anxiolytic- and antidepressant-like effects or prevented anxiogenic-like effects. The same was true for Lactobacillus helveticus R0052 and Bifidobacterium longum R0175 in rats. Probiotics have also been shown to boost levels of monoamine neurotransmitters in the striatum, as well as lower levels of brain-derived neurotrophic factor (BDNF) and corticosterone, according to research conducted on animals. Ganeau et al. reported that administration of preparations containing either Lactobacillus rhamnosus or Lactobacillus helveticus improved intestinal function and normalized corticosterone levels in rats that were subjected to MS stress. Lactobacillus reuteri treatment resulted in a decrease in plasma corticosterone levels and decreased nervous behavior in mice that had been stressed using the elevated plus-maze test. This was also connected with a reduction in the amount of anxious behavior displayed by the mice. According to Desbonnet et al. [16], an administration of Bifidobacterium infantis via the per os route was successful.

The usage of probiotics has been shown to be beneficial in the treatment of mood disorders through clinical study. According to the findings of one study, patients who took Lactobacillus casei strain Shirata and had lower pre-probiotic depression scores enjoyed the highest advantages, as evaluated by post-probiotic mood outcomes. These patients also used the probiotic. Therefore, patients with modest benefits benefit from this kind of therapeutic intervention since it enables them to better control their stress reactions and anxious behaviors and has an elevating effect on their disposition. Patients with the lowest baseline urine free cortisol levels were selected for the study to investigate whether or not the chronic co-administration of Lactobacillus helveticus R0052 and Bifidobacterium longum R0175 would be beneficial. This study investigated whether there was a connection between the frequency of these strains and severe depressive disorders. Previous preclinical studies had revealed that Bifidobacterium and Lactobacillus in the gut had a beneficial effect on stress response and depression disorder. According to the findings of a recent study, the gut microbiota of rats with depression, such as Lactobacillus in the guts of depressed persons are significantly lower than those found in healthy people. In addition, a research study that was randomized, double-blind, and placebo-controlled was carried out by Lew and coworkers. This study indicated that the anti-inflammatory properties of Lactobacillus plantarum P8 were responsible for the amelioration of stress and anxiety symptoms. According to the findings of recent clinical investigations, a significant connection exists between the state of one's mental health and the composition of one's microbiota. In addition, the advantages of using individualized probiotic supplements for re-establishing a functional gut-brain axis and improving one's mental health were brought to light [16].

The connections between the bacteria in the gut, a person's mental health, and depression. In the sucrose/saccharin preference test, often known as the SPT, anhedonia, which is a characteristic feature of depression, is reflected in the percentage of sucrose/saccharin solution that is ingested. After spending 48 hours in a tank containing water and either 1% or 2% sucrose/saccharin solution as part of the SPT, each animal was placed for an additional 24 hours in two identical bottles containing water and either 1% or 2% sucrose/saccharin solution. This process was repeated twice. Both the water and the sucrose/saccharin bottles were given a pre-experiment and post-experiment weight to discover which was preferred. A lower subjective well-being (SP) and a higher level of anhedonia are both suggestive of decreased consumption of sucrose and/or saccharin. Antibiotic treatment lowered SP in mice, which may emphasize the importance of the gut microbiome in the development of depressive traits. The antibiotics can kill up to 90 percent or more of the good bacteria that live in the stomach. In addition, intestinal microbiota transplantation from anhedonia-vulnerable rats significantly increased depressive-like behaviors in fake germ-free mice. This was demonstrated by a decreased sucrose/saccharin preference index (SPI). When faecal microbiota from depressed people is transplanted into rats with low levels of the microbiome, the recipient animals begin to exhibit behaviors that are like those of depressed people. The forced-swim test (FST) and the tail suspension test (TST) are two methods that can be used to examine rodents for indications of hopelessness, which is another hallmark of depression. To test FST, for example, mice were individually placed in a cylinder that measured 25 centimeters in diameter and 35 centimeters in height. The cylinder was filled with 20 centimeters of water and maintained at a temperature of 23 °C by an automated forced-swim system called YH-FST (Yihong Co., Ltd., Wuhan, China). The mouse was moused to life after a period of dormancy lasting five minutes. A piece of
adhesive tape was positioned in the TST approximately 2 centimeters away from the tip of the mouse's tail. The tape had a hole punched in it, and one by one, the mice were strung up on the string. The duration of the interval of inaction was ten minutes, and it was captured on film. As a behavioral indicator of desparation, the length of time a person can sit still throughout both the FST and the TST is taken into consideration. It was established that the gut microbiota plays a role in the regulation of depressed behavior by the fact that germ-free (GF) mice exhibited less immobility during the FST and TST when compared to specific pathogen-free (SPF) animals and healthy controls. This was the case for both tests. On the other hand, GF mice that have been exposed to the microbiota of MDD patients exhibit a shorter duration of immobility during the central open field test (OFT) and a longer duration of immobility during the FST and TST [17].

