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Interaction between Gut Microbiota and Medicinal Food Homology in Depression

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Abstract

Depression can be counted as the most severe mental disease in the world nowadays, which lacks effective curing treatments. With an increasing number of patients, developing effective treatments with fewer side effects is essential. Medicinal food homology has been proven to influence the pathogenesis of depression positively. Gut microbiota plays a vital role in exerting the antidepressant effect of substances from the medicinal food homology, as they facilitate different chemical processes and increase the bioavailability of the substances. This review summarizes the correlation between gut microbiota and depression and provides new pathways for effective treatments of depression.

Keywords

Medicinal Food Homology, Gut Microbiota, Depression, Antidepressant, Pathogenesis

1. Introduction

Depression is a severe and persistent mental illness common in clinical practice, with an estimation of at least 5% of adults who have suffered from depression in 2023 [1]. It is characterized by the symptoms of sleeping and eating disorders, a loss of interest, and a depressed mood [2]. With the increased pace of modern society, the incidence of depression has been rising and will continue to grow in the long term. The impact of depression has an extensive range, from a depressed mood to suicidal action.

Meanwhile, the pathogenesis of depression is complex. It is categorized into four mechanisms: the monoamine hypothesis, the imbalance of the hippocampus-pituitary-adrenal (HPA) axis, neuroplasticity chaos, and inflammatory stimulation [3]. Many chemically synthesized antidepressants are proven to be not very practical nowadays, with delayed responses and even severe side effects [4].

Medicinal food homology is where a plant possesses both medicinal properties and the ability to be edible, which contain functions in the prevention and treatment of various health issues. The concept of medicinal food homology has been growing, with easier accessibility and the lack of side effects [5]. It's been popular in recent years, and it is a route for curing mental illness, especially depression [6]. However, the mechanism of medicinal food homology for curing depression remains unclear, which requires further studies.

Gut microbiota refers to all of the microorganisms living in the digestive system. Recent research has suggested that gut microbiota plays a vital role in depression. Through the adjustments on the imbalance of the HPA axis, inflammatory response, and disorders of neurotransmitters, medicinal food homology could remit the depressive behaviors. Recently, it has been found that gut microbiota strongly correlates with medicinal food homology substances [7]. The substances from medicinal food homology have low bioavailability, requiring the help of gut microbiota to digest, absorb, and chemically modify them to increase their bioavailability [8]. Therefore, this paper is intended to explore the chemical modifications between gut microbiota and medicinal food homology substances that affect the pathogenesis of depression and provide future research on a therapeutic target for depression.

2. The Pathogenesis of Depression

2.1. Monoamine Hypothesis

Monoamine neurotransmitters are an essential class of excitatory neurotransmitters.

The imbalance of excitatory neurotransmitters, including serotonin, norepinephrine, and dopamine, was found in depressed patients, suggesting that the mechanism behind depression is abnormal levels of one or more monoamine neurotransmitters [9]. For instance, the discovery of the antihypertensive drug reserpine could cause depression by depleting the concentration of monoamine neurotransmitters in the brain. Similarly, the depletion of tryptophan, an amino acid essential for 5-HT synthesis, has been shown to cause depressive symptoms in cured patients [10]. Many early antidepressants were developed based on the theory of monoamine depletion, such as monoamine oxidase inhibitors, tricyclic antidepressants, and selective serotonin reuptake inhibitors, which can increase the concentration of monoamine neurotransmitters in the inter-synaptic space and improve depressive symptoms [11]. In short, the monoamine hypothesis is one of the pathogenesis of depression.

2.2. Imbalance of HPA Axis

The hypothalamus-pituitary-adrenal (HPA) axis is a feedback loop pathway in which stress activates hormone pathways that induce the body to respond to a perceived threat, such as a fight or flight situation. When stressed, the hypothalamus secretes corticotropin-releasing hormone (CRH), then stimulates the pituitary gland to secrete adrenocorticotropic hormone, stimulating the adrenal cortex to release corticotropic hormone (CORT). Elevated corticosteroids increase the excitability of the nervous system and keep the body in a hyperactive state. After stress, CORT decreases CRH concentrations through negative feedback regulation, normalizing the entire HPA axis. Being under stress in the long term may cause continuous excitement of the HPA axis, which may cause an imbalance of the HPA axis, resulting in an overstimulating body, therefore resulting in the symptoms of depression [12]. In conclusion, the imbalance of the HPA axis is one of the pathogenesis for depression.

