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# Investigating the Impact of Medicine and Food Homology Substances on Depression Based on Gut Microbiota

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## Abstract

Depression is a common mental disorder, primarily caused by alterations in the function of monoamine neurotransmitters and receptors, neuroendocrine disruptions, as well as inflammation and immune imbalances. Its global incidence has been increasing year by year. Most current antidepressant drugs are associated with prolonged administration and significant side effects. As microorganisms residing in the human gut, disruptions in the gut microbiota can influence the pathogenesis of depression. Medicine and food homology substances, with both therapeutic and nutritional properties, have shown great potential in treating depression. This paper explores how medicine and food homology substances influence the pathogenesis of depression through the modulation of gut microbiota, aiming to provide new insights for depression treatment.

## Keywords

Depression, Pathogenesis, Gut Microbiota, Medicinal Food, Treatment

## 1. Introduction

In recent years, the prevalence of depression has been rising annually, making it the leading cause of illness and disability among adolescents worldwide, significantly impairing individuals' daily lives [1]. As a common mental disorder, depression is characterized by prolonged low mood, cognitive decline, and other related symptoms. Current treatment options for depression primarily include an-

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tidepressant medications and psychotherapy, although these approaches are often associated with significant side effects and poor treatment adherence. Therefore, identifying safer and more effective treatment strategies has become a key area of research.

The pathogenesis of depression involves a complex interplay of multiple factors, including alterations in monoamine neurotransmitters, receptor dysfunction, and other molecular changes [2]. The gut microbiota—an ecosystem of microorganisms residing in the human gastrointestinal tract—has been increasingly recognized for its role in the development and progression of depression, anxiety, and related disorders. Compared with healthy individuals, patients with depression exhibit significant disturbances in the composition and structure of their gut microbiota [3]. Similar imbalances have been observed in animal models of depression. Modulating the gut microbiota can influence the course of depression, highlighting its potential as a therapeutic target. The bidirectional communication between the gut and brain, known as the gut-brain axis, plays a critical role in this process. Through mechanisms such as immune modulation and neurochemical signaling, the gut microbiota can impact brain function and emotional regulation, contributing to the onset and progression of depression.

The concept of "medicine and food homology" denotes the dual function of certain foods as both nutritional sources and therapeutic agents [4]. In recent years, this concept has garnered significant attention, particularly regarding its potential applications in the treatment of depression. The therapeutic effects associated with medicine and food homology are believed to be intricately connected to their impact on gut microbiota.

## 2. Pathogenesis of Depression

### 2.1. Disruption of Monoamine Neurotransmitters and Receptor Function

Disruption of monoamine neurotransmitter systems is one of the key factors in the onset of depression. Serotonin (5-hydroxytryptamine, 5-HT) and norepinephrine (NE) are the primary neurotransmitters involved in regulating emotional responses, cognitive processes, and other physiological activities within the central nervous system. Research has shown that the levels of 5-HT and NE are lower in individuals with depression compared to healthy controls [5]. Additionally, dopamine receptors play a crucial role in brain function and are implicated in the pathogenesis of various psychiatric disorders. Studies indicate that patients with major depression exhibit lower levels of dopamine D1 and D2 receptors, which are associated with a hypoactive dopaminergic system and thought to contribute to the development of depression. Therefore, dysfunction of monoamine neurotransmitters is regarded as one of the significant mechanisms underlying depression.

### 2.2. Neuroendocrine Dysregulation

Neuroendocrine dysfunction, which induces varying degrees of impairment in the

limbic system, has been shown to be closely associated with the onset and progression of depression. The hippocampus, a key structure in the limbic system, plays an important role in stress neuroendocrine regulation and emotional control. It is highly sensitive to stress and vulnerable to damage. Studies have shown that depression is associated with hippocampal atrophy, reflected by a significant reduction in hippocampal volume [6]. The hypothalamic-pituitary-adrenal (HPA) axis is a crucial endocrine pathway responsible for maintaining neuroendocrine homeostasis and regulating physiological functions. The HPA axis regulates the secretion of corticotropin-releasing hormone (CRH) from the hypothalamus, which stimulates the anterior pituitary to release adrenocorticotropic hormone (ACTH). ACTH then acts on the adrenal cortex to promote cortisol secretion [7]. Cortisol, a hormone responsive to stress, typically increases in response to emotions such as anxiety and tension. The HPA axis plays a pivotal role in modulating cortisol release, which helps to alleviate emotional distress in patients.