Potential mechanisms underlying the involvement of the microbiota-gut-brain axis in depression

Although the specific mechanism by which the microbiota-gut brain brain axis impacts depressive symptoms is yet understood, there is accumulating evidence that pathways in the nervous system, endocrine system, immune system, and metabolic system all play essential roles in this conversation (Figure 3 and 4). This article explains how the neuronal, endocrine, and immunological signaling systems are engaged in the bidirectional interaction between gut microorganisms and the central nervous system, which can affect depressive diseases. This article also discusses how this relationship can affect the risk of developing depression. Because of its position and the blood flow that it receives, it is essential to recognize that the liver is responsible for coordinating and taking part in essential immunological activities. Intestinal flora is responsible for regulating the expression of monoamine neurotransmitters such as 5-HT, DA, and GABA. These neurotransmitters play a crucial role in the formation and plasticity of brain circuits that are important for mood and behavior. It is possible to prevent or cure hyperactivity of the HPA axis, which is demonstrated by increased production of cortisol, adrenocorticotropic (ACTH), and corticotropin-releasing hormone (CRH). This can be accomplished by altering the function of the microbiota-gut-brain axis through changes in the gut microbiota. The mucosal system is the immune system's first line of defense against potential pathogens. A few of the fundamental roles that the mucosal immune system (MIS) plays are providing defense against infectious agents, preventing the introduction of alien antigens, fostering oral tolerance, and ensuring that the mucosa remains in a state of homeostasis. Through the portal vein, germs and their metabolites can directly reach the liver from the digestive tract, where they play an important part in the innate immune response. The liver also plays a vital role in the adaptive immune response. By restoring a healthy equilibrium between pro- and anti-inflammatory cytokines, such as IL-6, IL-1, and TNF-a, alterations in the gut microbiota might reduce the symptoms of depression. Changes in the gut microbiota, which may result in elevated levels of BDNF expression, have been hypothesized to have a role in the development of depressive symptoms. The etiology of depression is influenced by each of these different pathways [18].

The Control of the Proliferation of Brain-Derived Neurotrophic Factor The Brain-derived Neurotrophic Factor, often known as BDNF, is a member of the neurotrophic family. It has been linked to a broad variety of events, including cell differentiation, the survival of neurons, the formation of synapses, and the development of neuroplasticity. The absence of BDNF makes it more likely that neuroplasticity will be hindered, which may also lead to the development of depressive symptoms. Multiple studies have concluded that the blood BDNF levels of depressed patients are significantly lower than those of healthy controls. Ketamine is one example of a treatment for depression that has been shown to improve mood as well as cognitive performance by elevating BDNF activity through mTOR signaling [19, 20]. It has been demonstrated that probiotic treatment for behavioral impairments can influence the microbiota of the stomach as well as the expression of BDNF. This is in addition to the fact that probiotic treatment has the potential to be either a preventative or therapeutic method. Bercik et al. discovered that giving oral antimicrobials to SPF mice led to a temporary alteration in their gut flora, which boosted levels of BDNF in the hippocampus. This was done to reduce the effects of depression. It has been shown that the expression of brain-derived neurotrophic factor (BDNF) in the hippocampus of stressed mice is elevated after two weeks of pretreatment with probiotics (a combination of Lactobacillus helveticus R0052 and Bifidobacterium longum R0175). BDNF is known to improve learning and memory, as well as reverse synaptic dysfunction. In addition, the administration of Lactobacillus helveticus NS8 increased both the BDNF mRNA expression in the hippocampus as well as the behavioral performance of rats acting out a model of chronic stress-induced depression. Alterations in the gut microbiota, which are responsible for regulating BDNF levels, may influence depressive symptoms [21].

