The Role of Gut Microbiota in the Progression of Parkinson’s Disease and the Mechanism of Intervention by Traditional Chinese Medicine

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Abstract: Parkinson’s disease (PD) is a common degenerative disease of the nervous system that seriously affects the quality of life of the patients. The pathogenesis of PD is not yet fully clear. Previous studies have confirmed that patients with PD exhibit obvious gut microbiota imbalance, while intervention of PD by regulating the gut microbiota has become an important approach to the prevention and treatment of this disease. Traditional Chinese medicine (TCM) has been shown to be safe and effective in treating PD. It has the advantages of affecting multiple targets. Studies have shown TCM can regulate gut microbiota. However, the specific mechanism of action is still unclear. Therefore, this article will mainly discuss the association of the alteration of the gut microbiota and the incidence of PD, the advantages of TCM in treating PD, and the mechanism of regulating gut microbiota by TCM to treat PD. It will clarify the target and mechanism of TCM treating PD by acting gut microbiota and provided a novel methodology for the prevention and treatment of PD.

Keywords: Parkinson’s disease, gut microbiota, traditional Chinese medicine, pathogenesis

Parkinson’s disease (PD) is a common neurological degenerative disease in the elderly, characterized by lesions of the substantia nigra and striatum. The main symptoms of this disease are tremor, muscle rigidity, bradykinesia, and unstable posture.¹ An annual increase in the incidence of PD has been noted in the elderly population. The prevalence rate of the elderly over 65 years old with this disease is as high as 1–2%, and the incidence rate of the group over 85 years old reaches 4%.² PD has caused a serious burden on both patients and their families. Current treatments for PD either increase/replace DA, or prevent the breakdown of DA, or prolong the action of levodopa to help control tremors.³ Medications and surgery have been used to treat PD, but both have moderate side effects and often produce disappointing results.⁴,⁵ Therefore, it is particularly important to focus on addressing different treatment strategies for this disease. The clinical application of Traditional Chinese Medicine (TCM) is gradually supported by clinical evidence. However, the specific mechanism of action is still unclear. TCM is usually taken orally and is absorbed in the intestinal tract. A variety of studies have shown TCM regulate gut microbiota.⁶–⁸ Gut microbiota refer to the assembly of microorganisms, such as bacteria, archaea, eukaryotes, and viruses, which colonize the intestine.⁹ Gut microbiota have been shown to be closely associated with PD.¹⁰ However, it remains unclear whether Chinese herbal medicine can be used to treat PD by acting on the gut microbiota. The present study addressed this hypothesis.

The Association of the Alteration of the Gut Microbiota and the Incidence of PD

Alterations of Gut Microbiota Composition in PD Patients

The human intestine has been reported to contain a high number of microorganisms (microbiota). Microbiota comprise a higher number of genomes than those noted in human cells.¹⁰ Therefore, retaining the stability of the gut microbiota is
the key to maintain normal physiological activities of the human body. Previous studies have shown that the imbalance of the gut microbiota is closely related to the occurrence of type 2 diabetes, obesity, and atherosclerosis.\textsuperscript{11} As a common neurological disease, PD has been studied for nearly two centuries. However, the mechanism of PD remains unclear. A large number of studies have found a close relationship between disorders of the gut microbiota and the incidence of PD, the gut microbiota of PD patients is disordered [Table 1]. Several groups of differences are evident between patients and control groups. Previous studies have shown that the number of \textit{Lactobacillus} in the feces of PD patients is higher, while the numbers of \textit{Prevotella}, \textit{Clostridium} and \textit{Bacteroides fragilis} are lower. In addition, the decline in the number of \textit{Prerevotella} may result in decreased mucin synthesis and increased intestinal permeability.\textsuperscript{12} In the feces samples of PD patients, the numbers of anti-inflammatory-related bacteria, such as \textit{Coprococcus}, \textit{Blautia}, and \textit{Roseburia} were significantly reduced. This bacterial species may promote the occurrence of inflammation in the colon.\textsuperscript{13} In addition, a previous study indicated that the numbers of \textit{Butyricicoccus} and \textit{Clostridium XIVb} of PD patients were significantly increased compared with the corresponding numbers noted in the healthy control group, which may be related to the cognitive impairment of PD.\textsuperscript{14} In PD patients, \textit{Christensenellaceae} and \textit{Desulfovibrionaceae}, \textit{Bifidobacterium}, \textit{Collinsella}, \textit{Bilophila}, and \textit{Akkermansia} are relatively abundant. By contrast, \textit{Lachnospiraceae}, \textit{Roseburia}, \textit{Lachnospiraceae}, and \textit{Faecalibacterium} exhibited lower abundance.\textsuperscript{15} Nishiwaki et al used a meta-analysis to compare 223 PD patients with 137 healthy controls and demonstrated that the numbers of \textit{Akkermansia}, \textit{Catabacter}, and of the bacterial species \textit{Akkermansia} were increased, while those of \textit{Roseburia}, \textit{Faecalibacterium}, and \textit{Lachnospiraceae ND3007} were decreased.\textsuperscript{16} A previous study utilized two large datasets from a Microbiome/Metagenome-wide association study to specify changes in the gut microbiota of patients with PD. Specific pathogenic bacteria were identified in PD patients, such as \textit{Porphyromonas}, \textit{Prevotella Corynebacterium}, \textit{Bifidobacterium}, and \textit{Lactobacillus}, their abundance was decreased, whereas the abundance of short-chain fatty acid (SCFA)-producing bacteria, such as the \textit{Rumenococcus} and \textit{Lactosporaceae} was also decreased in PD patients, moreover, PD exhibited an increase in the abundance of \textit{Bifidobacterium} and \textit{Lactobacillus}, which are probiotics for sugar metabolism that may become conditional pathogens in PD.\textsuperscript{17} In general, the data indicated that the composition of the gut microbiota of PD patients had changed, which was