### 2.3. Inflammation and Immune Dysregulation

Depression is associated with a reduction in immune cell numbers and impaired immune function [8]. This dysfunction in peripheral immune responses leads to an abnormal increase in pro-inflammatory cytokines, exacerbating inflammation and affecting neuroendocrine function. Studies have shown that levels of inflammatory markers, such as hypersensitive C-reactive protein (hs-CRP) and interleukin-6 (IL-6), are elevated in patients with postpartum depression compared to healthy individuals. Another study demonstrated that interleukin-18 (IL-18), an immune-regulatory cytokine with protective properties, is also elevated in depressed patients compared to the general population [9].

## 3. Gut Microbiota and Depression

### 3.1. Basic Concept of Gut Microbiota

Microorganisms, representing the largest symbiotic system in the human body, encompass bacteria, fungi, and other entities. The gut microbiota refers to the community of microorganisms residing within the human intestinal tract. These microbes coexist in a specific proportion and interact synergistically to maintain the normal physiological functions of the host. The dominant bacterial phyla in the gut microbiota are Firmicutes and Bacteroidetes, which collectively account for approximately 98% of the total microbiota composition [10]. Research has demonstrated that the gut microbiota is involved in various physiological processes, including metabolism, immune regulation, and neural development. Disruptions to the gut microbiota can influence the progression of multiple systemic diseases, such as depression, through intricate interactions between the gut and other organs [11].

### 3.2. Alterations in the Gut Microbiota of Depressed Patients

Studies have revealed significant differences in the gut microbiota composition between depressed patients and healthy individuals. The diversity and abundance

of gut microbiota are notably altered in those with depression [12]. Alpha-diversity ($\alpha$-diversity) refers to the diversity within a single microbial community or sample, typically measuring species richness and evenness. In contrast, beta-diversity ($\beta$-diversity) assesses the differences in microbial composition between distinct samples or groups, reflecting the extent of community variation. While there are no significant changes in the $\alpha$-diversity of the gut microbiota, the $\beta$-diversity shows marked differences. Specifically, the abundance of Bacteroidetes increases significantly, while the levels of Proteobacteria and Actinobacteria also rise moderately. On the other hand, the abundance of Firmicutes decreases. The experiment by De Palma and others also provides evidence that gut bacteria are one of the factors contributing to anxiety and depression behaviors [13]. The researchers used a group of mice with normal gut microbiota and a group of germ-free mice as a control. Mice from both groups were separated from their mothers for 3 hours daily, for a duration of 3 to 21 days, to induce varying levels of stress. However, the germ-free mice did not exhibit anxiety- and depression-like behaviors, while the mice with normal gut microbiota did. When gut microbiota were implanted into the germ-free mice that had experienced stress, the researchers observed the development of anxiety- and depression-like behaviors, further demonstrating the role of gut microbiota in depression.

### 3.3. Role of Gut Microbiota in the Pathogenesis of Depression

The hypothalamic-pituitary-adrenal (HPA) axis is a critical neuroendocrine system involved in stress response. Dysregulation of the negative feedback mechanism of the HPA axis under chronic stress leads to increased secretion of corticotropin-releasing factor, adrenocorticotropic hormone (ACTH), and glucocorticoids. These changes can alter brain regions related to emotion, such as the medial prefrontal cortex, hippocampus, and amygdala, disrupting brain homeostasis and contributing to the onset of depression. It is now widely recognized that the gut microbiota and the HPA axis interact via the "microbiome-brain-gut" axis [14]. Short-chain fatty acids (SCFAs) are major metabolites produced by the fermentation of dietary fiber by gut microbiota. These include acetate, propionate, and butyrate, in a ratio of approximately 3:1:1. SCFAs play an essential role in the microbiome-gut-brain axis by reducing inflammation, promoting anti-inflammatory responses in neurons, and alleviating intestinal inflammation [15]. As mentioned earlier, inflammation is a key contributor to the development of depression. Additionally, research has shown that both acetate and butyrate influence serotonin (5-HT), a neurotransmitter that is closely linked to depression, further demonstrating how gut microbiota disturbances can impact depression by modulating neurotransmitter systems [12].

A growing body of evidence supports the role of gut microbiota in modulating various neurobiological processes associated with depression. **Table 1** summarizes the major factors involved in depression and indicates the extent to which the gut microbiota directly contributes to each pathway.