Risk factors for dysbiosis

The genesis of gut dysbiosis is complicated, and there are a few different risk factors that could be involved. For instance, the use of antibiotics has been linked to both short-term and long-term changes in the microbiota that are found in the gut. Alterations that can be reproduced in the gut flora have been connected to obesity and diets that are heavy in both fat and sugar. In addition, environmental factors at different times of a person's life can also influence gut dysbiosis. For example, the diversity of an infant's microbiome might change based on the mode of delivery, the nutrition, and the environment of the hospital. The presence of dysbiosis in the gut has also been linked to the presence of xenobiotics and social stresses. Both genetic and environmental variables have a role in the development of the microbiome that lives in the human stomach [22].

The microbiota-gut-brain pathways: focus on gut peptides

The brain is in constant communication with the digestive system, and this communication can go in either direction. This form of communication may play a significant part in the modulation of physiological effects that range from the operation of the gastrointestinal tract to the brain and behavior, including the feeling of visceral events such as nausea, satiety, and pain. The digestive tract's ability to both produce and move its contents is altered when the body is under stress. Researchers are actively investigating the therapeutic significance of such two-way communication as well as variations in the composition of the gut microbiota. The information that is acquired by the gastrointestinal tract's sensory receptors may be used as the foundation for the conversion into neuronal, hormonal, and immunological signals that are the basis of the bidirectional gut-brain relationship. These impulses can be processed singularly or in combination by the central nervous system (CNS) of the brain. In the sections of the text that are appropriate to do so, the neurological and immunological mechanisms are explored. Check out and if you're interested in reading in-depth analyses of the published research on brain and immunological pathways. In addition, a simplified representation of the neurological and immunological pathways that are involved in the gut microbiota-brain axis may be found in Figure 1 [23–25].

The gut endocrine system is composed of several types of EECs that line the GI tract. These EECs respond to the consumption of food by secreting gut peptides and other signaling molecules, such as serotonin. This occurs most frequently after the consumption of carbs and fats. The subtypes of EECs are determined by both the location of their secretions and the chemical class (including peptides) of their secretions (Figure 2). EECs make up a little less than one percent of the epithelial cells that line the intestinal lumen. Enterochromaffin, also known as EECs, was recently found to govern serotonin release onto primary afferent nerve fibers by Bellono et al. in an excellent study. These nerve fibers extend into intestinal villi and express 5-HT3

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Figure 3 Gut microbes and fundamental morphological processes Gut microorganisms and their products drive or influence fundamental developmental processes. (A) Different ways allow gut microbes to send signals to the brain. (B) The colonization of GF animals or the reduction of gut flora by antibiotics influence fundamental neurodevelopmental processes. Neurogenesis, microglial development, myelination, and the expression of neurotrophins, neurotransmitters, and their receptors are all processes that are affected by alterations to the blood-brain barrier (BBB). Reproduced with permission. Sharon G, Sampson TR, Geschwind DH, Mazmanian SK. The Central Nervous System and the Gut Microbiome. Cell 2016;167(4):915 – 932. Copyright 2016, Elsevier.

receptors, which enables them to sense and send information from the gut to the neurological system. Peptides, which are signaling molecules in EECS and are produced by specific brain cells (where they are known as neuropeptides), are short amide-bonded chains of amino acids (typically including roughly 50 amino acid residues). Peptides can bind to receptors at a distance from the site of their release; nevertheless, they are efficiently broken down by endogenous enzymes, which prevents them from building up in tissues. In addition to this, mammals contain more than a hundred distinct peptides, the majority of which are responsible for controlling satiety and digestion. These peptides are particularly important for the gut-brain relationship. Not only are there peptides that govern the gastrointestinal tract in EECS and the central nervous system, but there are also peptides that control the gastrointestinal tract in the enteric nervous system. Intrinsic sensory neurons, for example, are known to express calcitonin gene-related peptide as well as tachykinins, which are commonly referred to as substance P. The secretion of gastrin from G cells in the stomach is triggered by gastrin-releasing peptide, which controls the formation of gastric acid and the motility of the intestinal tract. The interaction of vasoactive intestinal peptide with nearby postsynaptic targets is necessary for the regulation of the circadian cycle, as well as the suppression of the synthesis of gastric acid and the absorption of intestinal lumen. It is reasonable to assume that these peptides can perform additional functions in addition to their primary signaling role given the widespread expression of peptides and their receptors in the brain as well as the stomach, as well as the ease with which they can enter the bloodstream. This provides evidence that gastrointestinal peptides may play a role, albeit most likely an indirect one, in neuropsychiatric illnesses. The dynamic profile of gut peptides includes their direct link with mood disorders, which suggests that this axis may be a target for psychobiotics to prevent and treat problems of this nature [25–28].