2.3. Neuroplasticity Disorder

Growth and adaptation at the neuronal level are more broadly called neuroplasticity.

In particular, synapses are created and eliminated rapidly, and connectivity circuits are altered during adaptation and learning. The latest research shows that symptoms at this cellular level in depressed patients mainly include a decrease in hippocampal neocytogenesis, neuronal apoptosis, and hippocampal shrinkage [13]. Notably, the neurotrophic factors modulate changes in neuroplasticity. Neurotrophic factors are an important class of signaling molecules in the brain, responsible for axon localization, neuronal growth, synaptic maturation during development, and synaptic plasticity. This family of proteins includes nerve growth factor, brain-derived neurotrophic factor (BDNF), and others. Among them, BDNF plays a vital role in synaptic plasticity and the pathology or treatment of many psychiatric disorders [14]. Recently, studies have found that a decrease in BDNF increases susceptibility to stress-induced depression, decreases serum BDNF levels in patients diagnosed with depression, and recovers BDNF in patients with depression [15]. To sum up, an adjustment in neuroplasticity might be a therapy target for treating depression.

2.4. Inflammatory Response

A growing body of research data supports the link between inflammation and depression, with patients with depression exhibiting increased concentrations of inflammatory cytokines in the brain and peripheral and microglial activation [16]. People with autoimmune diseases and severe infections are more likely to suffer from depression, and treatment with cytokines such as interferon and interleukin can trigger depression [17]. Meta-analyses concluded that interleukin-1β (IL-1β), interleukin-6(IL-6), tumor necrosis factor-α (TNF-α), and C-reactive protein (CRP) in peripheral blood are inflammatory markers in patients with depression [18]. Therefore, inflammatory responses are also a pathogenesis for depression.

3. Correlation between Gut-Microbiota and the Pathogenesis of Depression (Table 1)

3.1. Gut Microbiota and Monoamine Hypothesis

The monoamine hypothesis states that deficiencies in critical neurotransmitters such as serotonin, norepinephrine, and dopamine cause depression [19]. Interestingly, the gut microbiota affects them by producing precursors or influencing the metabolism of these neurotransmitters. Short-chain fatty acids (SCFAs), one of the leading products of gut microbiota, correlate with depression. More importantly, certain gut bacteria produce SCFAs that can affect serotonin production in the gut [20]. An imbalance in the gut microbiota may lead to a decrease in levels of these neurotransmitters, which can lead to depressive symptoms. For instance, studies have shown the relationship between indigenous bacteria from gut microbiota and serotonin, showing the ability of gut microbiota to influence the production of serotonin [21]. Meanwhile, the disorder of gut microbiota leads to the imbalance of neurotransmitters, therefore being one of the pathogenesis of depression [22]. Studies have shown that patients with depression often have changes in the composition of the gut microbiota, which may affect brain function and mood through the gut-brain axis [23].

3.2. Gut Microbiota and the HPA Axis

The hypothalamic-pituitary-adrenal (HPA) axis plays a vital role in the body's response to stress. Patients with depression often observe dysregulation of the HPA axis, resulting in elevated levels of cortisol and other stress hormones [24]. The gut microbiota could regulate the HPA axis by producing metabolites and signaling molecules that affect brain function. For example, certain gut bacteria, such as *L. helveticus MCC*1848 and *L. kefiranofaciens ZW*3, produce SCFAs, fatty acids that can affect the integrity of the blood-brain barrier and regulate inflammation [25]. Notably, an imbalance in the intestinal flora may increase intestinal permeability, allowing bacterial endotoxins to enter the bloodstream and triggering systemic inflammation that causes the imbalance of the HPA axis and leads to depressive symptoms [26]. All in all, chaos in gut microbiota leads to the imbalance of the HPA axis, therefore affecting symptoms of depression.

