REVIEW
NEUROSCIENCE

Diseases & Research

# Update Review of the Relationship Between Gut Microbiota and Neurodegenerative Diseases

Yefeng Wang[1], Jing Guo[1], Yu Fu[1], Yuying Li[1], Chongming Wu[1,2,#]

[1] School of Chinese Materia Medica, Tianjin University of Traditional Chinese Medicine, Tianjin 301617, China
[2] Tianjin Key Laboratory of Therapeutic Substance of Traditional Chinese Medicine, Tianjin 301617, China

**Abstract:** Neurodegenerative disease is characterized by progressive deterioration of function or structure of nerve cells in central nervous system, mainly manifested as declined cognitive function and impaired motor behavior. Its morbidity and mortality continue to increase with age, and cause a heavy economic and social burden. Gut microbiota is proved to influence behavior through the microbiota-gut-brain axis, and possess tight relationship with neurodegenerative disease such as Alzheimer's Disease (AD). Although several studies have assessed the crucial role of gut microbiota in neurodegenerative disease and summarized some potential mechanisms, the more systematic and comprehensive knowledge in this field still need to be updated timely to boost interventions in neurodegenerative disease based on gut microbiota. For this purpose, we firstly analyzed how the gut microbiota changed in the state of neurodegenerative diseases. Then, we investigated the influence of gut microbiota on the onset and progression of neurodegenerative disorders. Finally, we proposed effective interventions for managing neurodegenerative disease from the perspective of gut microbiota. This updated review provides effective intervention strategies for neurodegenerative disease based on microbiota-gut-brain axis.

**Keywords:** Gut microbiota; Neurodegenerative disease; Microbiota-gut-brain axis; Microbial metabolites.

## Introduction

Neurodegenerative disease is gradually becoming prevalent among aging populations, and poses serious menaces to their health. At present, the common neurodegenerative disease includes Alzheimer's disease, Parkinson's disease, multiple sclerosis, etc[1]. Generally, these diseases are characterized by high incidence, rapid progression, high disability rate, and high mortality, imposing heavy economic burdens on patients and society[2]. The pathogenesis of neurodegenerative disease is complex and involved in several mechanisms. One of the recognized mechanisms is the injury of central nervous system, which further lead to neuronal damage, affecting normal physiological functions and significantly impacting human survival and health[3]. However, the peculiar structure (blood-brain barrier) of the central nervous system leads to a certain drug cannot be adequately delivered to the injured brain, bringing enormous challenges for drugs development[4]. This prompts us to find safe and effective treatment methods for neurodegenerative diseases.

As the second most important genome of the human body, gut microbiota plays an integral part in host metabolism, immune response, intestinal mucosal integrity, and intestinal permeability, thus participates in the development of several disease, such as ulcerative colitis[5], coronary artery disease[6], hyperlipidemia[7], mental disorder[8], and so on. Compelling research has shown the presence of reciprocal signals between the central nervous system and the gut, termed as "gut-brain axis"[9]. Gut microbiota, as living organisms in the gastrointestinal tract, can affect host emotions and cognitive functions. Conversely, neurological disorders can also lead to disruption of gut microbiota. These dual-directional regulations are defined as "microbiota-gut-brain axis"[10], and contributes to several diseases. The intricate "gut-brain axis" involves the central nervous system, enteric nervous system, and autonomic nervous system, establishing a connection between the gut and the brain. Mechanistically, gut microbiota-derived metabolites, such as short chain fatty acids (SCFAs) and bile acids (BAs), can activate related signaling molecules to regulate the function of central nervous system. Meanwhile, the production of some important neurotransmitters, such as serotonin (5-HT), gamma-aminobutyric acid (GABA) and dopamine, is associated with some specific gut bacteria. Additionally, the levels of hormone (ghrelin, leptin and glucagon-like peptide-1), regulated by gut microbiota, also participated in the functional regulation of central nervous system[11,12]. Therefore, "microbiota-gut-brain axis" has been recognized as an essential mediator in the pathogenesis and progress of neurodegenerative diseases.

This updated review mainly focused on elaborating the alterations of gut microbiota in neurodegenerative diseases, and investigating how microbiota-derived metabolites affecting its occurrence and development. Importantly, we proposed the interven-

# Correspondence: Chongming Wu. E-mail: cmwu@tjutcm.edu.cn. Address: School of Chinese Materia Medica, Tianjin University of Traditional Chinese Medicine, Tianjin 301617, China.
*Received 11 April 2024; Revised 15 May 2024; Accepted 6 June 2024; Available Online 21 June 2024*
DOI: 10.54457/DR.202401007

tion strategies for neurodegenerative disease based on gut microbiota.

## Neurodegenerative disease alters the gut microbiota community

The gut microbiota refers to the microorganisms residing in the human gastrointestinal tract, constituting an essential component of the host intestinal microbial ecosystem[13]. Gut microbiota maintains host physiological functions and body health via regulating host immune function, endocrine system, nervous system, and enhancing intestinal barrier function[14]. Recent studies have highlighted the presence of a bidirectional signaling pathway between the gut microbiota and the brain, referred to as the microbiota-gut-brain axis (MGBA)[15]. A mounting number of studies have revealed the alterations of gut microbiota among neurodegenerative disease[16-18], indicating that targeting the gut microbiota could be a promising approach to help alleviating symptoms of neurodegenerative diseases.

