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Research Progress of Polyphenols in the Prevention and Treatment of AD by Regulating Intestinal Flora

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Abstract: The human gut microbiota is known as the "second brain". Intestinal flora is a large number of microorganisms in the human gut, which is a highly diverse bacterial homeostasis system. If this homeostasis is out of balance, the intestinal flora will be disturbed, which will affect the physical health. A growing body of research has shown that intestinal flora participates in two-way communication between gut and brain through gut-brain axis (GBA) and is strongly associated with Alzheimer's disease (AD). At present, there is still a lack of effective treatment for AD. Recent studies have shown that polyphenols play a neuroprotective role by exerting their anti-inflammatory and antioxidant effects. This topic refers to a large number of recent literatures in the same field and makes a comprehensive review of them. It was found that polyphenols with complex structure could not be directly digested and absorbed by human organism, and their bioavailability was low, which affected the effective play of their health effects. The secretory enzymes in the intestinal flora convert them into small molecular metabolites that are biologically active and easy for the body to absorb. At the same time, polyphenols can the composition and function of intestinal flora by acting on its growth or metabolism, and further act on immune, endocrine and intestinal neural pathways in GBA, forming a complex network of relationships. By exerting its neuroprotective effect, it is expected to achieve the purpose of preventing and treating AD.

Keywords: Alzheimer's Disease, Intestinal Flora, Gut-Brain Axis, Polyphenols

1. Introduction

Intestinal flora accounts for 95% of the human intestinal microbial community, which is a highly diversified bacterial homeostasis system, and its homeostasis is affected by many factors such as diet structure and drugs. If the imbalance of this state occurs, intestinal flora will be disturbed, thus affecting the body's health [1]. Recent studies have found that intestinal flora participates in two-way communication between gut and brain through gut-brain axis (GBA), which is closely related to Alzheimer's disease (AD) [2]. The imbalance of intestinal flora leads to increased permeability of intestinal epithelial mucosal barrier and blood-brain barrier (BBB), and bacteria and their metabolites are absorbed into the blood and reach the brain tissue with the blood circulation, directly affecting brain function [3]. In addition, the imbalance of intestinal flora can activate the inflammatory response of intestinal immune system and cause high reaction of the enteric nervous system (ENS), which indirectly affects the occurrence and development of AD through immune, endocrine and enteric nervous pathways of GBA [4, 5]. At present, there is still a lack of effective treatment for AD. Polyphenolic phytochemicals have become a research focus in the prevention and treatment of AD in recent years due to their anti-inflammatory and antioxidant effects.

Polyphenols have multiple phenolic hydroxyl groups in their molecular structure. Polyphenols with complex structure cannot be directly digested and absorbed by human organism, and their bioavailability is low, thus affecting the effective play of their health effects [6]. The secretory enzymes of intestinal flora can convert them into small molecular metabolites with biological activity that are easy for human body to absorb, while the plant chemicals of polyphenols can change their composition and function by

acting on the growth or metabolism of intestinal flora [7]. Some polyphenols can penetrate the BBB to exert their neuroprotective effects [8]. This review reviews the research progress of polyphenols in the prevention and treatment of AD by regulating immune, endocrine and enteric neural pathways between intestinal flora and brain.