3.3. Gut Microbiota and Inflammation

Inflammation is an essential factor in the pathogenesis of depression. Recent research shows that the gut microbiota is vital in regulating immune response and inflammation [27]. Representatively, the disorders of gut microbiota could lead to an overactive immune response and an increase in pro-inflammatory cytokines such as IL-6 and TNF-α. Furthermore, these cytokines could cross the blood-brain barrier (BBB), causing neuroinflammation and being associated with depressive symptoms [28]. Studies have found that patients with depression typically exhibit increased levels of these inflammatory markers, suggesting an association between gut microbiota, systemic inflammation, and depression [29] [30].

3.4. Gut Microbiota and Neuroplasticity

Decreased neuroplasticity has been linked to depression. In fact, the gut microbiota could influence neuroplasticity by producing neurotrophic factors such as BDNF. SCFAs are an essential determinant in the synthesis of BDNF [31]. SCFAs produced by gut bacteria could enhance the expression of BDNF and promote neurogenesis and synaptic plasticity. An imbalance in the gut microbiota may lead to decreased levels of SCFAs and BDNF, impairing neuroplasticity, which contributes to depressive symptoms [32]. In short, gut microbiota can change neuroplasticity, therefore being one of the pathogenesis of depression.

Table 1. Summarization of mechanisms of medicinal food homology product.

Product	Source	Gut microbiota	Chemical process	Correlation with pathogenesis	Citation
Tetrahydrocrucumin	Curcumin	*E. coli DH*10*B*	Hydrogenation	Neuroprotective and anti-neuroinflammatory properties	(Cheng *et al.*, 2012; Cheng *et al.*, 2012)
Caffeic acid	Ferulic acid		Methylation	Regulation of pro-inflammatory Cytokine expression and modulation of neural signaling mechanisms	(Habtemariam, 2017; Zheng *et al.*, 2019; Liu, Shen, *et al.*, 2017)
Urolithins	Ellagic acid	*Gordonibacter urolithinfaciens, sp.*, *Gordonibacter pamelaeae DSM* 19378 *T*, *Bifidobacterium pseudocatenulatum INIA P*815	Dihydroxylation	Inhibits LPS-induced BV-2 microglial inflammation	(Mc *et al.*, 2021; Xu *et al.*, 2018)
Equol	Daidzein	*Anaerobic bacterium Eggerthella strain Julong* 732	Deglycosylation	Balancing the HPA axis, reduces the production of pro-inflammatory cytokines	(Kim *et al.* 2010; Lalita Subedi *et al.*, 2017)
Gallic acid GA	Epigallocatechin-3-O-gallate	*Enterobacter aerogenes*, *Raoultella planticola* (*klebsiella planticola*)	Deglycosylation	Modulating the inflammatory response	(Takagaki & Nanjo, 2010; Wen *et al.*, 2022)
3,4-dihydroxyphenylacetic acid	Quercetin	*Eubacterium ramulus* *Clostridium perfringens* *Bacteroides fragilis*	Hydroxylation	Regulating neuroinflammatory mediators	(Zhang *et al.*, 2014; Rinwa & Kumar, 2013)
Hesperetin	Hesperidin	*B. pseudocatenultam WC*	Deglycosylation	Modulates the expression of high mobility group protein 1 and inflammatory cytokines	(Parhiz *et al.*, 2014; Fu *et al.*, 2019; Kwatra *et al.*, 2020)
Baicalein	Baicalin	*E. coli HGU*-3	Deglycosylation	Regulating the NF-*κ*B pathway and lower pro-inflammatory cytokine levels	(Akao *et al.*, 2000; Yu *et al.*, 2019)

