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# The Impact of brain-gut microbiota composition on depression
# A new perspective

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**Abstract**

**Introduction and Purpose:** Recently, depression has significantly marked its presence in both the scientific and social spheres due to its connections with suicides. According to WHO data, it affects approximately 280 million people and as much as 5% of all adults worldwide. The primary treatment for this condition includes drugs such as SSRIs and SNRIs. However, in the last decade, numerous studies have demonstrated the impact of gut bacteria dysbiosis on brain functions and, consequently, its role in the pathogenesis of depression. Therefore, this paper focuses on the mechanisms and factors that negatively or positively affect the state of gut microbiota leading to depression, as well as on modern intervention methods in this field.

**State of Knowledge:** Recent clinical studies highlight that gut bacteria, in connection with the immune system, can influence brain function, including the pathogenesis of depression. According to scientists, this influence occurs through bacteria present in the gut, their metabolism, and its products. However, depending on the composition of the gut microbiota (i.e., bacterial taxa), the substances produced in the gut can have a positive or negative impact on brain function regulation, thus contributing to an increased risk of depression symptoms or to their alleviation and remission.

**Summary:** This review paper describes the currently known factors that negatively or positively affect the maintenance of a healthy gut microbiota composition, their effectiveness in microbiome modulation, and potential methods for treating gut bacterial dysbiosis, which often coexists in patients suffering from depression. It is important to note the significant individual variability in the context of changes in the depressive microbiome and the response to various modification methods. Therefore, when selecting appropriate therapy, cooperation with the patient will be crucial to achieve satisfactory results and avoid adverse effects.

**Keywords:** Microbiota transplantation, depression, "depression-associated microbiome," gut-brain axis, dietary interventions in depression.

## The Gut-Brain Axis

Depression is a common mental disorder characterized by high morbidity, disability, and mortality. According to the World Health Organization (WHO), around 350 million people worldwide suffer from depression. Currently, depression is considered the second most common disease after heart diseases, causing a significant burden on society, families, and individuals. Major depressive disorder (MDD) is an illness characterized by anxiety, reduced or delayed thinking. Several other symptoms also occur, such as irritability, frustration, feelings of worthlessness or guilt, low energy levels, insomnia, excessive sleepiness, changes in appetite or weight, difficulty concentrating, suicide attempts, or suicidal thoughts. Currently, pharmacological therapy is the main method of treatment for depression, but it is hindered by side effects, addiction, high cost, and poor patient compliance. Additionally, it often happens that pharmacological treatment is unsatisfactory, and the quality of life of patients is significantly reduced.

The idea that the brain and gut engage in continuous, bidirectional communication was recognized as early as Ancient Greece, where philosophers such as Hippocrates, Plato, and Aristotle postulated that the brain and the rest of the body are intrinsically connected [1].

This belief led to the understanding that to study disease processes, one should consider the whole person rather than isolated organ systems. It wasn't until the 1840s that William Beaumont experimentally demonstrated that emotional state affects the rate of digestion, thus implying the existence of the gut-brain axis. Although this concept was later acknowledged by prominent modern biologists such as Darwin, Pavlov, James, Bernard, and Cannon [2], it was only in the early to mid-20th century that the first scientifically recorded observations correlating changes in gut physiology with emotions were made. These studies were limited by simple techniques and a lack of research on the reciprocal effects of changes in gut physiology on mental functions.

New data have confirmed the connections between brain health and the gut, suggesting several mechanistic foundations. Changes in gastrointestinal (GI) function and GI symptoms have been reported to accompany an increasing number of central nervous system (CNS) disorders, and as in the case of Parkinson's disease, GI dysfunction can occur even before the appearance of central neurological symptoms [3]. Similarly, GI symptoms are an important component of brain-gut interaction disorders, such as irritable bowel syndrome (IBS), which is often associated with psychological symptoms and psychiatric diagnoses. Moreover, with the advent of brain imaging, the mutual interactions can be visualized for the first time, showing that stimuli from the gut can activate key brain areas involved in emotion regulation [2].