### Table 1 Bacterial Composition Alterations in PD Patients Compared to Healthy Controls

| Comparison | Microbiota | Reference |
|------------|------------|-----------|
| 52 PD patients and 36 spouses of PD patients | **Lactobacillus** (H)  
**Prevotella** (L) **Clostridium cocoides** (L)  
**Bacteroides fragilis** (L) | Hasegawa et al\textsuperscript{12} |
| 38 PD patients and 34 healthy controls | **Ralstonia** (H)  
**Blautia** (L) **Coprococcus** (L) **Roseburia** (L)  
**Faecalibacterium** (L) | Keshavarzian et al\textsuperscript{13} |
| 45 PD patients and their healthy spouses | **Butyricicoccus** (H) **Clostridium XIVb** (H) | Qian et al\textsuperscript{14} |
| 197 PD patients and 103 controls | **Christensenellaceae** (H) **Desulfovibrionaceae** (H) **Bifidobacterium** (H) **Collinsella** (H) **Bilophila** (H) **Akkermansia** (H)  
**Lachnospiraceae** (L) **Roseburia** (L) **Lachnospiraceae** (L) **Faecalibacterium** (L) | Cirstea et al\textsuperscript{15} |
| 223 PD patients and 137 controls | **Akkermansia** (H) **Catabacter** (H) **Akkermansia** (H) **Faecalibacterium** (L) **Roseburia** (L)  
**Lachnospiraceae ND3007**(L) | Nishiwaki et al\textsuperscript{16} |
| 535 PD patients and 320 controls | **Porphyromonas** (H) **Corynebacterium** (H) **Bifidobacterium** (H) **Lactobacillus** (H)  
**Oscillospira** (L) **Lachnospiraceae UCG-00** (L) **Lachnospiraceae ND3007_group** (L)  
**Agathobacter** (L) **Butyricicoccus** (L) **Blautia** (L) **Faecalibacterium** (L) **Lachnospiraceae** (L)  
**Fusobacterium** (L) **Roseburia** (L) | Wallen et al\textsuperscript{17} |

**Abbreviations:** H, High; L, low.
manifested as a decrease in the relative abundance of SCFA-producing bacteria and an increase in the relative abundance of *Akkermansia*. These changes may reflect the changes in some PD-specific gut microbiota.

The Imbalance in the Gut Microbiota Can Promote the Occurrence of PD Through the ENS-Vagus Nerve Pathway