2. Immune Pathway

2.1. GBA Immune Pathway Involving Intestinal Flora in AD Occurrence

Bacteria have a symbiotic relationship with their hosts, and about 70 percent of the body's immune system is also found in intestinal lymphatic tissue. Therefore, intestinal microbiota-host interaction is crucial in the development and maintenance of immunity [9]. The human gut is exposed to a large number of harmful bacteria and their metabolites, and the body can normally defend against their damaging effects. However, when the body is in the aging process, such exposure may be harmful to health due to increased permeability of gastrointestinal mucosa and BBB [10]. Bacterial metabolites constitute a large class of proinflammatory complement and innate immune activators, which have the potential role of inducing proinflammatory cytokines, activating complement and altering immunogenicity in the brain. One of the main components of the outer membrane of Gram-negative bacilli, Lipopolysaccharides (LPS) has strong antigenicity, which can break the tight connection between intestinal epithelial cells and promote the translocation of intestinal flora to intestinal lamina propria. On the one hand, LPS acts in gut-associated lymphoid tissues (GALT) in the intestinal lamina propria, stimulates the differentiation of effector T cells in GALT, and promotes T cell brain infiltration [11]. On the other hand, LPS enter the bloodstream and act on the BBBS. They are recognized by the Toll-like receptors 4 (TLR4) of the vascular endothelial cells, which form complexes that activate the NF-κB signaling pathway, lead to the synthesis and secretion of inflammatory factors, impair the BBB and induce neuroinflammatory cascades. This eventually leads to neurodegeneration [12, 13] (Figure 1). TLR4 can be widely expressed in a variety of cells in human body, mainly distributed in monocyte/macrophage, coronary endothelial cells, etc. In human brain, it is mainly distributed in periventricular vascular plexus, microglia and astrocytes [14]. Activation of TLR receptors amplifies inflammatory signals and becomes an important driving force for sustained chronic inflammation in AD [15]. Zhang et al. found that the concentration of LPS in the plasma of AD patients was 3 times that in normal patients, and the increase of LPS concentration leads to the destruction of intestinal barrier function and the enhancement of intestinal inflammatory response, which further indicates that intestinal flora may be involved in the pathological process of AD [16]. TLR4 and its association with cytokines have not been thoroughly examined in the brains of subjects affected by Alzheimer's disease. Miron's previous work has used quantitative reverse transcription polymerase chain reaction (qRT-PCR) in the brains of patients with Alzheimer's disease after death, and observed that the expression of TLR4 and Tumor necrosis factor α (TNF-α) genes significantly increases. The expression trend of interleukin1 (IL-6) gene was increased [17]. In addition, bacteria-derived amyloid protein can also activate a large number of signaling pathways in glial cells, driving a series of inflammatory reaction processes and promoting the occurrence and development of AD [18].

2.2. Improving Effects of Polyphenols on GBA Immune Pathway in Which Intestinal Flora Participates in AD

Some polyphenols have the function of regulating the composition of intestinal flora, avoiding the growth of pathogens and inhibiting inflammation. These effects are extended to the potential prevention and treatment of AD. Epigallocatechin-3-gallate (EGCG) is the most important active ingredient in green tea. After review of relevant data, a study showed that EGCG was used to intervene Sprague Dawley (SD) rats injected with E. coli LPS, and found that the levels of inflammatory factors TNF-α and IL-1β in peripheral blood and hippocampus tissue of rats in the LPS treated group were significantly higher than those in the control group treated with normal saline. And EGCG intervention could significantly reduce the levels of inflammatory factors. In addition, in vitro experiments of this study showed that EGCG effectively inhibited the release of TNF-α and IL-1β in cultured macrophages isolated from rat hippocampal tissue [19]. Resveratrol is a kind of polyphenol mainly found in grape and Polygonum cuspidatum. It has antioxidant and anti-inflammatory effects, and can regulate the composition of intestinal microorganisms and effectively repair the damaged intestinal epithelial mucosal barrier [20]. Palomera-Ávalos used LPS intraperitoneally injected C57 male mice to activate inflammation in the brain. TLR4 gene expression and NF-κB protein level in the hippocampus of the mice were significantly higher than that of normal mice, while the expression of TLR4 gene and the level of TNF-α and IL-6 were significantly decreased in the hippocampus of mice treated with resveratrol [21]. A rat model of chronic neuroinflammation was prepared by intraperitoneal injection of lipopolysaccharide to investigate the effects of resveratrol on spatial learning and memory function in the model rats. The results of this study indicated that res alleviated LPS-induced spatial learning and memory decline in rats, which may be related to decreased mRNA expression levels of TNF-α, IL-1, and COX-2 genes in hippocampus [22]. iNOS are mainly found in the cytoplasm of inflammatory cells of white blood cells and are associated with many diseases such as inflammation, tumors and degeneration. iNOS expression was found in the brain of patients with AD after autopsy. Some studies have also suggested that resveratrol can inhibit the activation of NF-κB, induce the apoptosis of mutant cells, and strongly inhibit the expression of iNOS and the production of NO in active macrophages, and its inhibitory effect on the NF-κB pathway may be