**Table 1.** Key factors of depression and the role of gut microbiota.

| Factor | Involvement of Gut Microbiota | Mechanistic Pathway |
|---|---|---|
| HPA Axis Dysregulation | Directly influenced | Through gut-brain axis modulation of stress response |
| Inflammatory Response | Directly influenced | Through SCFAs and other pathways modulating inflammation |
| Altered Monoamine Neurotransmission | Directly influenced | Via modulation of 5-HT synthesis and metabolism |

## 4. Potential Ameliorative Effects of Medicine and Food Homology in Depression

### 4.1. The Basic Concept of Medicine and Food Homology

Medicine and food homology means substances possess both medicinal and dietary functions. In traditional Chinese culture, dialectical reasoning is a fundamental method of understanding the world, and it holds that some substances are not only food but also act as medicine under certain circumstances. This concept is known as "medicines and food from the same source" [4]. The foundational basis for this belief can be traced to the *The Huai-nan-tzu, which states: "Shennong tasted hundreds of herbs and encountered seventy poisons in one day." Thus, traditional medicine and food homology extracts have been used in China for thousands of years in disease prevention and treatment.

### 4.2. Mechanisms by Which Medicine and Food Homology Substances Regulate Depression through the Gut Microbiota

Most conventional medications are associated with prolonged treatment cycles and significant side effects. As a result, increasing attention has been given to components from medicine and food homology substances, such as vitamins, flavonoids, saponins, and other bioactive compounds. These active ingredients typically require metabolism by the gut microbiota after ingestion, which is essential for their absorption and pharmacological activity. Studies have shown that extracts from medicine and food homology substances could enhance the abundance of beneficial gut bacteria while reducing harmful bacteria, thus helping to maintain gut microbiota diversity [16].

#### 4.2.1. Impact on the Monoamine System

The monoamine system is a classic target for antidepressant therapies, involving neurotransmitters such as serotonin (5-HT), norepinephrine (NE), and dopamine (DA). Medicinal food substances can alleviate depressive symptoms by enhancing the activity of these neurotransmitters. Theanine, an amino acid found in tea, has been shown to increase the levels of 5-HT, NE, and DA, thereby improving mood. Modifying theanine chemically can enhance its permeability in the brain, thus

strengthening its antidepressant effects. Curcumin, a yellow pigment extracted from turmeric, inhibits monoamine oxidase, thereby increasing the concentrations of 5-HT, NE, and DA in the brain.

#### 4.2.2. Regulation of the Hypothalamic-Pituitary-Adrenal (HPA) Axis

The HPA axis plays a crucial role in stress responses and the pathogenesis of depression. Medicine and food homology substances could alleviate depressive symptoms by regulating the HPA axis and reducing excessive cortisol production. Glycyrrhizin, the main active compound in licorice, increases the expression of glucocorticoid receptors, inhibiting the overactivation of the HPA axis and lowering cortisol levels. Modifying glycyrrhizin, such as by conjugating it with polyethylene glycol, can enhance its stability and bioavailability. Hesperidin, a flavonoid derived from citrus peel, reduces HPA axis activity and mitigates stress-induced cortisol elevation. Combining hesperidin with cyclodextrin can increase its water solubility and absorption, further enhancing its antidepressant effects.

#### 4.2.3. Enhancement of Neuroplasticity

Neuroplasticity, which involves neuronal growth, synapse formation, and repair, is a key mechanism in the treatment of depression [17]. Medicine and food homology substances can enhance neuroplasticity by increasing the expression of brain-derived neurotrophic factor (BDNF) [18]. Resveratrol, a polyphenolic compound found in grape skins, upregulates BDNF expression, promoting neuronal growth and synaptic formation, thus improving depressive symptoms. Chemically modifying resveratrol, such as by encapsulating it in microspheres, can prolong its release in the body and improve its stability. Ginsenosides, important components of ginseng, promote neural regeneration and synaptic plasticity by increasing BDNF expression in the hippocampus and prefrontal cortex.

#### 4.2.4. Reduction of Inflammatory Responses

Depression is often accompanied by inflammatory responses, and inflammation is considered a key factor in the pathogenesis of depression. Medicine and food homology substances could reduce depressive symptoms through their anti-inflammatory effects [18]. Apigenin, a flavonoid found in citrus fruits, reduces the activation of the NLRP3 inflammasome and decreases the production of inflammatory cytokines such as IL-1$\beta$, thereby alleviating depressive symptoms. Combining apigenin with biomolecules can enhance its anti-inflammatory and antidepressant effects. Vitamin B6, an essential coenzyme in serotonin synthesis, helps to alleviate depression by reducing inflammation in the brain. Zinc, an essential trace element, alleviates depressive symptoms by modulating 5-HT receptors and decreasing inflammation. Combining zinc with other nutrients in complex nutritional formulations can enhance absorption and boost its antidepressant effects.

### 4.3. Components of Medicine and Food Homology Substances

Dietary therapy has been recognized as a modifiable risk factor for mental health

disorders. Western diets, which are high in sugar, fats, and processed foods, have been linked to the onset of depression. In contrast, diets rich in plant-based foods, such as the Mediterranean diet, which includes vegetables, fruits, nuts, and other whole foods, seem to offer protective effects against depression.