4. Substances of Medicinal Food Homology That Impact Depression

4.1. Curcumin

Curcumin is a flavonoid polyphenol derived from *Rhizoma Curcumae Longae*

[33]. Due to its anti-inflammatory properties, it has been used to treat neurological, cardiovascular, and gastrointestinal disorders [34]. Gut microbiota facilitates the conversion of curcumin into biologically active and neuroprotective metabolites. For instance, *E. coli DH10B*, a strain found in the human gut, expresses an enzyme known as nicotinamide adenine dinucleotide phosphate oxidase (NADPH)-dependent curcumin/dihydro curcumin reductase [35]. This enzyme converts curcumin into dihydro curcumin, metabolized to tetrahydro curcumin (THC) [35]. A notable point is that THC exhibits more substantial neuroprotective and anti-neuroinflammatory properties compared to curcumin alone [36]. For example, THC-mediated protection against conditions like Alzheimer's disease involves inhibiting microglial apoptosis, suggesting THC's potential to alleviate psychiatric disorder symptoms through improved neuroinflammation [36]. Therefore, it also proves the fact that Curcumin could be used to treat symptoms of depression.

4.2. Ferulic Acid

Ferulic acid is a cinnamic acid derivative found in medicinal and edible plants such as *Ferula foetida*, which is found to have antidepressant effects [37]. Through the interaction with receptors or enzymes, regulation of pro-inflammatory cytokine expression, and modulation of neural signaling mechanisms, ferulic acid could improve depressive symptoms [38]. Caffeic acid, a methylated metabolite of ferulic acid produced by intestinal flora, has a higher bioavailability. The gut microbiota converts ferulic acid into caffeic acid, which could cross the BBB and enter the central nervous system (CNS) to exert anti-neuroinflammatory and antidepressant effects [39]. Gut flora-produced demethylases enhance the biological activity of caffeic acid by increasing its polarity and decreasing its lipophilicity, thereby facilitating its absorption and activity in the brain [40]. For instance, ferulic acid significantly ameliorated behavioral and neurochemical abnormalities in both prenatal stress stimulation and chronic unpredictable mild stress models. This effect was mediated through the downregulation of the central nuclear factor-kappa B (NF-κB) signaling pathway, resulting in reduced levels of pro-inflammatory molecules, including IL-1β, IL-6, and TNF-α. Furthermore, ferulic acid inhibited the activation of NOD-like receptor thermal protein domain associated protein 3 (NLRP3) inflammasome and subsequent inflammatory cytokines, demonstrating its potential as a therapeutic agent in stress-induced disorders by modulating key inflammatory pathways [41] [42]. As a result, caffeic acid exhibits more substantial anti-neuroinflammatory and neuroprotective effects than ferulic acid.

4.3. Ellagic Acid

Ellagic acid is a dimeric derivative of gallic acid. It is a polyphenolic dilactone with antidepressant effects derived from *Punica granatum*. Ellagic acid-rich foods are associated with a wide range of health benefits owing to their antioxidant and anti-inflammatory activities [43]. However, the bioavailability of ellagic acid is extremely low. Urolithins are the principal products of ellagic acid metabolism by intestinal flora, for example, *Gordonibacter urolithinfaciens*, *Gordonibacter pamelaeae DSM* 19378 *T*, and *Bifidobacterium pseudocatenulatum INIA P*815. Ellagic acid may be metabolized to urolithin A, B, or C [44]. Significantly, urolithins could penetrate the BBB, especially urolithins A and B, which have relatively more robust lipophilicity, enabling them to exert anti-neuroinflammatory effects. In vitro studies demonstrated that urolithin inhibits lipopolysaccharide (LPS)-induced BV-2 microglial inflammation, reducing levels of pro-inflammatory cytokines like IL-6 and TNF-α and enhancing cell viability [45]. In addition, Urolithin A and B exert anti-neuroinflammatory effects by inhibiting the transcription of pro-inflammatory factors such as TNF-α, IL-6, and IL-1β through activation of the NF-κB and phosphoinositide-3 kinase signaling pathways [46]. Therefore, by inhibiting both microglial inflammation and neuroinflammation, a product with higher bioavailability from Ellagic acid, urolithin, can be used to adjust symptoms of depression.

