

The Impacts of The Intestinal Microbiome on The Development of Depression and Its Mechanisms

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Abstract. Depression is a chronic mental disease that seriously harms human health and has a variety of complications. A rising body of evidence indicated that communication between intestinal microorganisms and their hosts potentially play an important role in disease and health concerns. Intestinal flora exists in human digestive tract and is abundant, as well as a significant environmental component in the transformation of human physiology. Dysregulation of intestinal flora is related to depression, and its mechanism includes hypothalamic-pituitary-adrenal (HPA) axis, inflammatory response, monoamine neurotransmitter imbalance, neurotrophic factor imbalance, cross-reaction mechanism and so on. This paper summarizes the mechanism and influence of intestinal microflora in depression in recent years, so as to provide some reference for revealing the mechanism of depression.

Keywords: Intestinal Microbe, Depression, Inflammatory Response, Gut-Brain Axis

1. Introduction

In today's rapid economic development, rapid social development of the environment, people's way of life has also undergone a huge change. Due to economic, social, family and other factors, people's life competition pressure is increasing, people's psychological state is depressed for a long time, which also leads to depression and other mental diseases are increasing. Depression is a chronic mental disease that seriously harms human health and has many complications. The World Health Organization (WHO) released data in January 2015 that showed that more than 264 million people worldwide suffered from depression [1]. Depression destroys people's spirits and poses a serious threat to people's lives. Yearly, around 800,000 individuals die from depression, with over 80% of those suffering from depression going undetected [1]. Up to now, the causes of depression are still unclear, but it is almost attributed to a combination of biological, psychological and social factors.

Microbiome and microbiome relate to a particular time and location in all microbial organisms, and microbiome alludes to the study of symbiosis or pathology on plants and animals of microbial ecological units. Gut microbiome, which is a broad term for the microbial community that lives in the human gut, contains trillions of microbes. However, the relationship between humans and intestinal microbes is extremely complex, which is closely related to human health and even affects all aspects of human life. According to the previous studies, Maladjustment or disruption of gut microbes can affect mental health and lead to obesity, allergic diseases and neurological disorders. Mental disorders include anxiety, autism, schizophrenia and depression [2].

Based on research with rodents grown in sterile conditions, psychological response, tension and palliative care systems, and the brain's dopamine system have all been found to be influenced by the gut microbiota [3]. However, the brain-gut axis has traditionally been known to be a two-way message queue, in order to elucidate the interaction among the psyche and intestinal bacteria, the microbial gut-brain axis idea has evolved. Since the mechanism of depression has not yet been clarified, this paper discusses the probable contribution of intestinal bacteria in the genesis of depression from the standpoint of monoamine neurotransmitters, based on the microbial-gut-brain axis mechanism, brain-

derived neurotrophic factors, inflammatory factors, and axis of the hippocampus, endocrine, and pituitary gland.

2. The Mechanism of Intestinal Microbiome on Depression

Microorganisms are closely related to human life and can maintain human health and prevent diseases. It shows a critical role in maintaining health as well as preventing diseases. Intestinal microorganisms play a critical part in the body's regular immunological and epidemic prevention systems, in addition to enhancing digestion and absorption of nutrients. Therefore, the intestinal microbiome is inextricably linked to human health. The bacterial species in the human gut are complex and numerous. The intestinal microbiome contains more than 1000 kinds of intestinal bacteria. Intestinal microbes are classified as good bacteria, dangerous bacteria, or neutral bacteria depending on whether they are pathogenic. Good bacteria, also known as probiotics, can maintain good health and promote the body to absorb more nutrients. Harmful bacteria are also known as pathogenic bacteria, will produce more carcinogens and harm human health. Neutral bacteria, also known as opportunistic pathogens, play a dual role in certain conditions, such as intestinal flora disorder, the decline of human immunity, will lead to the occurrence of some intestinal diseases. More than 90% of them belonged to Bacteroidetes and Firmicutes, while proteobacteria, Clostridium and actinomycetes were less [4]. However, if the number and type of human intestinal microbe change, intestinal flora disorder will result in a series of diseases.