#### 4.3.1. Tea

Catechins, a major source of polyphenols in the diet, can cross the blood-brain barrier and exert protective effects against depression. Recent studies have also highlighted the potential antidepressant properties of folate. Additionally, the amino acid theanine, found in tea, has been shown to have notable antidepressant effects. Klaus W. Lange and others [19] conducted a review of 20 observational studies and 17 experimental studies, among which data from 29 studies involving participants aged 18 to 80 demonstrated an inverse relationship between dietary polyphenol intake and the risk of depressive symptoms.

#### 4.3.2. Mushrooms

Psilocybin, a natural neurotoxin produced by psychedelic mushrooms, is a psychoactive compound known for inducing intense hallucinations. Once classified as an illegal drug, psilocybin remains a controlled substance in many countries, including China. However, clinical trials have revealed its potential therapeutic effects on depression. A study by Goodwin *et al.* [20] in 2022 indicated that 233 adult patients with depression from the United States, Canada, and Europe were randomly assigned to three groups in a 1:1:1 ratio, receiving doses of 25 mg, 10 mg, or 1mg of psilocybin, and the treatment lasted for 6 to 8 hours from 2019 to 2021. On the second day of administration, the patients' scores on the Montgomery-Åsberg Depression Rating Scale (MADRS) showed a significant decrease, with a dose-dependent effect and minimal adverse reactions. Subsequent studies revealed that a single 25 mg dose of psilocybin, combined with psychological support, exhibited a strong antidepressant effect.

#### 4.3.3. Apigenin

Apigenin, a flavonoid compound, is widely found in various fruits and vegetables. Compared to other foods, it has advantages such as low toxicity and non-mutagenicity. Chronic, low-level stress can contribute to the development of depression, and the behavioral despair model is commonly used to mimic major symptoms of human depression. In the behavioral despair mouse model, apigenin was shown to regulate levels of norepinephrine, dopamine, and serotonin [18]. This model includes both acute stress tests, such as the forced swimming and tail suspension tests, and chronic stress tests, such as restraint stress. Mice injected with apigenin at doses of 12.5 and 25 mg/kg showed a significant reduction in immobility time. At higher doses, apigenin increased dopamine levels in the amygdala.

#### 4.3.4. Soy Isoflavones

Soy isoflavones are plant-derived phytohormones extracted from soybeans and are classified as polyphenolic compounds. In a study using a chronic stress-in-

duced depression rat model, soy isoflavones were shown to significantly improve depressive behaviors by increasing levels of key neurotransmitters, including serotonin, norepinephrine, and dopamine. Additionally, soy isoflavones were found to enhance the diversity of gut microbiota, increasing their biotransformation capacity. These effects have been confirmed in animal models, where soy isoflavones alleviate depressive-like behaviors via modulation of the gut microbiota and HPA axis dysregulation [21].

#### 4.3.5. Curcumin

Curcumin, a phenolic antioxidant extracted from the rhizomes of turmeric and other *Curcuma* species, possesses strong anti-inflammatory properties. It has been shown to reduce the accumulation of proteins in the brain related to memory and mood, leading to improved cognitive function and mood regulation.

The functional characteristics and mechanisms of each medicinal and food homology substance discussed in this section are summarized in **Table 2**.

**Table 2.** Summary of the role of medicine and food homology substances.

| Substance | Role |
|---|---|
| Tea | Enhances 5-HT, NE, DA levels; reduces oxidative stress and inflammation |
| Mushrooms | Modulates serotonin receptors; induces rapid antidepressant effects |
| Apigenin | Regulates NE, DA, 5-HT; reduces inflammatory cytokines |
| Soy Isoflavones | Improves monoamine neurotransmission; enhances gut microbiota diversity |
| Curcumin | Inhibits monoamine oxidase; reduces neuroinflammation and modulates mood-related proteins |

## 5. Conclusion

The pathogenesis of depression is complex and interconnected with multiple fields. Compared to other medications currently in use, medicine and food homology substances offer distinct advantages, such as high efficacy, safety, and low toxicity, particularly through the modulation of gut microbiota [22] [23]. While these substances show significant potential in the treatment of depression, scientific research on their mechanisms remains limited. Further investigation is needed to clarify the precise mechanisms of these active ingredients and establish unified standards for diagnosis and efficacy evaluation. This paper summarizes the pathogenesis of depression, explores the influence of gut microbiota, examines the relationship between medicine and food homology substances and gut microbiota, and highlights key antidepressant medicine and food homology substances. These findings offer valuable references for the prevention and treatment of depression.

## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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