At present, a variety of studies have shown a close relationship between the occurrence and development of PD and the disorders associated with dysfunction of the gut microbiota (Figure 1). The main pathological features of PD are accumulation of α-syn in Lewy bodies in cells and accumulation of Lewy neurites in axons and dendrites. α-syn was initially discovered in 1980 in the gastrointestinal tract, suggesting that this protein of the nervous system may originate from the gastrointestinal tract. On this basis, Break proposed that this pathogen of PD initially caused intestinal lesions and destroyed the enteric nervous system (ENS), this situation caused the intestinal nerves to produce Lewy bodies, which act on the vagus nerve reaching the substantia nigra and striatum and finally cause the development of PD. Furthermore, Svensson et al demonstrated by the removal of the abdominal vagus nerve that this operation could significantly reduce the risk of PD. These studies provide strong support for the Break hypothesis. The latter was confirmed in animal experiments. By using rotenone to induce PD-like neuropathy in mice by intragastric administration, it was shown that neuropathy initially appeared in the intestinal ENS of mice, whereas, this change was finally present in the substantia nigra of experimental mice. Previous studies have shown that following injection of α-syn into the intestinal wall of rats, this protein is transported from the intestine to the brain. These results indicate that ENS is one of the starting sites of α-syn accumulation and that it is closely related to the occurrence of PD. Qin et al demonstrated that the disturbance of gut microbiota could activate intestinal glial cells, leading to the accumulation of α-syn, which can enter the substantia nigra, translocate to the vagus nerve, and cause PD. Sampson et al transplanted the feces of PD patients and normal subjects into sterile mice. As a result, the mice developed dyskinesia and abnormal intestinal function. When antibiotics were provided to PD mice, which were pre-induced by bacterial endotoxins, it was found that the inflammation of the substantia nigra was improved. The antibiotics could reduce the activation of microglia and increase the number of dopaminergic neurons in the compact substantia nigra. This evidence indicated that the change of the gut microbiota was
closely related to the occurrence of PD. The aforementioned evidence indicated that the dysbiosis of gut microbiota was closely related to the occurrence of PD.

**Dysbiosis of Gut Microbiota Further Exacerbates the Severity of PD**

The imbalance of the gut microbiota is not only closely related to the occurrence of PD, but it is also inseparable from the development of the disease. The accumulation of α-syn in the brain can induce microglia to differentiate into M1 type microglia that secrete pro-inflammatory factors, such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), interleukin-1β (IL-1β), and interleukin-12 (IL-12). Previous studies have shown that IL-6, IL-1β, and other inflammatory factors can stimulate the secretion of corticosteroid releasing hormone and adrenocorticotropic hormone causing abnormal activation of the Hypothalamic–pituitary–adrenal (HPA) axis. It has also been shown that overactivation of the HPA axis can lead to disorders of the gut microbiota. This exacerbates the imbalance of the gut microbiota of patients with PD, leading to the development of PD.

Depression is a common complication of PD. The risk of depression in PD patients is 30% higher compared with patients who do not suffer from PD. As a neuroprotective factor, Brain-derived neurotrophic factor (BDNF) can regulate the growth and remodeling of nerve cells. Previous studies have shown that the decrease in the content of BDNF in the brain of PD patients will affect the function of neurons in the amygdala, leading to depression, the increase in the levels of BDNF can improve depression-like behavior in PD patients. The change in the BDNF-mediated signal transduction is the common basis for accelerating dopaminergic damage and can alter different brain structures to cause depression-like behavior in PD. Therefore, the lack of BDNF levels is one of the important mechanisms leading to the development of depression in PD. Gut microbiota can affect the levels of BDNF in the brain. Previous studies have shown that the ability of gut microbiota to fight depression and improve spatial memory may be achieved by restoring BDNF concentration in the brain. Feng et al demonstrated that compared with the control group, the levels of BDNF in the brain of the rats in the antibiotic group were significantly decreased, which demonstrated that the gut microbiota could affect the expression of BDNF in the brain.

During the treatment of PD, Levodopa (L-DOPA) is mainly used to replace the deficiency of DOPA. However, the long-term intake of L-DOPA can cause dyskinesia, which is manifested as involuntary, aimless, irregular and repetitive movements of the limbs, trunk and face, these effects are the main causes of disability in PD patients. In PD, dyskinesia significantly reduces the quality of life of patients and increases the cost of treatment. 5-hydroxytryptamine (5-HT) is derived from the raphe nucleus of the brainstem, it is an important neurotransmitter and vasoactive substance, which acts extensively throughout the body. Previous studies have shown that the number of dopamine cells in the patient’s body is constantly reduced with the continuous development of the disease. Concomitantly, exogenous L-DOPA is absorbed by 5-HT cells and competes with 5-HT for entry into the vesicles at the end of the 5-HT neurons, this leads to decreased concentration of 5-HT. In the PD monkey model experiment, long-term L-DOPA treatment caused a reduction in the 5-HT levels in the striatum, hippocampus or amygdala. However, the 5-HT levels of the healthy control group did not significantly change. All these data indicate that the abnormality of the serotonergic system is an important cause of PD-associated dyskinesia. It has also been shown that in sterile mice, the expression of tryptophan hydroxylase 1, which is the rate-limiting enzyme for the synthesis of 5-HT is reduced. The intestinal 5-HT levels are reduced, leading to weakening of the intestinal motility. Following administration of probiotics, the intestinal motility of sterile mice was enhanced, and the activity levels of the 5-HT4 receptors were enhanced in vivo. Previous studies have shown that probiotics can increase the levels of 5-HT in the brain of rats. Human-derived bacteria and intestinal bacteria, which are found in mice, were implanted into sterile mouse intestines. This led to an increase in gene transcription of the 5-HT synthesis rate-limiting enzyme and to a concomitant increase in its protein expression in mice, which in turn resulted in increased levels of the 5-HT positive markers in mouse tissues.