There are many factors that cause depression, environmental factors and the type and number of gut microbes in a person's body will have a certain impact on whether humans suffer from depression, and the microbiology group involved in maintaining digestion, metabolism, and furtherly influenced the body-growth, development, contributed to immune system function and resistance to pathogens and other physiological homeostasis [3]. In order to confirm the link between gut flora structural changes and sadness, researchers conducted a study, there are studies of transplanting fecal microorganisms from depressed patients into the intestines of the guinea pigs of the test animals, and after a certain period of time, the mice show anxiety and anxiety, and at the same time give them favorite foods, but do not show pleasant and excited phenomena, which shows obvious symptoms of depression. In addition, the intestinal flora of mice was studied, and it was found that structural changes in the intestinal flora were accompanied by changes in tryptophan metabolism. After many repeated trials, the results are basically the same, and the intestinal flora appears to play a function in depression regulation [5]. Relevant studies have pointed out that the types and quantities of microorganisms in the intestinal flora of depressed patients are different from those in normal populations, which are specifically manifested in the amount of actinomycetes, Bacteroides, and Proteus is significantly higher. Lactic acid bacteria are the main source of probiotics, mainly including Lactobacillus, Bifidobacterium and Enterococcus, which regulate the homeostasis of the human intestine and maintain the stability of the intestinal flora. The Lactobacillus spp. and Bifidobacterium have a preventive effect on psychiatric diseases, among which the content of Lactobacillus rhamnosus and Bifidobacterium longum has a positive effect on reducing negative emotions such as depression in patients. Lactic acid bacteria may achieve an improving effect on depression through multiple pathways and multiple targets, which indicates that some lactic acid bacteria in the intestine may take a multi-channel and multi-target approach to act on related pathogens to achieve the effect of inhibiting depression [6].

2.1. The Brain-Gut Axis and the Intestinal Microbiota

The impact of the intestinal flora on the inflammatory response, cognitive ability, and personality has attracted attention in recent years. In the previous five years, PubMed has published almost 90% of the more than 4,000 publications on microbiota. Microorganisms inside the colon are considered to interact with gut endothelial cells and phagocytes, causing a variety of neurologic and chemical issues, including inflammatory diseases. A substantial association between the stomach and the mind,

which is developed during the prenatal stage but has an impact on an individual's life, has been demonstrated in several observations and mouse models [7]. The gut microbiota is essential for the transmission of signals between the brain and other organs, as well as in the interaction between human fitness and the chronic inflammation. Every adult has more than 1 kilogram of bacteria in their gut, which weighs about the same as the human brain.

In the past ten years, the relationship involving gut microbes or the central nervous system is increasingly being researched, at the same time, researchers discovered a strong link between the mind, the stomach, and the gastrointestinal system, which has also changed the cognition of the form of emotion and behavior regulation to a certain extent, and expanded the concept of the intestinal brain axis into a microbial intestinal and cerebral neuraxis. The brain-gut axis can be bidirectional regulated to maintain the stability of human physiological state. If the brain-gut axis is dysfunctional, it may lead to a series of physiological and psychological diseases, brain - axis through two-way communication network will be emotional, cognitive function and brain gut function organic together, the autonomic nervous and stomach nervous systems make up this system, and neuroendocrine, intestinal endocrine and immune system [8], and in the pathogenesis of depression most of scholars believe that depression is linked to the body's hypothalamus - pituitary - adrenal axis neuroendocrine. Brain-gut axis may also regulate the immune physiological state of the body through stress response, hormone level changes and immune state [9].

There are some relevant studies, they show that intestinal microbes can be interfered with by many simple methods, such as adjusting diet structure, changing sleep rhythm and taking antibiotics, which can cause disorders of intestinal microbes, and thus more likely to cause depression and other psychological diseases [10]. Pressure correlation between mental illness such as depression, may cause some gastrointestinal disorders, including IBS and IBD, and this effect has a relation with the change of mood affect body through the brain shaft neuroendocrine, enteric nervous disorders, which can lead to an imbalance in the body related metabolites, resulting in related to the intestinal microbial flora disorder symptoms such as abdominal. According to statistics, more than 50% of IBS are associated with depression-like mood, which further confirms the interaction between intestinal microbes and depression [11].