related to its ability to reduce the activity of IκB kinase [23]. In the experiments on macrophages activated by resveratol and LPS, it can reduce the expression of iNOS in a dose-dependent manner, and its mechanism may be to reduce the stable state mRNA level of iNOS protein in cytoplasms by inhibiting LPS-induced NF-κB in macrophages [24]. In addition, it has been studied that the combination of resveratrol and lipid-core nanocapsules can prevent or ameliorate neurogenic inflammation caused by Aβ [25]. Curcumin is a polyphenolic substance extracted from the rhizome of curcumin family and araceae family. A previous study showed that curcumin could improve the mucosal barrier function of intestinal epithelium, maintain the integrity of intestinal mucosal barrier, and significantly reduce the secretion of IL-1β in intestinal epithelial cells and macrophages induced by LPS, thus improving the chronic inflammatory process [26].

3. Endocrine Pathway

3.1. GBA Endocrine Pathway Involved in Intestinal Flora When AD Occurs

An important component of GBA's endocrine pathway is the Hypothalamic-pit uitary-adrenal (HPA) axis. When the body is in a state of stress, the HPA axis releases cortisol, which can regulate the activity of intestinal immune cells and the release of cytokines, affect intestinal permeability, and change the composition and function of intestinal flora. At the same time, intestinal flora is disordered and harmful factors are released, causing damage to brain tissue by regulating the activity of HPA axis [27] (Figure 1). Animal experiments showed that germ-free mice exhibited stronger HPA axis response compared with Specific Pathogen Free (SPF) mice under stress, with high levels of corticotropin and corticosterone increased and inflammatory response enhanced, which could be reversed by colonization of the normal intestinal flora of SPF mice [28]. The release of the pro-inflammatory factor IL-6 activates the HPA axis and leads to dysregulation of the glutaminergic system by reducing the expression of glutamate transporters in astrocytes. The increase of extracellular glutamate leads to the influx of Ca^{2+} into neurons, and the overload of Ca^{2+} will lead to neurotoxicity and can react with reactive oxygen species to activate cysteine protease and trigger apoptosis cascade reaction, leading to neuron death [4]. In addition, there are more than 20 kinds of intestinal endocrine cells in the gut, which constitute the largest endocrine organ of the human body. About 95% of 5-Hydroxy-tryptamine (5-HT) was synthesized by enterochromaffin cells and enteric intermuscular nerve plexus, and its anabolic and physiological functions were regulated by intestinal flora [29]. As an important neurotransmitter, 5-HT plays an important role in the GBA signaling pathway and the occurrence and development of AD (Figure 1). An animal study showed that 5-HT reuptake inhibitors increased the extracellular content of 5-HT in mouse brain tissue and significantly decreased the content of β-amyloid protein (Aβ) by 25% [30].

The influence of the hypothalamic-pituitary-gonadal axis on AD has also attracted much attention in recent years. The release of estrogen is regulated by the hypothalamic-pituitary-gonadal axis. Epidemiological investigations have found that postmenopausal women increase their susceptibility to AD due to rapidly declining estrogen levels, decreased cognitive ability and memory ability. These findings suggest that estrogen deficiency may be one of the risk factors for AD [31]. Estrogen can regulate the composition of intestinal flora and maintain the integrity of intestinal epithelial barrier. Intestinal flora can also transform binding estrogen into biologically active estrogen, thus affecting the estrogen level throughout the body [32]. It has been found that estrogen could ameliorate the decreased abundance of intestinal microbiome and the decreased ability of short-term memory and spatial memory in rats after ovariectomy [33].

3.2. The Improvement Effect of Polyphenols on GBA Endocrine Pathway Involved in Intestinal Flora During AD Occurrence

At present, the main studies on the improvement of nerve function injury by polyphenols by regulating HPA axis include Res and quercetin. Ali's research team demonstrated that Res exerts a neuroprotective effect by regulating the activity of the HPA axis and reducing serum Cort levels in animal experiments [34]. In addition, another animal experiment showed that Res can significantly improve the learning and memory ability of rats and increase the level of 5-HT in the hippocampus, suggesting that Res can restore the cognitive impairment that occurs during normal aging process by preventing the decline of 5-HT neurotransmission [35]. Quercetin is high in plants such as rutin, quercetin and hypericin. In previous studies, quercetin was used to intervene in cognitively impaired male Wistar rats, and it was found that quercetin can significantly reduce the expression of inflammatory factor IL-6 caused by the activation of microglia cells in rat brain tissue, thus inhibiting the hyperresponse of HPA axis and reducing the content of serum Cort [36].