In summary, it has been shown that various reasons can cause gut microbiota disorders, leading to the activation of intestinal microglia. This leads to accumulation of α-syn in the enteric nerve. As the disease progresses, α-syn can move along the vagus nerve into the substantia nigra, resulting in the occurrence of PD. The accumulation of α-syn in the brain can cause abnormal activation of microglia in the brain and hyperfunction of the HPA axis, further aggravating the intestinal dysbiosis and leading to neurotransmitter disorders in the brain, which exacerbate PD. The management of PD...
by regulating the gut microbiota is considered to be a new treatment method. At present, various types of drugs have been developed that can regulate the gut microbiota. TCM plays an important role among them.

**The Advantages of TCM in Treating PD**

Traditionally, L-DOPA, which is a dopamine receptor agonist, monoamine oxidase B inhibitors, and other drugs have been used for the treatment of PD. Previous studies have shown that long-term use of these chemicals can cause significant side effects, including nausea, constipation, headaches, and sleep disturbances. At present, the conventional treatment targets of the westernized methods are relatively simple and can cause various adverse events. These treatment methods do not follow a personalized treatment plan. Considering the disadvantages of the long-term use of westernized medicine, an urgent need is required to identify other, safer, and more effective ways to treat PD.

TCM has been used for centuries to treat tremors with optimal results. Until now, the treatment of TCM is still popular in various Asian countries, including China, Japan, and South Korea. In the past few decades, several active substances and potential molecular targets of Chinese herbal medicine have been discovered. Chinese medicine is rich in various substances, such as protein, amino acids, trace elements, vitamins, and other nutritional active substances. The advantage of the application of TCM is its ability to target multiple proteins, which can be used to directly treat PD. In addition, it can also synergize with western medicine to reduce the adverse effects caused by the latter and increase its therapeutic effects. Various TCM include compounds, such as flavonoids, Madecassoside, baicalein, resveratrol, and forsythiae, which can protect neurons and potentially prevent the development of PD.

In addition to showing optimal laboratory efficacy in preventing PD, TCM has also achieved satisfactory clinical results. A randomized study indicated that the Chinese herbal compound Bu Shen Huo Xue Yin could improve the motor symptoms of PD patients. Besides, Chinese medicine can also improve the motor and non-motor symptoms of PD. Sleep disorders are common non-motor symptoms of PD, a randomized study indicated that Yang Xue Qing Nao granules could significantly improve sleep dysfunction. In addition, TCM treatment exhibits certain advantages compared with the corresponding western-based approaches. Firstly, it can improve clinical symptoms and the quality of life of the patients, while prolonging the therapeutic effect of L-DOPA by reducing its dose usage and decreasing the occurrence and severity of L-DOPA-induced dyskinesia [Table 2].

**The Mechanism of TCM in Regulating PD is Mediated via the Gut Microbiota**

Gut microbiota play an important role in the occurrence and development of PD. TCM protects the intestinal mucosal barrier, and restores the diversity of intestinal microbes by regulating the amount and proportion of gut microbiota and metabolites, which not only can decrease release of pro-inflammatory cytokines from the gut into the bloodstream, but also increase the level of SCFAs and certain neuroactive factors, that exerts anti-oxidative, anti-inflammatory, anti-apoptotic via neuronal mechanism, endocrine mechanism, and immunological mechanism. This in turn can protect dopamine neurons in the brain and prevent the development of PD. [Figure 2]

| Advantages                                                      | Reference                        |
|----------------------------------------------------------------|----------------------------------|
| TCM can be used to directly treat PD                           | Mu et al.49, Zhang et al.51       |
| To synergize with western medicine to reduce the adverse effects caused increase its therapeutic effects | Wang et al.52, Zhang et al.56     |
| To improve the motor and non-motor symptoms of PD              | Yang et al.52, Pan et al.53       |
| To improve the quality of life of the patients                 | Gu et al.54                      |

[Table 2 The Advantages of TCM in Treating PD]
Figure 2 TCM prevents the development of PD by regulating the Gut Microbiota. By adjusting the ratio of beneficial/harmful bacteria in the gut microbiota, TCM can increase the concentration levels of SCFA and Ghrelin, which are metabolites of the gut microbiota. This enhances the expression levels of tight junction proteins in the intestine, protects the intestinal mucosal barrier, and reduces the body LPS levels, thereby reducing the secretion of pro-inflammatory cytokines. In addition, it can regulate the function of intestinal endocrine cells and intestinal immunity. By affecting the function of various cell signaling pathways, TCM exerts anti-oxidative, anti-inflammatory, anti-apoptotic, and other functions, and in turn protects dopamine neurons in the brain from further injury. ▲ indicates an increase and ▼ signifies a decrease in the relative process.