Studies have shown that in mice after acceptance of intestinal microbiome cannot absorb antibiotics, corresponding mice intestinal microbial flora structure will change, and the central nervous system of BDNF expression increased, this study suggests that gut microbes change may cause the neurotransmitter, which cause some mental illness [12]. Monoamine neurotransmitters mainly include 5-HT (5-hydroxytryptamine), norepinephrine, dopamine, etc. It is generally believed that the generation of positive emotions and emotions is due to the secretion of sufficient monoamine neurotransmitters in the brain. When monoamine neurotransmitters are insufficient in the brain, depressive symptoms will be caused, and the increase of these neurotransmitters will produce antidepressant effects [13]. Taking 5-HT as an example as figure 1 shown, the intestine releases approximately 90% of 5-HT of the body. Intestinal flora can produce tryptophan or affect its metabolism and synthesis, Tryptophan as a precursor of 5-HT, gut microbes activate the enzyme indoleamine 2,3 dioxygenases, IDO (indoleamine 2,3 - two-plus oxygen), dog urine acid, by reducing the content of tryptophan, resulted in a reduction in the amount of 5-HT, triggering depressive symptoms. In addition, 5-HT_{1R} (5-hydroxytryptamine receptor) has an essential role in the advancement of depression. The receptor is found in the hippocampal region of the brain, which is related to mood. 5-HT regulates the central nervous system through the trigeminal nerve and thus alleviates depression symptoms [14].

2.2. Mechanism of inflammatory response

Gut microbes are a key factor affecting the body's immune function and building the immune system. If the intestinal microbiome is disturbed, the immune system will have disorders and disorders. And once the immune system is out of whack, it will lead to an inflammatory response. Studies have pointed out that when intestinal flora is disordered, various intestinal microorganisms

cause immune activation and inflammatory reactions around [15]. Various types of inflammatory substances reach the center in various ways, transfer inflammatory signals to the center, and enhance the activation of neurons and glial cells in the center, resulting in depression, including pro-inflammatory factors IFN- γ , IL-6, TNF- α , TGF- β and IL-23, and other inflammatory factors.

Nowadays, with the deepening of the understanding and research of depression, Inflammatory factors are now being implicated in a growing number of studies as one of the major causes of depression. Existing studies have shown that depression patients contain pro-inflammatory factors, some of them is higher in healthy people [16]. Exogenous pro-inflammatory cytokines administration, like IFN- α , can induce depression [17]. Increased levels of the NLRP3 inflammasome, as well as other inflammatory markers, can cause depression. At the same time, inflammatory factors will affect the phosphorylation of BDNF receptor, and then interfere with BDNF signal transduction [18]. As shown in figure 2, Effects of inflammatory cytokines on the monoamine, glutamate, and BDNF neurotransmitter systems in the brain. One of the main pathophysiology of neurodevelopmental, and neurodegenerative illnesses, like depression and Alzheimer's disease, is microbial immune brain interaction. Mainly reflected in: Intestinal microbes have a vital function in cerebral development and behavior. Microbes in the gut play a pivotal part in neuroinflammatory reactions, repair of brain damage, activation of autoimmunity, and neurogenic immunity. Because gut microbes regulate the function of immune cells in the central nervous system. It can be seen that intestinal microorganisms can be used as a bridge with the state of inflammatory response, and it also proves that the development of intestinal microbiota imbalance may play a more direct and important role in mental diseases such as depression. Considering depression is an inflammatory condition, antidepressant and anti-inflammatory medications can be used together to alleviate depressive symptoms.