**Probiotics and prebiotics**

The word "probiotic" originates from the Greek phrase "pro bios," which translates as "for life." Since ancient times, the products of lactic acid fermentation have been acknowledged for the positive effects that they have on human health. Élie Metchinski, a scientist who won the Nobel Prize and has written extensively about probiotic bacteria and the positive benefits they can have, is credited with the development of the first concept. He believes that the lactic acid bacteria that are normally found in the human stomach are responsible for the potential benefits that can increase longevity. In modern parlance, "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host" is how probiotics are described. Lactobacillus and Bifidobacterium strains make up many of them, with some Streptococcus and Enterococcus tossed in for good measure [27]. Prebiotics provide many health benefits, including anti-inflammatory activity, enhanced intestinal health (by eradicating dysbiosis and sealing the intestinal epithelium), immune system stimulation, lactose intolerance inhibition, cancer prevention, and favorable effects on mental health [28–30]. It is essential to emphasize the fact that most bacteria are first obtained during birth, and that diet is then responsible for their maintenance and growth after that point. A diet that is well-rounded can help maintain a healthy balance of microorganisms in the body. When dealing with a situation like this, it is possible to take additional dosages of probiotic bacteria. "Psychobiotics" are defined as "probiotics that, when consumed by people with psychiatric illnesses in sufficient quantities, generate a health benefit." This definition was provided by Dinan et al. Research conducted on both animals and humans demonstrates that psychobiotics improve gut health, as well as modify serum cytokine, cortisol, and brain neurotransmitter and protein levels. These changes, in turn, lead to alterations in behavioral parameters. There are numerous microorganisms that have the potential to regulate neuroactive metabolites. Some of these metabolites include catecholamines, 5-hydroxytryptamine (5-HT), and gamma-aminobutyric acid (GABA). These metabolites all play significant roles in the functioning of the brain and the mental health of an individual. It is common knowledge that the amino acid GABA can lessen the amount of activity occurring in the brain by inhibiting synaptic transmission and elevating the membrane potential of neuronal membranes. Lower levels of the neurotransmitter gamma-aminobutyric acid (GABA) have been associated with mood and anxiety disorders [31, 32]. This explains why impairment of the GABAergic system has been connected to mood disorders. Lactobacillus plantarum, Lactobacillus paracasei, Lactobacillus rhamnosus, and Lactobacillus brevis are examples of GABA-regulating bacteria that can be found in dietary sources [33–35]. The amounts of serotonin can also be influenced by particular bacterial strains. Second, the amino acid tryptophan is used in the production of the monoamine neurotransmitter serotonin. Enterochromaffin cells in the intestine are responsible for the production of the vast majority of 5-HT. The neurotransmitter serotonin is involved in a wide variety of physiological processes, in addition to its role in the regulation of mood and cognition. This helps to explain why an imbalance in the serotonergic system is considered to be one of the primary causes of depression. There are a number of bacterial species that are known to be able to disrupt the 5-HT pathway. These bacteria include Escherichia coli, Klebsiella pneumoniae, Morganella morgani, Lactobacillus plantarum, Lactococcus lactis subsp. cremoris, and Streptococcus thermophilus. A select group of bacteria, such as Bifidobacterium species, Escherichia coli, Staphylococcus aureus, Klebsiella pneumoniae, and Morganella morgani, are responsible for regulating catecholamines including adrenaline, noradrenaline, and dopamine. Other bacteria in this group include Morganella morgani. Some of these strains have been included in enhanced functional foods with the goal of improving health and having a significant impact on the regulation of neurometabolites [35–38]. Look at Figure 5.