Abbreviations: EECs, Enteroendocrine cell; SCFA, Short-chain fatty acids; TCM, Traditional Chinese Medicine; Treg, regulatory T cell; LPS, lipopolysaccharide; ZO-1, Zonula occludens-1; GLP-1, Glucagon-like peptide-1; Th, Helper T cells; Treg, regulatory T cell; IL-1, interleukin 1; IL-6, interleukin 6; IL-8, interleukin 8; TNF-α, Tumor necrosis factor-α.

Regulation of the Structure of the Gut Microbiota and Their Corresponding Metabolites

As mentioned in the aforementioned sections, a high number of studies have shown that patients with PD present with dysbiosis of gut microbiota, which can be summarized as a decrease in the number of beneficial bacteria and an increase in the abundance of pathogenic bacteria. TCM is a type of multi-target medicine. Previous studies have shown that Chinese herbal medicine can regulate the structure of gut microbiota and their metabolites.

Prevotellaceae can participate in the biosynthesis and degradation of mucin in the intestine. The levels of mucin are positively related to the permeability of the intestine.59 When the levels of mucin decrease, external pathogens are more likely to enter the intestinal submucosal nerve plexus.60 Prevotellaceae bacteria can affect the level of auxin in the human body and the change in auxin content can further affect the function of the substantia nigra striatum, which alters the patient’s nerve function.61,62 Lyciumbarbarum can increase the relative abundance of Prevotellaceae.63 Hu et al demonstrated that following Hua Feng Dan and 70W (Rannasangpei) treatment of PD mice for 35 days, the abundance of Prevotellaceae in the intestine was significantly increased.64

SCFA are important metabolites of the gut microbiota, mainly produced by Bacteroides, Bifidobacterium, Lactobacillus, Clostridium, Rosella, and Prevotella.65 SCFA reaches the central nervous system via the blood circulation and can strengthen the blood-brain barrier by increasing the expression levels of tight junction proteins. It also nourishes the nerves and exhibits anti-inflammatory effects.66 Moreover, SCFA exhibits extensive effects on nerve regeneration genes; it inhibits histone deacetylase activity, upregulates the expression levels of brain-derived nerve growth factor and glial cell-derived neurotrophic factor, and protects dopaminergic neurons from further injury.67 Unger et al demonstrated that the composition of the gut microbiota of PD patients was significantly changed and that the concentration of the SCFA mixture in the feces was significantly reduced, which caused enteric nervous dysfunction and gut microbiota...
imbalance. Astragaloside IV is an effective ingredient of TCM that can increase the levels of SCFAs produced and their generation in vivo. Previous studies have shown that berberine can improve the structure of the gut microbiota, repair the damaged microflora enzyme system, and convert the polysaccharides that are not fully absorbed in the intestine into SCFAs. Hydroxysafflor yellow A is an extract of Safflower. Administration of this extract to mice can significantly increase the concentrations of acetic, butyric, and propionic acids in their intestines. This process is related to the increase in the level of SCFA production. Xiexin Tang can increase the production capacity of intestinal microbe-derived SCFA by increasing the mRNA and activity levels of the key SCFA synthesis enzyme acetate kinase.

Regulation of Intestinal Immunity

Previous studies have shown that the intestine is the largest immune organ of the human body, which is mainly composed of intestinal epithelial cells, intestinal intraepithelial lymphocytes, laminal lymphocytes, mesentry-associated lymph nodes, and other tissues. Gut microbiota can promote the development of the intestinal mucosal immune system and maintain the homeostasis of the intestinal environment.