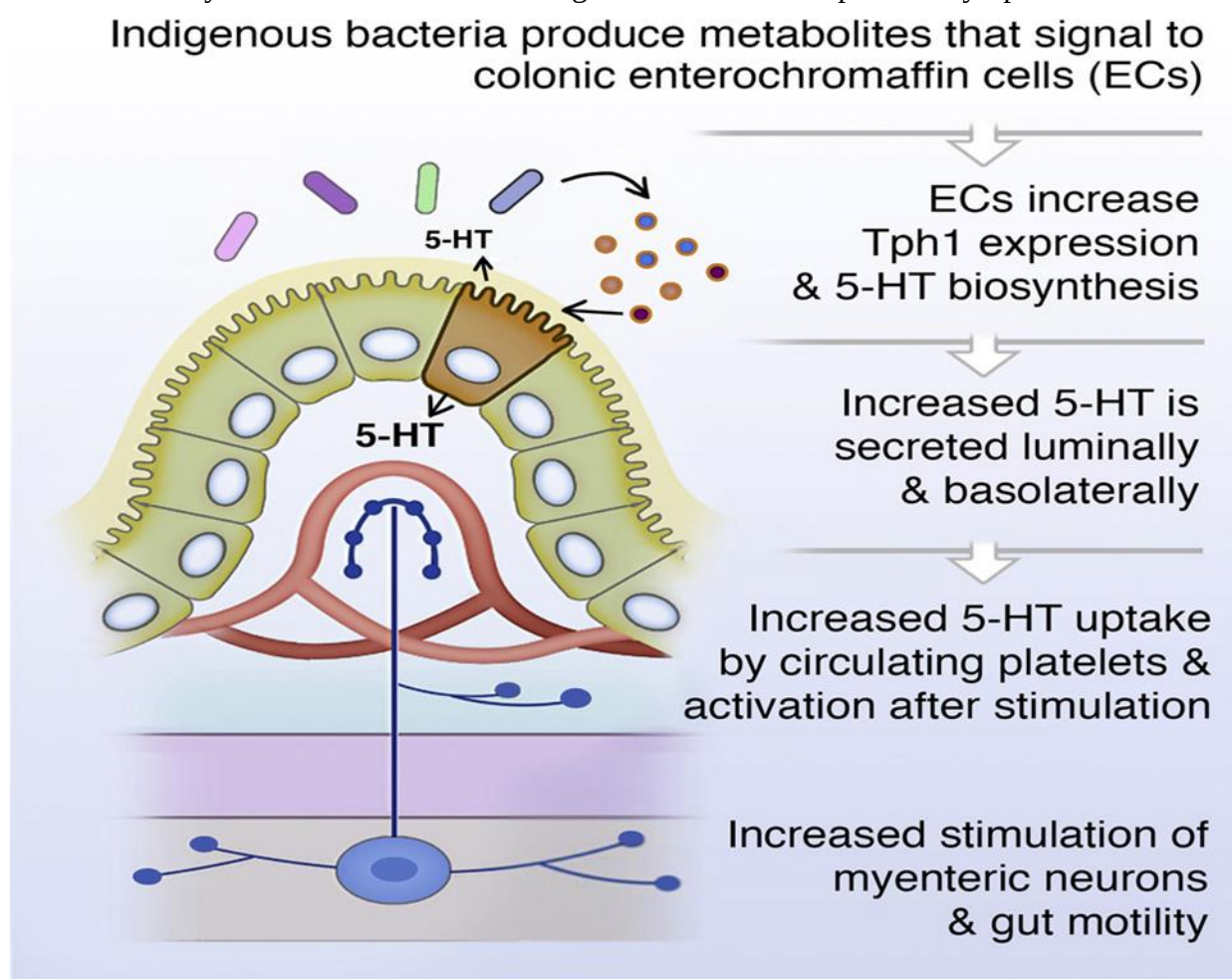


Figure 1. 5-HT in the intestine [19].

