

The Regulation of Depression by the Mediterranean Dietary Pattern: Targeting the Gut Brain Axis

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Abstract. Depression has become one of the leading causes of disability worldwide, affecting approximately 300 million people. Many factors can trigger depression, including social, psychological, and biological factors. The existing treatment methods for depression have certain limitations, and the rise of nutritional psychiatry plays a crucial role in treating mental illnesses. The Mediterranean diet has attracted widespread attention due to its high content of dietary fiber, polyphenols, and omega-3 polyunsaturated fatty acids, as well as its anti-inflammatory, antioxidant, and intestinal barrier-enhancing effects. The substances contained in its grains and olive oil have prebiotic-like effects, which can promote the proliferation of beneficial bacteria and improve the intestinal microbiota. The gut-brain axis is a bidirectional pathway (neural, endocrine, and immune pathways) between the central nervous system and the gastrointestinal tract. Adhering to a Mediterranean diet is associated with a reduced risk of depression. This article focuses on the gut-brain axis and systematically introduces how the Mediterranean diet improves the occurrence of depression by regulating gut microbiota and protecting intestinal function.

Keywords: Mediterranean diet, depression, neuroinflammation, brain-gut axis.

1. Introduction

According to the latest global burden of disease data released by The Lancet, from 2010 to 2021, the number of years of life lost due to disability caused by depression has risen to the second highest in the world [1]. Depression, as one of the main causes of disability worldwide, is characterized by aversion to things and prolonged low mood for at least two weeks. It is a common mental disorder, and its pathophysiology is complex and involves multiple factors. Its occurrence is closely related to social, psychological, and biological factors, for example, if there are family conflicts, significant life changes, or material dependence, chronic diseases, etc. According to data from the World Health Organization, about 300 million people worldwide are troubled by depression. The number of deaths caused by suicide exceeds 700000 every year [2]. Most of the existing methods for treating depression have limitations. Medications taken for a long time not only fail to take immediate effect, but also develop drug resistance, and have poor efficacy for some patients, leading to a series of adverse reactions. Studies have shown that nearly half of depression patients have little response to depression treatment, about two-fifths of patients have a response but will relapse, and some unresponsive patients who receive treatment still have no effect and may worsen their condition [3].

The rise of nutritional psychiatry has provided a new direction for mental illness. Poor diet can cause emotional problems and the occurrence of mental illness. Therefore, different diets can be used to intervene in diseases. Diet, as a lifestyle that can be regulated, is gradually gaining attention in the field of mental health [4]. Recent studies have revealed the central role of the gut-brain axis in many diseases. Intestinal microbes show significant therapeutic prospects in gastrointestinal cancer, Alzheimer's disease, Parkinson's disease, autism and other neurological diseases, and metabolic diseases such as type II diabetes. In the field of mental health, there is ample evidence to suggest that the gut microbiota interacts closely with various mental illnesses through the Gut brain axis, and depression is one of the widely studied typical examples [5]. The Mediterranean diet stands out among various dietary patterns due to its positive impact on brain and mental health. Research has shown that there is a significant association between higher adherence to the Mediterranean diet and lower risk of depression in the Chinese population, although this dietary pattern is widely adopted in

the Mediterranean region. A diet structure characterized by rich vegetables, fruits, and whole grains is not a typical component of the traditional Chinese diet [6].

Therefore, in the context of people's increasing emphasis on healthy lifestyles (including dietary improvements), promoting the Mediterranean Diet may bring more significant health benefits to the Chinese population, especially in compensating for the insufficient intake of related foods in the current dietary structure [6]. However, currently, there is limited systematic elucidation of the regulation of depression by the Mediterranean dietary pattern targeting the gut-brain axis. Therefore, this article summarizes and organizes the relevant research on the regulation of depression by the Mediterranean dietary pattern targeting the gut-brain axis, providing a theoretical reference for subsequent related research.