Most aspects of GI physiology are under neural control, exerted by an extensive network of internal neurons and enteric glial cells that extend throughout the enteric nervous system (ENS), the GI smooth muscle, and the lamina propria of the mucosa, as well as by external innervation through primary afferent and autonomic fibers that connect the gut with the spinal cord and brain [4]. Even though the ENS can regulate gastrointestinal peristalsis mostly independently of CNS input, GI motility is also regulated by external factors related to the ENS, including the brain [5] and other sections of the autonomic nervous system (ANS), the gut-associated immune system, and the gut microbiome. The influence on the gut is not a one way route, as the gut also sends information to these various systems through complex pathways that function as bidirectional channels for homeostasis, and alterations in this communication are associated with diseases. Proper gut function is therefore critical not only for long-term survival but also for the homeostasis of the gut-brain axis. Exactly how gut-brain communication occurs in health and disease in humans remains an active area of research.

Our guts are inhabited by trillions of microorganisms, including bacteria, viruses, and fungi. Recent studies show that the gut microbiome may play an important role in the functioning of distant organs, including the brain [6] . The significant role of the gut microbiota in the pathogenesis of depression has been highlighted for a long time. However, a precise cause-and-effect relationship has not been demonstrated. It is hypothesized that depression is associated with microbial dysbiosis, defined as a change in microbial diversity due to an imbalanced microbiota and consequent functional changes [7] . One piece of evidence

supporting this hypothesis is the observed increased risk of severe mental disorders (e.g., psychosis, depression) following antibiotic therapy, even 5-10 years after treatment. A recent systematic review showed a link between antibiotic use and subsequent development of depression [8]. This is due to the impact of antibiotics on reducing the diversity of the gut microbiota.

Additionally, an unhealthy diet and exposure to environmental factors that affect the composition of the gut microbiota have been shown to be highly associated with the increased prevalence of depression in recent years.

Although there is increasing evidence for the role of the gut microbiota in the pathogenesis of depression, the ultimate role of dysbiosis still holds many mysteries. It remains unclear whether microbial dysbiosis is inherently causative or merely a consequence of pathological changes associated with depression. In recent years, emphasis has been placed on research into the modulation of the gut microbiome [9]. The ultimate goal of this research is to develop microbiota-based interventions for the treatment of depression, but the path to implementing clinical microbiological therapies is still long. Until then, antidepressants will continue to be the cornerstone of depression treatment.

At this point, we should not only focus on the development of microbiota-targeted interventions but also on the impact of the gut microbiota on the effectiveness of antidepressants. Therefore, in this review, we aim to describe the mechanisms of dysbiosis formation and the influence of factors (such as diet, medications, and therapies) that can negatively or positively affect the development of gut microbiota dysbiosis. We believe that the potential present in these factors could lead to the transformation of clinical therapy in the treatment of depression.

**Depression and Gut Microbiota Dysbiosis**

The number of studies showing the relationship between dysbiosis and the occurrence of depression is increasing (Fig. 1). These studies demonstrate differences in the composition of the gut microbiota between healthy individuals and those with depression, particularly in the microbial richness of specific taxa and their diversity [10]. The most frequently observed changes include an increase in pro-inflammatory bacteria and a decrease in those with anti-inflammatory effects. This indicates a similarity to other conditions associated with systemic and gut inflammation, further supporting the inflammatory hypothesis of depression. The gut microbiome in depression is most affected in bacteria from the phyla Firmicutes, Actinobacteria, and Bacteroidetes, with a notable increase in the Bacteroidetes to Firmicutes ratio. These changes are characterized by an enrichment of Bacteroides and a reduction in populations of Blautia, Faecalibacterium, and Coprococcus [10]. Additionally, a significant focus has been on the increased presence of Eggerthella and the decreased presence of Sutterella, which have been repeatedly observed in patients with depression. It is hypothesized that due to lifelong evolution within the host, the aforementioned changes in the gut microbiota become increasingly pathogenic, leading to potential differences in microbiological features in patients with depression of different ages.

There are also regional variations in the composition of the gut microbiota - several taxa have been predominantly identified in patients from China, such as increased numbers of

Eggerthella and decreased numbers of Coprococcus and Fusicatenibacter [11]. It should be noted that studies still do not provide information about the causality of this condition. In studies involving the transplantation of gut microbiota from patients with depression into rodents, it was observed that microbial dysbiosis precedes the onset of depression and may play a causal role in depression. However, there is also evidence that the pathological changes occurring in depression can cause dysbiosis and lead to its exacerbation, creating a vicious cycle in the described mechanism [12].