The intestinal mucosal immune system is mainly composed of three parts. The first involves the antibacterial peptides secreted by intestinal epithelial cells; the second contains the immunoglobulin A secreted by the B lymphocytes, which can prevent bacterial translocation; the third part involves immune cells, such as dendritic cells, B lymphocytes, T lymphocytes, and innate lymphocytes. Autopsy analysis of brain tissues indicated that cluster of differentiation 4 (CD4+) and cluster of differentiation 8 (CD8+) T cells in the substantia nigra of PD patients exhibited significant lymphocyte infiltration and microglia activation. The administration of the T cell signal transduction inhibitor FK506 in the α-syn overexpression rat model can significantly reduce the activation of substantia nigra microglia and the number of CD4+ T cells, thereby increasing the survival of dopaminergic neurons. CD4+ T cells can differentiate into helper T cells (Th1, Th2, and Th17) and regulatory T cell (Treg) subsets. They interact and inhibit each other by secreting cytokines, forming a network that maintains a stable internal environment. Tregs induce apoptosis of effector T cells through cell-to-cell contact and the action of soluble factors. Treg cells can reduce the activation of microglia and increase the survival rate of neurons. This function may be achieved by inhibiting Th17.

Treg cells can upregulate the expression of certain neurotrophic factors, such as BDNF, while they downregulate the expression of inflammatory factors, which can induce apoptosis of activated microglia. This study demonstrated that compared with the healthy control group, the Treg cells of PD patients exhibited a weaker effect in inhibiting the proliferation of effector T cells and the release of cytokines. The inhibitory effect of Tregs, which were isolated from PD patients, on effector T cells from healthy allogeneic donors was decreased, indicating that Treg cell dysfunction was involved in the progression of PD. In contrast to these observations, Th17 cells promoted the deterioration of neuroinflammation mediated by IL-1, IL-6, IL-17, TNF-α, and IFN-γ. All these data indicate a close association between immune system imbalance and PD. Gut microbiota play a key role in regulating the dynamic balance of intestinal immune cells. Garidou et al provided mice with a high-fat diet, which caused disturbances in the gut microbiota of the ileum, resulting in a decrease in Th1 cells in the lamina propria. Previous studies have shown that Treg cells in the intestinal mucosa can be induced by intestinal symbiotic bacteria that differentiate and proliferate. For example, Bacteroides fragilis in the intestine can induce Treg development through polysaccharide A, while Clostridium can promote the proliferation of Treg cells. Chinese medicine exerts multiple effects on the regulation of the intestinal mucosal immunity. Polysaccharides and Ginsenosides from American ginseng restored the composition of the gut microbiota, and increased the abundance of various beneficial mucosal-related flora, such as Clostridium, Bifidobacterium, while decreasing the abundance of several harmful bacteria, such as Escherichia coli, Shigella, and Ruminococcus to stimulate small intestinal CD4+ T cells and immunoglobulin A secreting cells, and regulate the intestinal immune barrier. Grape seed procyanidin extract significantly increased the proportion of Tregs in the mouse intestinal mucosa and decreased the expression levels of TNF-α, IL-1β, and IL-6. Grape seed procyanidin extract treatment increased the abundance of slime mold, suggesting that it may have a regulatory effect on the intestinal immune balance. Clematichinenoside AR is a saponin extracted from TCM. It can inhibit the function of IL-10+/− mouse Th17 cells and promote the Treg cell response. The specific mechanism may be related to the inhibition of the PI3K/Akt signaling pathway. Activated PI3K and Akt play an important role in the differentiation of Th17.
cells\(^{47}\) and the inactivation of the PI3K/Akt signaling pathway is involved in the regulation of the immune balance by inducing T cell differentiation to counteract the activity of Th17 cells.\(^{88}\) Dendrobium polysaccharide stimulates intraepithelial lymphocyte and lamina propria lymphocyte to secrete cytokines. It also increases the content of IL-10 and regulatory T cells, which is important for maintaining intestinal immune homeostasis and the integrity of the mucosal barrier.\(^{89}\) TCM exhibits a significant therapeutic effect on intestinal immune barrier damage. By regulating the gut microbiota and enhancing the defense function of the intestinal immune barrier, TCM can be used for the treatment of PD.

**Regulation of Intestinal Endocrine Cells and Products**

Enteroendocrine cell (EECs) are derived from intestinal stem cells. Although EECs account for less than 1% of the entire gastrointestinal lumen epithelial cells, their number exceeds the sum of all endocrine cells in other organs of the body.\(^{90}\) EECs secrete more than 20 different types of hormones, and are considered to be the largest and most complex endocrine organ in the body.\(^{91}\) Studies have shown that EECs also have electrical excitability and chemical sensitivity, allowing the production of gastrointestinal hormones or peptides under various stimuli, and releasing them into the blood to play a systemic role.\(^{92}\) Previous studies have shown that a variety of hormones secreted by intestinal endocrine cells are closely related to PD. Glucagon-like peptide-1 (GLP-1) is a polypeptide hormone secreted by small intestinal L cells, which can efficiently pass through the blood-brain barrier and influence neuronal pathways associated with neuroinflammation, thus having a certain neuroprotective effect.\(^{93}\) GLP-1 receptor agonists or analogs activate GLP-1 to stimulate cell proliferation, which can improve dopaminergic neurotransmission, neuron and synaptic function, disease motor symptoms, and exert an optimal neuroprotective effect.\(^{94}\) Ghrelin is mainly produced by enteroendocrine cells and promotes the release of the growth hormone. It also participates in a variety of endocrine regulation processes and exerts anti-apoptotic and anti-oxidant effects. Finally, it exerts neuroprotective effects by antagonizing 1-methyl-4-phenyl-1,2,3,6-tetrahydropyran-induced neurotoxicity.\(^{95,96}\)