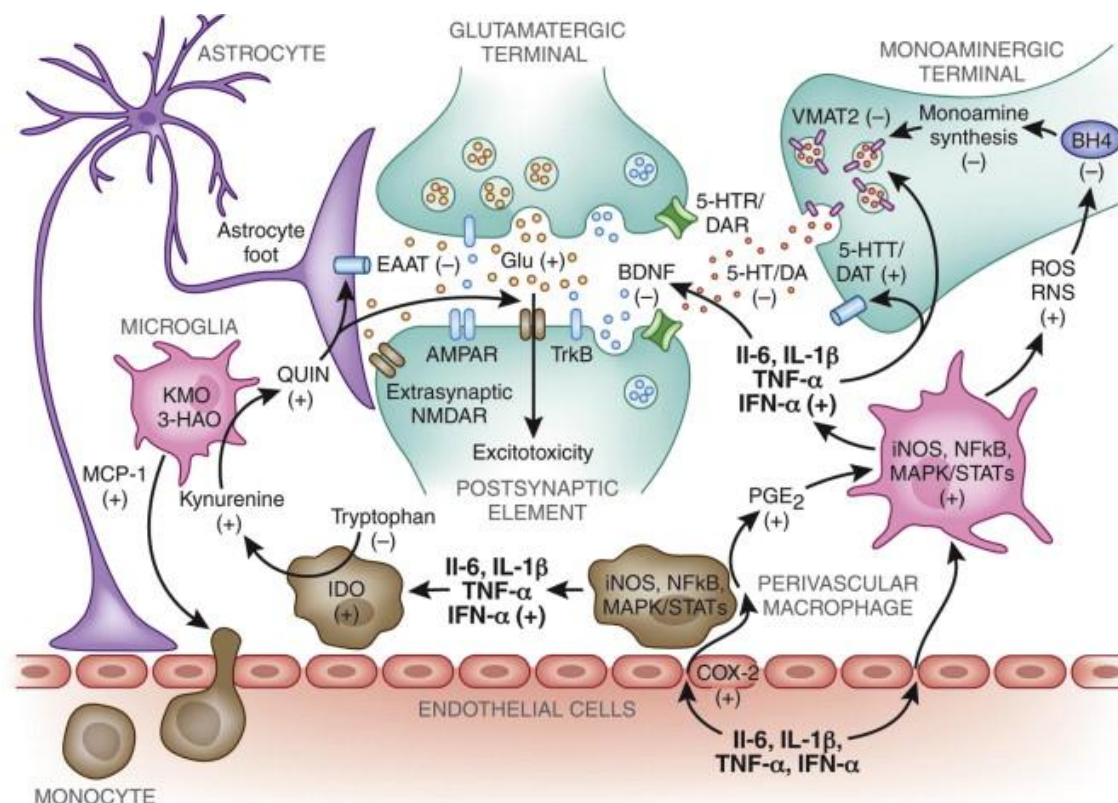


Figure 2. Neurobiological pathways of inflammatory cytokines in depression [20]

3. Intestinal Microbiota and Depression

3.1. Alistipes Affects the Pathogenic Bacteria of Depression

Several studies have revealed that intestinal flora abnormalities and aberrant microorganisms disrupt the brain-gut axis, culminating in neurological diseases. Depressed patients had higher levels of Enterobacteriaceae and Alistipes in their stools than the healthy control group [21]. Alistipes are often found in the intestinal tract, and are pathogenic in colorectal cancer, and are related to the mental signs of depression [21]. Alistipes is a gram-negative and obligate anaerobic subordinate of Bacteroidetes, which is a symbiotic bacterium in the intestinal tract. The study suggests that because Alistipes is an indole, its availability is reduced, most likely due to changes in the gut-brain axis as Alistipes grows [22]. Because tryptophan is a precursor to serotonin, increased Alistipes abundance may disrupt the digestive system's balance. As a result, serotonin availability is diminished, which is linked to depression [22]. Bacteria in the gut communicate with the central nervous system through a complex two-way pathway called the microbiome - gut - brain axis (figure 3). While most Alistipes make indole and can metabolize tryptophan, certain species do not produce indole when tryptophan is present [23]. Therefore, there may be multiple mechanisms of this interaction, and further research is needed.