4.4. Daidzein

Daidzin, an isoflavone present in the edible plant *Radix Pueraria lobatae.* The antidepressant effects of Daidzein are significantly enhanced through its metabolism by gut microbiota, which converts it into equol, a highly bioavailable and neuroprotective metabolite. In the gut, daidzein is reduced to (3R)-dihydrodaidzein by the *anaerobic bacterium Coprobacillus strain MRG*-1. This intermediate is further converted to (3S)-equol via (3S, 4R)-tetrahydrodaidzein by the anaerobic bacterium *Eggerthella strain Julong* 732 [47]. S-equol, the predominant form in animals, demonstrates superior permeability across the intestinal and BBB after experiencing the chemical process of deglycosylation [48]. Reports have shown that S-equol could play a significant role in balancing the HPA axis [49]. By modulating cortisol production and other stress-related hormones, S-equol could alleviate symptoms associated with HPA axis dysregulation, in particular, depression. Additionally, S-equol could reduce the production of pro-inflammatory cytokines like IL-6, interleukin-10, and IL-1β, which are often elevated in individuals with depression [50]. This dual action of lowering both cortisol levels and inflammatory markers positions S-equol as a potent agent in improving depressive symptoms.

4.5. Epigallocatechin-3-O-Gallate

Epigallocatechin-3-O-gallate (EGCG) is a major catechin found in green tea, and studies have shown the possibility of curing depression. Recent research has demonstrated that EGCG is metabolized by gut microbiota into gallic acid (GA) and other bioactive compounds [51]. This process of deglycosylation and hydrolysis involves specific gut bacteria such as *Enterobacter aerogenes* and *Raoultella planticola* [52]. These bacteria initiate the hydrolysis of EGCG, breaking it into more bioactive forms. For instance, gallic acid could more effectively cross the BBB, thus enhancing their potential therapeutic effects in the CNS. After being metabolized by gut bacteria, GA plays a significant role in modulating the inflammatory response associated with depression. By inhibiting the expression of inflammatory mediators such as IL-1β and TNF-α, GA can reduce systemic inflammation, a crucial factor in the HPA axis dysregulation observed in depression [53]. In short, the evidence above suggested the possibility of GA being used in medicine industries to cure the unbalanced and inflammatory response relating to the HPA axis, therefore improving symptoms of depression.

4.6. Quercetin

Quercetin, a flavonol with the molecular formula $C_{15}H_{10}O_7$, is found in various medicinal and edible plants such as *Radix Platycodonis* and *Hippophae rhamnoides* [54]. Interestingly, Quercetin relies on Gut microbiota for metabolism. Gut microbiota, including *Eubacterium ramulus*, *Clostridium perfringens*, *and Bacteroides fragilis*, convert quercetin into its primary metabolite, 3,4-dihydroxyphenylacetic acid (DOPAC) through hydroxylation [55]. This microbiota-mediated transformation is essential for quercetin's antidepressant effects. For instance, DOPAC reduces depression symptoms by regulating neuroinflammatory mediators such as IL-6, TNF-α, and IL-1β in the brain [56]. Similarly, these effects are observed in various stress-induced depression models, including chronic unpredictable stress (CUS) and lipopolysaccharide-induced models, where the presence of quercetin mitigated behavioral and neurological damage [57]. Besides, the interesting point found in various studies is that quercetin, without metabolism of the gut microbiota, did not possess an antidepressant effect [56]. Therefore, gut microbiota plays an important role in the antidepressant effect of quercetin. To conclude, quercetin is transformed into DOPAC with the help of gut microbiota and regulates neuroinflammatory mediators, proving its potential curing target for depression.