Leptin (LEP) is mainly secreted by fat cells, whereas a previous study has found that endocrine cells can also secrete it. LEP can significantly improve the neurological function of patients with PD.\(^{97,98}\) Taken together, this evidence indicates that EECs play an important role in the occurrence and development of PD. Previous studies have found that the gut microbiota can regulate the secretion of gastrointestinal hormones, such as GLP-1, Ghrelin, and LEP.\(^{99,100}\) TCM plays an important role in the regulation of ENSs. Ginseng soluble dietary fiber increases the abundance of beneficial bacteria, such as *Firmicutes* and *Bacteroides* and regulates the levels of hormones, such as GLP-1, Ghrelin, and cholecystokinin.\(^{101}\) Banana resistant starch can improve the diversity of the gut microbiota and adjust the overall structure of intestinal microbes, by increasing the ratio of *Bacteroides/Firmicutes* and the relative abundance of *Cyanobacterium*. It also downregulates the relative abundance of *Deferrribacteres* and *Tenericutes*. Banana resistant starch can inhibit the proliferation of *Turicibacter, Romboutsia*, and *Oligella*. Their abundance and the expression levels of Ghrelin are negatively correlated.\(^{102}\) The Sangzhi alkaloids of the Chinese medicine can regulate the total amount of SCFA-producing bacteria in the intestine, which causes upregulation in the expression of the GLP-1 syngenesis-related gene proglucagon, and promotes the synthesis of GLP-1.\(^{103}\) The Shenqi compound can improve the imbalance of the gut microbiota, increase the proportion of *Bacteroides*, butyrate-producing bacteria, and other beneficial bacteria, as well as promote the secretion of GLP-1 by L cells.\(^{104}\) In addition, Sorghum resistant starch extracted from sorghum has also been shown to regulate the structure of the gut microbiota and promote the synthesis of LEP.\(^{105}\) Panax notoginseng saponins increase the abundance of *Akkermansia muciniphila* and *Parabacteroides distasonis*, which shape the intestinal microbiota of mice and increase the levels of LEP.\(^{106}\) TCM can regulate ENSs, increase the synthesis of gastrointestinal hormones, such as GLP-1, Ghrelin, and LEP, and exert a therapeutic effect on PD by affecting the gut microbiota.

**Regulation of the Intestinal Mucosal Barrier**

The intestinal mucosal barrier is mainly composed of mechanical, biological, immune, and chemical barriers. The most important interaction in the mechanical barriers involves the tight junctions,\(^{107}\) which are composed of tight junction proteins, including cytoplasmic proteins, such as claudin-1, occludin, zonula occludens-1 (ZO-1), the junction adhesion molecules, and the cytoskeleton. The intestinal mucosal barrier has a barrier and fence
function.\textsuperscript{108} When the expression levels of claudin-1, occludin, and ZO-1 in the intestinal mucosa are reduced, the tight junctions become unstable and the “gap” between cells increases.\textsuperscript{109} In parallel, the permeabilization of the cells increases, leading to intestinal mucosal barrier damage.\textsuperscript{110} The increase in intestinal permeability and the translocation of bacteria and inflammatory bacterial products, such as lipopolysaccharide (LPS), may cause inflammation and oxidative stress in the gastrointestinal tract, which may trigger the accumulation of α-synuclein in ENS, the latter promotes neuroinflammation by enhancing the activation of astrocytes and microglia.\textsuperscript{111} Concomitantly, the destruction of the gastrointestinal barrier will further change the structure of the gut microbiota, which is conducive to the colonization of inflammatory bacteria.\textsuperscript{112} In Keshavarzian’s study, PD patients indicated increased intestinal mucosal permeability and systemic poisoning of colon endotoxin.\textsuperscript{17} In patients with PD, the intestinal permeability or “intestinal leakage” increases and the deposition of α-syn in the ENS increases.\textsuperscript{113} In addition, the accumulation of α-syn in the colonic mucosa of PD patients also leads to impairment of the intestinal barrier function.\textsuperscript{114} Scutellaria-Coptis can upregulate the expression levels of the tight junction proteins claudin-1, occludin and ZO-1, which significantly improves intestinal epithelial damage and inhibits the excessive transport of lipopolysaccharide to the blood circulation.\textsuperscript{115} Fucoidan is an effective ingredient in seaweed. It has been shown that following fucoidan treatment, the levels of D-lactic acid, diamine oxidase, and endotoxin are decreased, whereas the expression levels of occludin, claudin-1, and ZO-1 are increased. The main functions of these proteins involve the repair of the intestinal barrier.\textsuperscript{116} Treatment of Dextran sodium sulfate-induced mice with Huang Lian Jie Du Decoction (HLJDD) significantly increased the expression levels of ZO-1 and occludin in the colon tissues. In addition, HLJDD intervention significantly inhibited the decrease in mucin secretion induced by dextran sodium sulfate. The aforementioned results indicated that HLJDD could protect the intestinal mucosa by increasing the expression of tight junction proteins and the secretion of mucus proteins.\textsuperscript{117} Salvia miltiorrhiza stems and leaves can also enhance the intestinal barrier function by upregulating the expression levels of the ileum and colon tight junction protein ZO-1, as well as those of occlusion and tight junction donor protein-5.\textsuperscript{118}