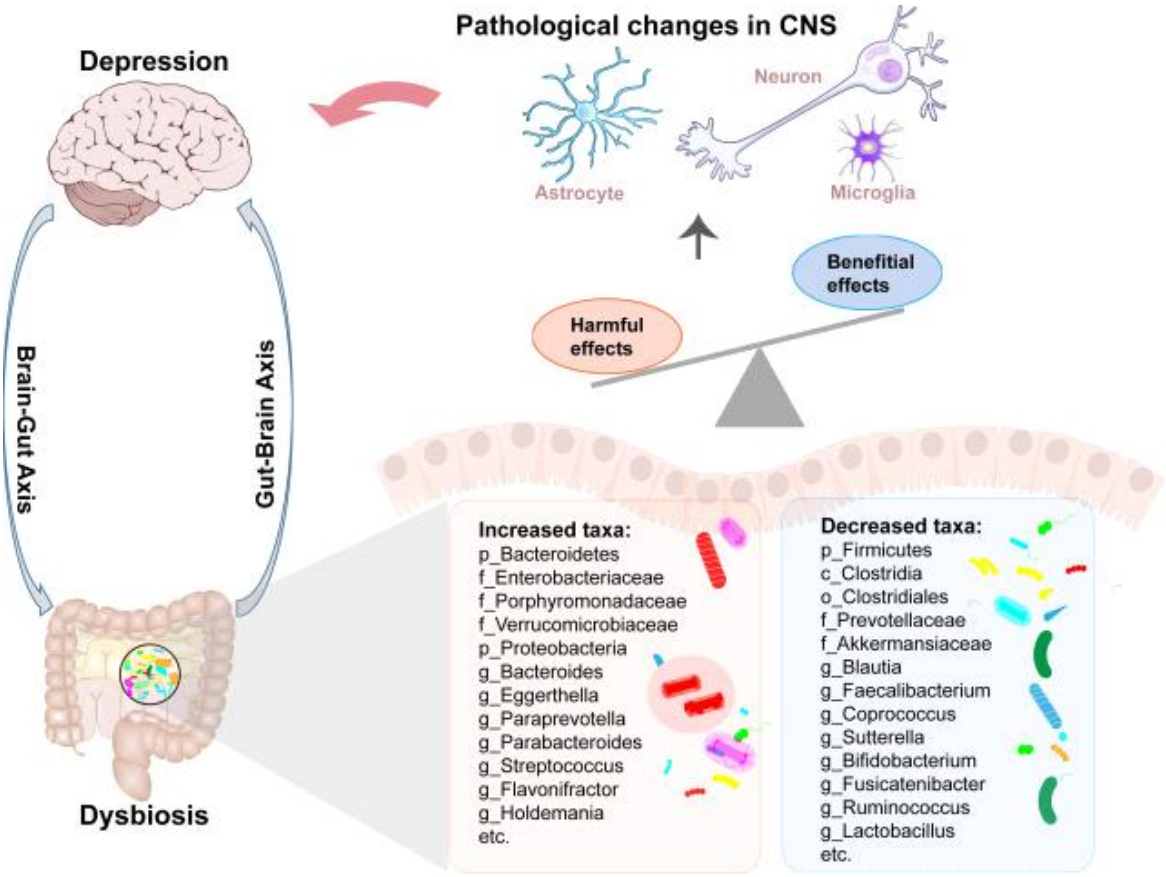


**Fig. 1** The association between dysbiosis and central pathological changes during the development of depression. CNS, Central nervous system.

## Metabolites

Gut bacteria produce many important mediators involved in interactions between the gut microbiota and the host. These include microbial metabolites resulting from the fermentation of substances from consumed food, host molecules modified by bacteria such as bile acids (BAs), and molecules directly produced by bacteria [13]. Changes in the composition of the gut microbiota in individuals with major depressive disorder (MDD) play a significant role in the pathogenesis of depression, leading to changes in the microbial metabolome. Metabolites originating from the gut microbiota have an ambiguous impact on depression. Short-chain fatty acids (SCFAs: acetate, butyrate, and propionate) are strongly linked to depression. It has been reported that SCFAs are depleted in patients with MDD, while their administration has shown antidepressant effects by improving depression-associated gut permeability and hypothalamic-pituitary-adrenal (HPA) axis reactivity, particularly butyrate [14]. There is also

strong evidence that SCFAs can cross the blood-brain barrier to increase levels of brain-derived neurotrophic factor and restore neurotrophin expression.
Neurotransmitters (e.g., serotonin and gamma-aminobutyric acid), produced directly or indirectly by the gut microbiota, can affect emotional behavior by modulating local gut physiology and regulating the function of distant organs once absorbed into the bloodstream.