4.7. Hesperidin

Hesperidin, a flavonoid polyphenol with the molecular formula $C_{28}H_{34}O_{15}$, is found in the edible plant *Pericarpium Citri Reticulatae* [58]. Studies have shown that this compound influences inflammatory mediators and signaling pathways involved in depression. In a rat model of chronic unpredictable mild stress, hesperidin alleviated depression-like behaviors by reducing neuroinflammation and inhibiting the NLRP3 inflammasome activation in the prefrontal cortex [59]. Hesperetin, the metabolite of hesperidin, formed from hesperidin by the action of the intestinal enzyme β-D-glucosidase, plays a key role in this process [60]. Various gut bacteria, especially *B. pseudocatenulatum WC* 0403, facilitate this conversion. In fact, hesperetin crosses the intestinal barrier more effectively than hesperidin, demonstrating more potent anti-neuroinflammatory and neuroprotective effects [61]. It modulates the expression of high mobility group protein 1 and inflammatory cytokines such as IL-1β, IL-6, and TNF-α through the NF-κB and P38 mitogen-activated protein kinase pathways, contributing to its antidepressant properties [62] [63]. In short, gut microbiota facilitates the transformation of hesperidin, making it easier to cross the intestinal barrier, therefore obtaining the chance to achieve a more efficient cure for depression.

4.8. Baicalin

Baicalin (MF: $C_{21}H_{18}O_{11}$), derived from *Radix Scutellaria*, shows the potential as a depression treatment due to its ability to inhibit critical pro-inflammatory mediators and signaling pathways, creating neuroprotective effects [64] [65].

After oral intake, baicalin is mainly transported to the colon, which is quickly hydrolyzed into baicalein by the enzyme β-glucuronidase from *E. coli HGU*-3 [66]. Baicalein crosses the BBB more efficiently than Baicalin [67]. This transformation enhances its ability to reduce neuroinflammation and mitigate depression-like symptoms by regulating the NF-κB pathway and significantly lowering pro-inflammatory cytokine levels in the cerebral cortex [68]. Additionally, baicalein suppresses the NLRP3 inflammasome and regulates pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α in the hippocampus and hypothalamus [69]. The regulation of pro-inflammatory cytokines and NF-κB pathways is crucial for alleviating neuroinflammation linked to depression, therefore making baicalin a potential substance used to treat depression.

5. Conclusions

To conclude, this review emphasizes multiple substances of medicinal food homology and summarizes the mechanisms and interactions with the gut microbiota, providing methods for curing depression. In recent research, the chemical process of gut microbiota and substances from medicinal food homology has been ignored. This review summarizes the interaction between polyphenol substances and gut microbiota while also analyzing their connection with depression, but certain elements remain unclear in this review. For instance, only eight typical medicinal food homology substances are mentioned and summarized in this review. Besides, the molecular structure of polyphenol substances before and after the chemical process remains to be determined. This review also lacks a direct experimental result from clinical studies that could prove the antidepressant effect of polyphenols after interacting with the gut microbiota in the human body.

It is essential for the summarization of more medicinal food homology substances for the discovery of a new curing target for depression in the future. Additionally, further clinical trials are required to prove the antidepressant effect of substances in the medicinal food homology in the human body, and the synergistic effects of these substances are worth discovering in the future. The comparison between each medicinal food homology substance is to spend time figuring out the best use of each substance in a specific scenario due to their varying antidepressant characteristics. With the development of computer science, artificial intelligence could be used to sort and give out suitable substances for patients with various diseases. Lastly, the structure differences of certain substances after experiencing a chemical process with gut microbiota need further summarization. In short, understanding medicinal food homology and the mechanism of gut microbiota that increases the bioavailability of these substances is crucial in providing a possible curing target for depression [70] [71].

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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Abbreviation

BBB	blood-brain barrier
BDNF	brain-derived neurotrophic factor
CNS	central nervous system
CORT	corticotropic hormone
CRH	corticotropin-releasing hormone
CUS	chronic unpredictable stress
DOPAC	3,4-dihydroxyphenylacetic acid
EGCG	epigallocatechin-3-O-gallate
GA	gallic acid
IL-1β	interleukin 1 β
IL-6	interleukin 6
LPS	lipopolysaccharide
NADPH	nicotinamide adenine dinucleotide phosphate oxidase
NF-κB	nuclear factor-kappa B
NLRP3	NOD-like receptor thermal protein domain associated protein 3
THC	tetrahydro curcumin
TNF-α	tumor necrosis factor-α
SCFAs	short chain fatty acids