Clinical trials have shown that the risk of developing AD in postmenopausal women is reduced by 30% to 40% after estrogen therapy [37]. Population studies have shown that estrogen therapy significantly increases the risk of endometrial cancer, ovarian cancer, and nonfatal myocardial infarction. Phytoestrogens are similar in structure and function to estrogen and have similar effects on the target organs of estrogen, providing possibilities for estrogen replacement to prevent and treat AD [38]. Soybean isoflavones (SIF) is the most common phytoestrogens with estrogen-like effects, and β-glucuronidase secreted by intestinal bacteria can improve the bioavailability of SIF [39]. An animal study by Mirahmadi showed that SIF can improve the spatial memory ability of rats with LPS-induced cognitive impairment, significantly reduce the expression of pro-inflammatory factors such as NF-κB and TNF-α in the

brain, and protect neurons from the neuroinflammatory damage mediated by LPS-activated microglia cells [40].

4. Enteric Neural Pathway

4.1. GBA Endocrine Pathway Involved in Intestinal Flora When AD Occurs

The stabilization of enteric nervous system (ENS) depends on the dynamic balance of intestinal microorganisms. ENS is considered to be a conduit for intestinal effects, regulating the abundance of immune cells in the gastrointestinal tract [41]. The animal experiments of Mallappa found that compared with wild-type mice, the gastrointestinal motility of TLR4 knockout mice was significantly delayed and the number of neurons was reduced [42]. AD is associated with the dysfunction of cholinergic neurons in brain tissue, which in turn leads to neurodegeneration and synaptic reduction, resulting in impaired working memory and progressive dementia [43]. More than 70% of intestinal neurons were cholinergic neurons, further supporting the potential influence of ENS in the pathological process of AD. Amyloid precursor protein (APP) is also usually expressed in ENS [44]. Mice genetically modified to express three mutant forms of APP (Lys 670 Asn, Met 671 Leu and Val 717 Phe) or to have a double mutant APP (Lys 670 Asn and Met 671 Leu) plus mutant presenilin 1 (PS1-dE9), In vivo, it is manifested by progressive high expression of Aβ in intestinal neurons, and this accumulation of Aβ is associated with decreased number of intestinal neurons, motility impairment, and increased susceptibility to intestinal inflammation [45]. So far, few studies have been conducted on the mechanism related to ENS in AD patients. Aβ immune response plaques were found in the intestinal mucosa of two AD patients at an early stage, but no follow-up study was conducted [46]. Only one study compared ENS in AD patients with healthy individuals and patients with other forms of dementia, and no loss of intestinal neurons was found [47].

4.2. Improving Effects of Polyphenols on Enteric Neural Pathways of GBA in Which Intestinal Flora Participates in AD Occurrence

Some studies have found that polyphenols have regulatory effects on intestinal flora and intestinal neuron activity. EGCG can improve intestinal flora disorder under high fat diet and significantly increase the abundance of intestinal flora [48]. In addition, EGCG can up-regulate the expression of acetylcholine, promote the transmission of intestinal cholinergic ganglion, and affect the activity of intermuscular plexus in the ileum of guinea pigs through the depolarization of intermuscular neurons [49]. Combining EGCG to regulate brain tissue neurons to activate stress signaling pathways and reduce the production of Aβ, suggesting that polyphenols may improve AD by regulating intestinal neural pathways involved in intestinal flora [50].