3.2. Protective Bacteria for Relieving Depression

The gut microbiome appears to be a significant environmental element, according to mounting data. It has the ability to create and transport neuroactive chemicals, which are thought to be crucial mediators in the gut-brain axis and work for depression. Among them, lactic-acid bacteria and bifidobacteria have a relieving and preventive effect on patients who are stressed and lead to depression, bifidobacteria in adolescence show anti-inflammatory effects in the human body, and the lack of this probiotic in the human intestine may lead to human susceptibility to depression. In addition, studies have shown that long-term intake of probiotics has a positive effect on fighting anxiety and depression, while Bifidobacterium bifidobacterium has been shown to have a beneficial

impact on diseases, and Bifidobacterium infants may have antidepressant properties[24]. Gut bacteria influence both the early reprogramming of the HPA axis and anxiety sensitivity over life. The biological stress system is underdeveloped at birth and develops further during the postnatal period, which coincides with bacterial colonization of the intestine. GF rats as figure 4 shown with depression can be treated with Bifidobacterium infantis, a bacteria located primarily in the digestive system of infants. Because of its antidepressant properties, this bacterium is classified as "psychobiotic" [25]. In addition, lactobacillus has also been shown to be associated with depression in rhesus monkey animal experiments, and the stress response caused by rhesus monkeys after isolation from their mothers has led to changes in the microbiome, reducing the level of lactic acid bacteria and bifidobacteria, so bifidobacteria and lactic acid bacteria are protective bacteria for alleviating depression [26].

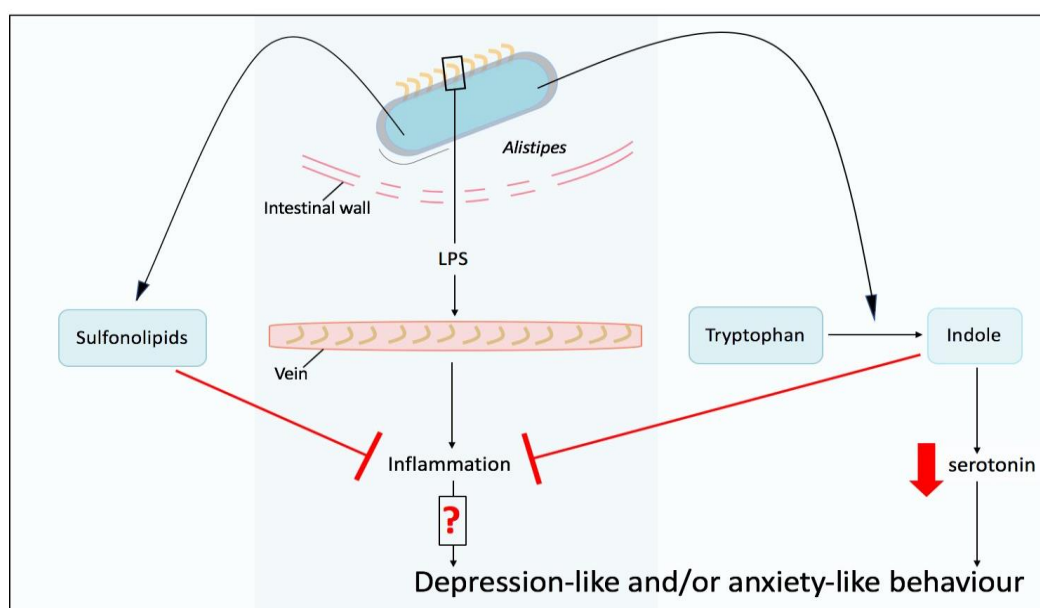


Figure 3. Dhaliwal G K. *Alistipes*: The influence of a commensal on anxiety and depression [27]