Furthermore, BAs exert effects by binding to their dedicated receptors, the farnesoid X receptor, and Takeda G protein-coupled receptors 5, which regulate the body's physiological metabolic responses. Disturbances in bile acid metabolism have been observed in individuals with MDD; concentrations of BAs, especially those modified by the microbiota, are negatively correlated with the occurrence of severe depressive symptoms. This suggests that higher BA levels may have a protective role in depression. The production of BAs is primarily associated with three taxa: Turicibacterales, Turicibacteraceae, and Turicibacter, whose populations decrease in individuals with depression.
Another important observed metabolite of the gut microbiota is trimethylamine-N-oxide (TMAO) derived from choline [15]. TMAO can cross the blood-brain barrier, influencing brain pathology and the development of neuropsychiatric disorders. There is a positive correlation between TMAO levels in blood samples and the severity of depression. Lipopolysaccharides (LPS), present in the outer membrane of all Gram-negative bacteria, also warrant attention as they cause microglial activation [16]. Lactate and B vitamins also play roles in the pathogenesis of depression [16]. The levels of these metabolites reflect, at least partially, the metabolic capacity of the gut microbiota.

**Antibiotics**
In modern times, where antibiotics are frequently used to treat many infectious diseases, their destructive impact on gut microbiota is well-known. One example is the common complication of Clostridium difficile-induced diarrhea following prolonged antibiotic therapy. Consequently, their use is suspected to play a significant role in increasing the risk of depression.
Exposure to medications is one of the critical modifying factors, with antibiotics being among the most common and potent. They can cause significant disruptions to gut microbiota, beginning within a few days of starting therapy and potentially lasting long after treatment has ended. For example, the use of ciprofloxacin is associated with the loss of gut microbial diversity and changes in microbiota composition within 3 to 4 days [17], and the effects of a short (7-day) clindamycin therapy on human gut microbiota can persist for up to 2 years, with many key taxa not returning to their original composition [17]. Studies also observe reductions in SCFA levels in the gut following exposure to certain antibiotics. There are numerous reports of the first occurrence of depressive symptoms in individuals after taking antibiotics, sometimes even leading to suicidal thoughts [17]. A useful piece of information in this context is that taking probiotics (often accompanying antibiotic use) has been associated with a noticeable reduction in depressive symptoms.

**Prebiotics**

Prebiotics are substrates selectively utilized by gut microbiota that confer health benefits to the host. Their intake promotes the growth of beneficial bacteria. Studies have clinically confirmed the antidepressant effects of various prebiotics [18]. The most well-documented prebiotics in depression therapy include fructooligosaccharides (FOS), galactooligosaccharides (GOS), polyphenols, inulin, and compounds from vegetables and herbs. In mouse studies, chronic administration of FOS and GOS prebiotics improved stress-induced depressive behaviors in male C57BL/6J mice [19].

The improvement in depressive behaviors was accompanied by normalization of gut microbiota, reduction of pro-inflammatory cytokines, and increased levels of acetate and propionate in the cecum, changes that are associated with behavioral improvement [19]. However, the studies are inconsistent in this matter. In a previous RCT, the effects of supplementation with probiotics (L. helveticus and B. longum) and prebiotics (GOS) on depression remission in patients with major depressive disorder (MDD) were compared. This study found that 8 weeks of probiotic supplementation, but not prebiotic supplementation, improved depressive symptoms [20]. In another RCT, administration of 4G-β-D-galactosylsucrose for 24 weeks improved self-efficacy in patients with depression but did not affect their depressive symptoms. Prebiotics do not exert direct effects on the body but indirectly benefit the host's health by promoting the growth of probiotics. Therefore, prebiotics are often used in combination with probiotics in the treatment of depression.