2. Concept and Mechanism of the Gut-Brain Axis

The gut-brain axis, as a holistic physiological concept, refers to the complex interaction network formed between the central nervous system and the gastrointestinal system through neural (incoming and outgoing), endocrine, and immune signals, in this system, gut microbiota communicates bidirectionally with key areas of the central nervous system through various direct and indirect pathways, furthermore, there is a mutual regulatory relationship among gut microbiota, enteric nervous system, and central nervous system. On the one hand, the nervous system continuously shapes the composition and function of the gut microbiota by regulating intestinal peristalsis, hormone release, acid, bicarbonate, and mucus secretion. On the contrary, metabolites produced by gut microbiota can not only pass through the intestinal epithelium and enter the systemic circulation, but some of the active molecules can also break through the blood-brain barrier and directly intervene in the physiological activities of the brain [5].

3. Mechanism of Action

3.1. The Impact of Gut Microbiota on Depression

Compared with healthy individuals, patients with depression have changed their gut microbiota, with anti-inflammatory and pro-inflammatory microorganisms being consumed, and an increase in Firmicutes and Bacteroidetes [7]. In the study of the microbiota gut-brain axis, prebiotics and probiotics have become key research objects, serving as effective means of regulating the host microbiota and potential strategies for treating emotional disorders such as major depression. Probiotics refer to live bacteria that can bring physiological benefits to the host after ingestion. The so-called prebiotics are usually fiber or carbohydrate substrates that are difficult for the host to digest. Although they are not microorganisms themselves, they can still have a positive impact on the body's health after being metabolized by symbiotic bacteria. The imbalance of gut microbiota refers to the disruption of microbial community structure or function, which is associated with various neurological and psychiatric disorders, such as autism spectrum disorder, depression, and anxiety. Recent studies have shown that the vagus nerve may be involved in the regulation of brain function and behavior by gut bacteria. For example, healthy mice fed with *Lactobacillus rhamnosus* showed a reduction in anxiety and depression like behavior in multiple behavioral tests, which is associated with changes in the expression levels of gamma aminobutyric acid receptors in some parts of the brain. But if the vagus nerve is cut off, the probiotic not only cannot alleviate behavioral abnormalities, but its effect on the expression of receptors in related brain regions also disappears. Similarly, in colitis model mice, although bifidobacteria can alleviate anxiety-like behavior, this effect is only observed in animals with intact vagus nerves [8]. The imbalance of gut microbiota caused by depression can induce various gastrointestinal symptoms, among which irritable bowel syndrome is the most common; Both of these conditions are associated with an increase in the number of Bacteroidetes and Firmicutes. Further research indicates that patients with irritable bowel syndrome not only have a higher risk of depression, but also a more common occurrence of gut microbiota

imbalance [5]. So, according to the above research, effective regulation of gut microbiota can reduce the occurrence of depression.

3.2. Regulation of Gut Microbiota by Mediterranean Diet

The Mediterranean diet is rich in dietary fiber (including soluble and insoluble types and oligosaccharides), represented by soluble dietary fiber such as β -glucan from cereal sources. It not only helps regulate blood sugar and cholesterol levels but also enhances the body's antioxidant capacity. At the same time, these substances also regulate the gut microbiota through probiotic-like mechanisms, promoting the proliferation of beneficial bacteria such as bifidobacteria and Bacteroidetes, thereby constructing a healthier and more stable microbial ecosystem and further enhancing gut immune defense function. Mediterranean Diet is rich in polyphenolic substances (derived from plant secondary metabolites such as tyrosine and phenylalanine), which have anti-inflammatory and antioxidant properties and can inhibit *Helicobacter pylori*, extra virgin olive oil, as a key source of polyphenolic substances in the Mediterranean dietary pattern, is closely associated with reduced inflammation, decreased oxidative stress, improved endothelial function, and multiple positive changes in overall metabolic health, the vast majority of dietary polyphenols can enter the intestine and, after absorption or biotransformation through the gastrointestinal tract, interact with the microbial community to regulate oxidative stress, inflammatory response, and immune homeostasis in the intestinal epithelium. The Mediterranean diet also contains abundant oily fish, which are a key source of polyunsaturated fatty acids needed to improve cardiovascular health. Besides fish and seafood, nuts can also provide polyunsaturated fatty acids. Of particular note is that studies have confirmed that omega-3 fatty acids derived from fish oil have anti-inflammatory properties and can reduce the effects of Firmicutes [9]. It can adjust the gut microbiota or increase its richness by adopting the Mediterranean diet to obtain the desired microbiota.