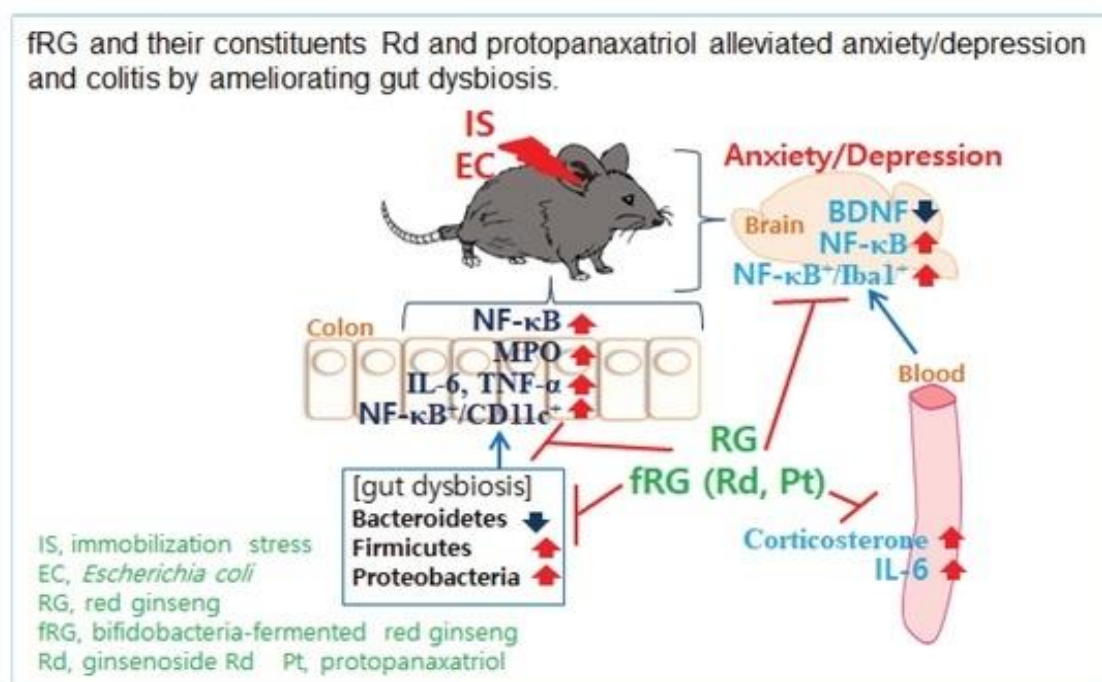


Figure 4. The relationship between fRG and anxiety/depression [8].

4. Conclusions

Nowadays, with the increasing incidence of depression, the pathogenesis of depression has become the research target of many scholars. As shown in a growing amount of evidence, depression and gut microorganisms are inexorably linked. Through the development of the central nervous system, gut bacteria can cause sadness. Through the brain-gut axis, intestinal bacteria change the balance of inflammatory agents and metabolites in the body, impacting neuroendocrine and intestinal neurological illnesses. Changes in the brain-gut axis can potentially create disruptions in the gut flora due to depression. According to the findings of the research, the activation of the NLRP3 inflammasome pathway was caused by alterations in the intestinal microbiome, which in turn triggers an inflammatory response in the central nervous. This pathway might have an influence in the development of depression. Changes in gut flora activate the NLRP3 inflammasome pathway, which activates the central nervous system's inflammatory response, according to the current research findings. Depression may be triggered by this process.

Nonetheless, understanding the involvement of the microbial gastrointestinal inflammatory body brain axis in the pathophysiology of depression is critical. We need a better knowledge of the extent to which the gut microbiome's function and composition vary, as well as the causal relationship between the gut microbiome and depression. Nowadays, although the research on intestinal microbiota and depression tends to be mature, the causal relationship between intestinal microbiota and depression and how intestinal microbiota participates in the pathogenesis of depression are not clear, so further research is needed. At present, to adapt the intestinal microbiota, maintain and restore the stability of them, and achieve the goal of treating depression, fecal transplantation, probiotic supplements, dietary conditioning, and other treatments can be utilized. In future research, we can use macrogenomics, high-throughput sequencing and other technologies to study the characteristics of intestinal flora in different syndromes of depression, investigate the link between intestinal microbiota and depression in depth, as well as propose a new research avenue for the treatment of depression.

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