**Psychobiotics**

Psychobiotics are a class of probiotics that specifically offer the most benefit to individuals suffering from psychiatric disorders, including depression [21]. This concept was proposed in 2013 in response to increasing evidence of the existence of the brain-gut-microbiota axis and its potential effects on psychiatric disorders. Currently defined psychobiotics mainly include probiotics with an adequate amount of beneficial bacteria and prebiotics that, when utilized by the gut microbiota, enhance their positive activity [22]. Psychobiotics are believed to connect many pathways and neural signaling networks, such as the enteric nervous system (ENS) and the vagus nerve, as well as immunological signaling networks involving interactions between microorganism molecular patterns and pathogen recognition receptors (PRRs) like TLRs, C-type lectins, inflammasomes, and SCFAs derived from gut microbiota [23]. Sources of probiotics mainly include human microbiota, fermented foods, soil associated with the environment, plants, and animals, while prebiotics are primarily derived from plants, fungi, animals, microbes, and chemical and physical modifications [22].

Systematic reviews and meta-analyses further suggest that psychobiotics have anxiolytic and antidepressant effects [21]. These effects have been confirmed in animal studies, where the underlying mechanisms of psychobiotics' antidepressant action were also investigated. In one study, the use of the MCC1848 strain from Lactobacillus helveticus alleviated depressive behaviors induced by mild social stress [24]. In another study, the Bifidobacterium breve CCFM1025 strain exhibited antidepressant-like effects in a group of animals in the CUMS model, as evidenced by improved depressive behaviors, transformation of gut microbiota communities, reduced inflammation, and balanced HPA axis hyperactivity [25]. Additionally, the CCFM1025 strain was noted to increase BDNF (brain-derived neurotrophic factor) levels

while reducing the activity of stress-related proteins and enhancing levels of SCFAs and 5-hydroxytryptophan [25]. Recent studies and reviews have focused primarily on Lactobacillus and Bifidobacterium strains, demonstrating that different strains have varying effects on mental health [23]. Besides the mentioned strains, many others within psychobiotics also improve depression. In another study, the Akkermansia muciniphila strain was used in a CRS depression mouse model, showing that it alleviated the depressive phenotype by restoring gut microbiota balance and metabolites and regulating corticosterone, dopamine, and BDNF levels [26].

Despite many promising studies, some have reported no effects of psychobiotics without improvements in depressive behaviors. However, plant-derived psychobiotics targeting the brain-gut-microbiota axis have already been developed and hold great potential as new antidepressant drugs [21].

**Fecal Microbiota Transplantation (FMT)**

FMT was developed to achieve a healthy composition and function of the gut microbiota, similar to probiotics. It is a procedure involving the transfer of a stool sample from a healthy donor to the intestine of the recipient. So far, it has been successfully used in the treatment of gastrointestinal and neuropsychiatric diseases [27]. In an animal study, transferring the fecal microbiota of healthy donors to anxious mice resulted in a reduction of anxiety and depression symptoms. Currently, attention is being paid to the connection between the occurrence of irritable bowel syndrome (IBS) and other gastrointestinal issues with depression. Fecal microbiota transplantation from a healthy donor reduced the severity of depressive behaviors in IBS patients and also reduced the risk of C. difficile infection in older patients [28]. It should be noted that there is a risk that fecal microbiota may be transferred from an unhealthy donor due to an error. In such cases, the FMT performed could cause unwanted effects, such as the development of depression in the recipient. According to a report, fecal microbiota transferred from patients with rheumatoid arthritis (RA) and depression caused depressive behaviors with an inflammatory background in mice, which in this case were recipients [29]. This highlights the need to take special precautions when performing the fecal microbiota transplantation procedure.

**Diet**

Improper nutrition impacts the pathogenesis and development of many diseases, including liver diseases, cardiovascular diseases, neurodegenerative disorders, metabolic syndromes, and psychiatric disorders, including depression. Some studies have highlighted the relationship between a diet rich in calories, simple sugars, saturated fats, along with low content of fruits, vegetables, fiber, and antioxidants, and increased risk of disease development, severity, and chronicity of symptoms [30]. Furthermore, the significant role of diet in the gut-brain-microbiota axis, which is involved in the pathogenesis of psychiatric disorders, including depression, is well-documented. Considering this evidence, along with other data suggesting the potential of a healthy diet in reducing the risk of depression and recurrent depressive symptoms, there is a suggestion that adopting healthy dietary habits [31],

along with adherence to selected diets such as the Mediterranean or ketogenic diet, may protect against the onset of depression.