Originally, the term "prebiotic" referred to a "non-digestible food ingredient that benefits the host by specifically stimulating the growth and/or activity of one or a limited number of bacteria already resident in the colon." Prebiotics are beneficial to the host because they encourage the growth of beneficial bacteria that are already present in the colon. Nevertheless, as time has passed and science has progressed, the definition of the term has been expanded to embrace the stimulation of bacteria not only in the colon but also in other parts of the human body [39]. This is because the phrase was originally...
only used to refer to the stimulation of bacteria in the colon. According to the International Scientific Association for Probiotics and Prebiotics, “a substrate that is utilized by host microorganisms with the view to conferring a health benefit” is the definition of a prebiotic. A wide variety of foods and natural products contain prebiotics, which is a type of carbohydrate that cannot be digested by the human body. This category contains oligosaccharides, fructans (fructooligosaccharides, inulin), and galacto-oligosaccharides, amongst other related substances. The fermentation of prebiotic carbohydrates by bacteria results in the production of short-chain fatty acids (SCFAs) such as butyric acid, acetic acid, and propionic acid. Both prebiotics and short-chain fatty acids (SCFAs) play an important part in maintaining the health of the intestines by acting as immune system boosters, sources of fuel for the gut microbiota, and antagonists of pathogenic gut bacteria. According to the findings of a number of studies, prebiotics not only help reduce the severity of diseases such as mental disorders, diabetes, irritable bowel syndrome (IBS), viral infections, and colon cancer, but they also help prevent the beginning and progression of these diseases [40–42].

**Postbiotics**

Although interest in exploring the effects of postbiotics has been heating up in recent years, the word “postbiotic” has been in use for over 20 years. Postbiotics are described as “a preparation of inanimate microorganisms and/or their components that confer a health benefit on the host” by the International Scientific Association for Probiotics and Prebiotics (ISAPP). There are many names for non-living microbes that could promote or maintain health, such as para probiotics, heat-killed probiotics, metabolites, and bacterial lysates [43, 44]. Each of these names refers to a specific type of non-living microorganism. Postbiotics are described as microbial cells that have been purposefully inactivated, with or without metabolites or cell components, that contribute to health advantages that have been established in scientific research. The definition of postbiotics was developed by a group of industry professionals. They point out that cellular components, such as pili and other components of the cell wall, are not considered to be postbiotics, even if several metabolites of bacteria, such as lactic acid, proteins, vitamins, and SCFAs, may be present in postbiotic preparations. In the same way that probiotics do, postbiotics have the potential to enhance epithelial barrier function, affect host microbiota, regulate immunological responses, modify systemic metabolism, and signal through the nervous system [42–45, 48]. Look at picture number 6.

A group of sixty young adults who were in the process of preparing to take the national exam for medical practitioners participated in a study to investigate the efficacy and health advantages of long-term supplementation with heat-inactivated, washed Lactobacillus gasseri CP2305 (CP2305). Thisconceptual framework has been employed in a great number of studies that investigated persistent mental strain; hence, it must be valid. For instance, a total of 41 males and 19 females took part in a clinical trial that lasted for 24 weeks and was controlled using a placebo and double blinding. During this time, the participants took either tablet containing CP2305 (1 , 1010 bacterial cells pre 2 tablets) or tablets containing a sugar pill once a day, [49–51]. The investigation indicated that CP2305 considerably reduced anxiety and sleep disturbance when compared to the placebo. The questionnaires used to measure mental and physical states demonstrated that the experiment's results. The inclusion of CP2305 in the diet was also shown by fecal microbiota analysis to have alleviated the deleterious effects of stress on the development of Streptococcus spp. and the reduction of Bifidobacterium spp. The findings of the study, which indicated that Lactobacillus gasseri CP2305 assisted young adults in coping with stressful situations, call for additional research into the mechanism that underlies these therapeutic advantages. In a second study, the effects of supplementation with postbiotic Lactobacillus paracasei MCC1849 (LAC-ShieldTM) on the mental health and cold symptoms of healthy individuals were studied. Ten hundred and ten milligrams of dried, heat-inactivated L. paracasei MCC1849 cells (10LP), three hundred and ten milligrams of dried, heat-inactivated L. paracasei MCC1849 cells (30LP), and ten milligrams of each of the following: For a period of twelve weeks, either the L. paracasei MCC1849 cell powder (30LP) or a placebo was utilized [52, 53].

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