3.3. The Mechanism of Action of the Mediterranean Diet on Depression

Animal experiments have shown that long-term consumption of olive oil in the Mediterranean Diet has a neuroprotective effect, which involves regulating the metabolism of neurotransmitters such as serotonin and dopamine, thereby reducing behavioral abnormalities. This finding provides a basis for its potential therapeutic value in depression and anxiety intervention. The PrediMED study, based on sample data from the Spanish population, showed that adhering to a Mediterranean diet can increase the serum concentration of brain-derived neurotrophic factor in patients with depression [10]. Low degree inflammation caused by pro-inflammatory cytokines may ultimately lead to the onset of clinical symptoms related to depression by inhibiting the expression of brain-derived neurotrophic factors, interfering with normal neurotransmitter metabolism, and inducing endothelial dysfunction, the Mediterranean Diet intervenes in the occurrence of depression by using anti-inflammatory and antioxidant polyphenols, as well as increasing omega-3 fatty acids, vitamins, dietary fiber, and other nutrients [11].

4. Components and characteristics of the Mediterranean diet

4.1. Definition and Core Components of Mediterranean Diet

The Mediterranean Diet is a traditional dietary pattern originating from the daily lives of residents along the Mediterranean coast, first defined by scientist Ancel Keys in the 1960s. At present, this dietary system has been widely recognized globally and has become one of the most extensively explored healthy eating patterns in scientific research. A major feature of the Mediterranean Diet is the daily consumption of a wide variety of plant-based foods, including extra virgin olive oil, beans, whole grains, nuts, fresh fruits, and vegetables, supplemented with moderate amounts of dairy products, fish, and wine [12].

4.2. Application of Mediterranean Diet

Among different dietary structures, the Mediterranean diet has received widespread attention for its potential promoting effects on psychological and brain health. The Alternative Mediterranean Diet Score, derived from the original scale constructed by Trichopoulou et al., advocates increasing the intake ratio of plant-based foods (including vegetables, legumes, and fruits) to monounsaturated fats, reducing consumption of saturated fats and processed meats, and allowing for moderate consumption of alcoholic beverages, the Alternative Mediterranean Diet Score, while retaining the core elements of traditional Mediterranean diets, has been promoted and applied to diverse populations outside the Mediterranean region [6]. In a cohort study of approximately 42500 women, after about 20 years of follow-up, participants who strictly followed Mediterranean Diet had a 16% to 22% lower risk of developing depression compared to those who did not follow [13].

5. Conclusion

The Mediterranean Diet, as one of the globally renowned and extensively researched diets, is rich in bioactive components such as dietary fiber, polyphenols, and polyunsaturated fatty acids. It can regulate gut microbiota composition, enhance intestinal barrier function, inhibit inflammation and oxidative stress, thereby affecting brain function and behavioral performance, especially playing an antidepressant role in pathways related to the vagus nerve. The substances contained in grains and olive oil in the Mediterranean Diet have prebiotic-like effects, which can promote the proliferation of beneficial bacteria such as bifidobacteria and Bacteroides, and improve the gut microbiota. Depression, as one of the leading causes of disability worldwide, has limitations in traditional treatment methods. Therefore, using diet to treat mental illnesses has become a new treatment direction. The gut microbiota plays a crucial role in this regard, so the imbalance of gut microbiota is closely related to depression.

Existing studies are mostly observational studies, with small sample sizes and a lack of long-term follow-up for intervention experiments. In future studies, larger sample studies and long-term follow-up can be conducted to explore the synergistic effect of Mediterranean diet and drug therapy, and there are significant individual differences in dietary response, which are influenced by various factors such as genetic background, baseline microbiota composition, metabolic status, etc. The plan can be adjusted according to individuals. Although the Mediterranean diet is widely used in the Mediterranean region, in the current situation where people are increasingly concerned about health, adopting the Mediterranean diet reasonably may have greater benefits for health.

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