**Mediterranean Diet**

The term Mediterranean diet (MD), one of the most globally recommended healthy eating patterns, refers to the dietary habits of populations surrounding the Mediterranean Sea. It is characterized by high consumption of fruits, vegetables, nuts, grains, legumes, and olive oil, moderate consumption of dairy products, poultry, and eggs, and low consumption of red meat, saturated fats, and wine.

Its effective impact is noted in the prevention and treatment of many diseases including cardiovascular diseases, neurodegenerative disorders, diabetes, metabolic syndrome, as well as obesity and psychiatric disorders such as depression. This is directly related to the abundance of nutrients with antioxidant and anti-inflammatory properties in this diet [32].

Regarding depression, components of the Mediterranean diet rich in vitamins B, C, and E, folic acid, selenium, magnesium, omega-3 polyunsaturated fatty acids (n-3 PUFAs), and phytoestrogens have shown protective effects [33]. The precise mechanisms of the positive impact of the Mediterranean diet are not fully understood, but recent evidence suggests that modulation of inflammatory pathways, oxidative stress, and the gut-brain-microbiota axis may provide a possible explanation, as individuals with depression have been found to exhibit elevated inflammation, oxidative stress, and dysbiosis. Evidence highlights a probable link between the anti-inflammatory and antioxidant potential of the Mediterranean diet and depression, as well as its impact on gut microbiota composition and restoration, likely due to the synergistic interaction among the diet's nutrients. For example, consumption of olive oil containing anti-inflammatory and antioxidant bioactive polyphenols like tyrosol may have neuroprotective effects on mental health by reducing levels of pro-inflammatory cytokines (such as IL-1, IL-6, TNF-α, and CRP), restoring antioxidant defense, scavenging free radicals, and influencing the metabolism of serotonin and dopamine through normalization of their levels [34]. Consumption of fruits, vegetables, and whole grains rich in fiber, folic acid, vitamins B, C, and E, and carotenoids may counteract inflammation and oxidative stress, modulate gut microbiota, and synthesize neurotransmitters influencing mood, appetite, and cognitive functions. Eggs in the diet contain vitamin B12, folic acid, tryptophan, and choline, which play a crucial role in serotonin, dopamine, and norepinephrine production [35]. Additionally, consumption of n-3 PUFAs (docosahexaenoic acid, eicosapentaenoic acid, and alpha-linolenic acid), found in fish and plant oils, may exert protective effects against the risk of depression and depressive mood [35] by regulating the hypothalamic-pituitary-adrenal axis, reducing the production of pro-inflammatory markers (such as TNF-α, IL-1β, and IL-6), and increasing levels of neurotrophic factors (such as BDNF), which play a crucial role in the development of the nervous system, neuron differentiation, and modulation of cognitive functions.

Based on this data, numerous cross-sectional studies have been conducted to investigate the relationship between adherence to the Mediterranean diet and potential reduction in depressive symptoms among individuals clinically diagnosed with depression. However, despite many promising findings highlighting the positive impact of adherence to the

Mediterranean diet in preventing depression or alleviating its symptoms, a small number of studies did not show a significant influence of adherence to the Mediterranean diet on reducing the risk of depression [35].

In conclusion, while a few studies have not found a clear link between adherence to the Mediterranean diet and the risk of depression, most studies suggest that adopting the Mediterranean diet, alongside pharmacological and behavioral therapies, may represent a potential complementary approach to counteracting depressive symptoms and even preventing depression itself. Additionally, it is important to note the lack of clinical studies assessing changes in gut microbiota composition in individuals with depression adhering to the Mediterranean diet.

Such studies could shed light on how and whether Mediterranean dietary intervention could transform gut microbiota components and functions and evaluate whether such an approach could be effective in preventing the development of this psychiatric disorder.

**Ketogenic Diet**

The ketogenic diet (KD) is a dietary pattern characterized by low carbohydrate intake, adequate protein consumption, and high fat content, which induces a state of ketosis where ketone bodies are utilized by tissues (including the brain) as an alternative energy source to glucose [35]. This diet is associated with a range of beneficial effects, including weight loss, improved glycemic control, and reduced risk of chronic diseases. Nevertheless, attention must also be paid to side effects such as constipation, nutrient deficiencies, changes in blood lipid levels, and the potential for ketoacidosis.