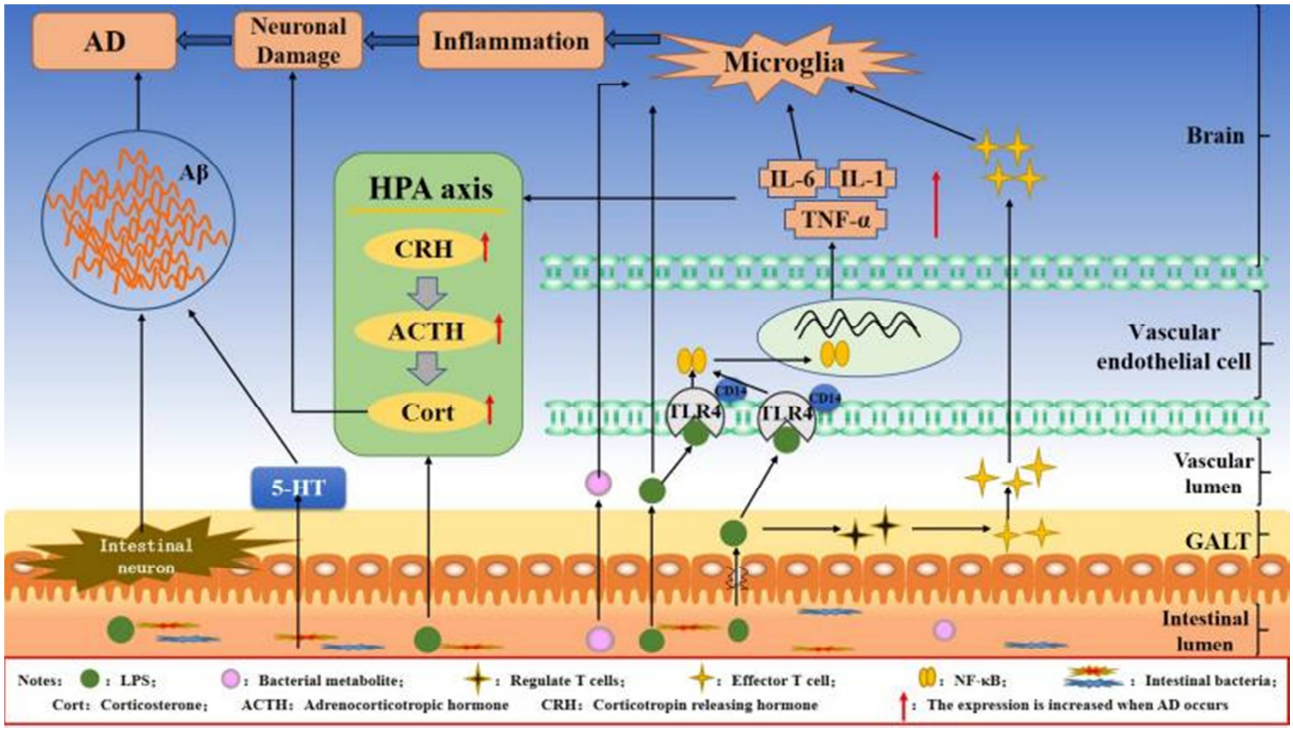

Figure 1. *Intestinal flora is involved in regulating the gut-brain axis.*

5. Conclusion

Polyphenols with complex structure could not be directly digested and absorbed by human organism, resulting in lower bioavailability. The secretory enzymes in the intestinal flora can convert them into small molecular metabolites that are biologically active and easily absorbed by the body. At the

same time, polyphenols affect the composition and function of intestinal flora by regulating the growth or metabolism of intestinal flora, and exert their neuroprotective effects on immune, endocrine, and intestinal nerve pathways in GBA, achieving the goal of preventing and treating AD.

6. Prospect

So far, the pathogenesis of AD has not been fully elucidated and effective prevention and treatment measures are lacking. Polyphenols are rich in food sources, and many animal studies have shown that polyphenols have anti-inflammatory, antioxidant and strong neuroprotective effects, which has a very broad application prospect in the prevention and treatment of AD. Polyphenols are absorbed and utilized by the human body in the gut, and their bioavailability and effects largely depend on their transformation through intestinal flora. However, there are few research data on the effects of polyphenols on intestinal flora and their role in the occurrence and development of AD by regulating the GBA, and further research and exploration are still needed. In addition, metagenomics and metabolomics studies can be combined to better understand the relationship between dietary polyphenol mixtures and gut flora, and to gain a deeper understanding of its effect on AD.

Author Contributions

Song Chenmeng contributed to the writing of the manuscript and the drawing of the mechanism diagram. Revisions of the manuscript were performed by all authors.

Song Chenmeng takes full responsibility for the content of the manuscript. Thanks to the other four authors for their revisions.

Conflict of Interest

None of the authors has any conflicts of interest to declare.

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