Study has shown that continuous inflammation can lead to imbalance in the expression levels of adhesion molecules and can cause damage to the intestinal mucosal barrier.\textsuperscript{119} LPS is considered to be the trigger of the low-grade inflammatory response, it is the main component of the cell wall of intestinal gram-negative bacteria.\textsuperscript{120} The increase in the abundance of Enterobacteriaceae in PD can increase the serum LPS concentration.\textsuperscript{121} LPS can induce the synthesis of TNF-α, IL-1, IL-6, IL-8, and other inflammatory factors and destroy the intestinal mucosal barrier.\textsuperscript{122} The expression levels of pro-inflammatory cytokines in PD patients were significantly increased.\textsuperscript{123} Berberine is the main ingredient of Coptis, which can significantly reduce the levels of serum LPS, IL-1β, TNF-α, and IL-6 in mice. This effect may be related to the increase in the expression levels of ZO-1 and occludin in the colonic mucosa and to the increase in the thickness of the mucosa.\textsuperscript{115} Gastrodia can reduce the levels of LPS in the serum by remodeling of the gut microbiota; they concomitantly reduce the expression levels of serum TNF-α, IL-1β, IL-6, IL-8, and other pro-inflammatory factors.\textsuperscript{124} Curcumin is an extract of turmeric that exhibits significant inhibitory activity against Enterococcus and Clostridium, by downregulating the expression levels of Toll-like receptor 4 mRNA and protein in the intestine, and inhibiting the release of key inflammatory molecules (IL-1β, TNF-α). Concomitantly, it increases the secretion of immunoglobulins and alleviates intestinal inflammation.\textsuperscript{125} The protection of the intestinal mucosa by TCM can prevent bacteria and their harmful metabolites from entering the blood, which is of important significance for the prevention and treatment of PD.

**Conclusion and Prospects**

Gut microbiota have received considerable attention as a new potential target for the treatment of PD. TCM has been reported as a safe and effective strategy for regulating gut microbiota and improving PD in clinical trials. Chinese herbal compounds or single Chinese medicines have been used to treat PD for thousands of years and have achieved optimal results. In recent years, a large number of studies have found that TCM has a regulatory effect on intestinal microbes. This article summarized the relationship between the gut microbiota and the occurrence and development of PD, and the underlying regulatory mechanism. It also explained that TCM could alter the structure of the gut microbiota and their metabolites to regulate intestinal mucosal barrier, inflammation, immunity, and intestinal endocrine activity. By regulating these processes TCM can be used to
treat PD. The present study provided a novel methodology for the prevention and treatment of PD by using TCM. At present, a limited number of studies have been reported on the treatment of PD with TCM via the regulation of the gut microbiota. The majority of these research studies focused on the effect of TCM on the gut microbiota and their metabolites. However, the molecular biological mechanism underlying the treatment of PD has been rarely examined. Therefore, additional research can be carried out in future studies on this topic. TCM affects multiple pathways and targets multiple proteins. Its mechanism of action is complex. Therefore, a systems-biology approach can be used in future studies in order to provide additional insight into the complex mechanism of action of TCM with regard to the treatment of PD.

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Disclosure
The authors of this study declare that they have no conflict of interest.

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