The ketogenic diet shows potential in the treatment of depression due to the fact that the brains of some individuals suffering from this condition are unable to efficiently utilize glucose as an energy source, leading to a decreased rate of brain metabolism and reduced production of mood-modulating neurotransmitters such as dopamine and serotonin [35]. According to researchers, increasing fat intake while simultaneously restricting carbohydrate intake causes the brain to adapt to utilizing ketones derived from fatty acid metabolism as an alternative energy source, which may positively impact mood regulation and brain function [35].

Animal studies highlight the positive impact of the KD on reducing inflammation and oxidative stress [35]. Guan et al., in a mouse model of depression, found that the KD has anti-inflammatory and antioxidant effects, which may contribute to reducing microglial activation (inflammatory cells) in the lateral habenula, a small brain region involved in mood regulation and reward processing [35]. Additionally, an increase in the neurotransmitter GABA has been shown during KD usage, a deficiency of which is often associated with anxiety and depression [36]. Besides GABA, the discussed diet may also increase glutamate levels, a neurotransmitter responsible for synaptic plasticity [35]. Finally, the ketogenic diet also contributes to an increase in brain-derived neurotrophic factor (BDNF), which promotes neuron differentiation, survival, and synaptic plasticity. However, the mechanism behind this regulation requires further research [35]. In contrast to previously listed studies, Huang et al. did not find significant effects on anxiety and depression in adult mice after 3 months of KD use [37].

Some studies suggest that the KD may alter gut microbiota composition, promoting the growth of species capable of utilizing ketone bodies as an energy source [35]. Moreover, it has also been reported that the KD reduces the relative abundance of harmful microbes belonging to the Firmicutes type (e.g., Lachnobacterium), while promoting the proliferation of A. muciniphila, a species of microorganisms from the Verrucomicrobia type [35]. It is worth mentioning that the A.muciniphila's ability to degrade mucin and produce SCFAs may account for the benefits associated with KD. In another study involving children with epilepsy, KD was associated with reduced levels of specific types of bacteria such as Bifidobacterium, Enterococcaceae, and Actinomyces [38]. Although the SCFA-producing bacterium Bifidobacterium is a well-known probiotic microorganism, its reduction after KD has been reported in several independent studies [35]. Given the limited number of these studies and their inconsistencies, further research is needed on the potential link between KD, gut microbiota, and depression.

In summary, KD may be beneficial for depression due to its influence on brain energy metabolism, inflammation, oxidative stress, neurotransmission, and gut microbiota. However, further research is necessary to better understand its real benefits.

## Conclusions

The gut-brain-microbiota axis is a complex and interactive system that includes networks of neural signals, immune signals, and chemical signals. All these networks appear to be involved in the pathophysiology of depression. Specifically, the autonomic nervous system, inflammatory activity, microglia, gut microbiota composition, and short-chain fatty acids (SCFAs) have drawn increasing interest in research aimed at understanding how the gut-brain-microbiota axis contributes to depression.

The mutual relationships between gut microbiota function and depressive disorders represent a milestone in defining the pathophysiology and disease progression, paving the way for modern clinical interventions encompassing diagnosis, treatment, and prognosis. Among these methods is the implementation of gut microbiota-based biomarkers for diagnostic, prognostic, and predictive purposes, as well as new therapeutic options aimed at modifying gut microbiota composition. Among these options, non-invasive and widely accepted prebiotics, probiotics, and dietary interventions (especially the Mediterranean diet) can significantly enhance the efficacy of standard antidepressant medications while reducing their side effects.

Simultaneously, education of both society and the medical community regarding harmful factors affecting the gut-brain axis balance, such as avoiding excessive and sometimes unnecessary antibiotic therapy or unhealthy diets, is crucial. It is worth noting that neuropsychiatric medications have been in use for a long time but have their limitations. Despite a large portion of patients receiving these medications, a significant number do not show any clinical benefit, which is a major concern associated with the widespread use of antidepressants. Therefore, increasing understanding of the mutual influence between medications taken and dietary patterns on gut health will be crucial for developing new depression treatment methods in the future.

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