### Alzheimer's disease

Alzheimer's Disease (AD), a progressive and insidious neurodegenerative disease, mainly manifests as the gradual loss of memory, the damage of language ability, the impaired cognition and mobility, severe patients even suffering from the loss of independent living ability[19]. The comparison between AD patients and healthy controls showed that the the levels of Firmicutes and Actinobacteria phyla were reduced in patients with Alzheimer's disease, while the abundance of Bacteroidetes phylum was increased, these changes may lead to neuroinflammation and the formation of Aβ plaques[20]. Additionally, families such as Lachnospiraceae and Veillonellaceae show slightly decreased in AD patients, while families like Enterococcaceae and Lactobacillaceae exhibit a slight increase[21]. According to the study conducted by Zhuang et al. although the abundance of Firmicutes is similar between AD and control groups, the abundance of Bacteroidetes is lower in the AD group, leading to a difference in the Firmicutes/Bacteroidetes ratio between the two groups[22]. Cattaneo et al. also noted that the abundance of pro-inflammatory bacteria is relatively higher, while the levels of anti-inflammatory bacteria were found to be lower in the Alzheimer's disease group compared to healthy age-matched controls. These changes in bacterial abundance may influence the peripheral inflammatory status of AD patients, leading to a significant increase in serum pro-inflammatory cytokine concentrations, exacerbating AD symptoms[23]. It is undeniable that alterations in gut microbiota composition are linked to Alzheimer's disease pathology. However, the changes of some bacteria are not consistent, which may be due to the inconsistent study cohorts and the redundancy of gut microbiota.

### Parkinson's disease

Parkinson's Disease (PD) is a prevalent neurodegenerative disorder that commonly affects middle-aged and elderly individuals, characterized by the damage of dopaminergic neurons in the midbrain substantia nigra and the buildup of α-synuclein (α-syn) protein aggregates[24]. As the second most prevalent brain disease, the prevalence of Parkinson's disease has exceeded 6 million, and still steadily growing[25]. Recent research suggests that PD may originate from the intestinal tract, and there is an obvious association between gut microbiota and the occurrence and symptoms of PD[26]. PD patients have a higher proportion of overgrown gut bacteria as compared to the normal population. It is reported that the abundance of *Streptococcus* genus in the PD patients was enhanced, whereas the abundance of *Lachnospira* and *Eubacterium* genera was significantly reduced[27,28]. The analysis of fecal microbiota in PD patients and healthy individuals using 16S rRNA gene sequencing revealed the significant changes in the abundance of families such as Bifidobacteriaceae, Lactobacillaceae, Enterobacteriaceae, Enterococcaceae, and Pasteurellaceae[29], indicating a correlation between changes of gut microbiota composition and clinical manifestations of the PD patients. Additionally, Scheperjans et al. found a decreased abundance of *Prevotella* genus in PD patients, which was positively correlated with the severity of gait and postural instability[30]. Another study found a significant decrease in cellulose-degrading bacteria such as *Ruminococcus* in the feces of PD patients, this could potentially result in a decrease in short-chain fatty acids (SCFAs) and an increase in the production of endotoxins and neurotoxins, thereby exacerbating the progression of PD[31]. These discoveries validate the relationship between gut microbiota composition and the onset, progression, clinical symptoms, and severity of Parkinson's Disease (PD).

### Multiple Sclerosis

Multiple Sclerosis (MS) is an autoimmune condition marked by inflammatory demyelination within the central nervous system. The main symptoms of patients consist of decreasing vision, limb weakness, sensory abnormalities, and ataxia[32]. In recent years, numerous studies have highlighted the close association between gut microbiota disturbances and the development of Multiple Sclerosis (MS). Early research by MIYAKE et al. have revealed the changes of 21 bacteria in MS patients , with decreased levels of anti-inflammatory bacteria such as *Prevotella* and *Bacteroides*, and increased levels of potentially inflammatory bacteria such as *Dorea* and *Blautia*[33,34]. Additionally, Cox et al. found a reduction in microbial genera associated with increased physical activity and cognitive function, as well as decreased abundance of genera associated with butyrate and propionate production in MS patients[35]. Notably, the occurrence of MS relapse seem to be related to the decrease in the abundance of the genus *Clostridium* and a rise in the prevalence of Firmicutes and *Archaea*[36]. The analysis of gut microbiota using metagenomic sequencing also revealed the dysbiosis of gut microbiota in MS patients compared to healthy individuals, with a significant decrease in fiber-degrading bacteria such as *Clostridium butyricum*, Escherichia coli, and Firmicutes[37]. To sum up, both the increase of harmful bacteria and the decrease of beneficial bacteria may cause inflammation in the gut and central nervous system, thus aggravating or triggering pathological changes of MS. Thus, dysbiosis of the gut microbiota has become recognized as an important potential factor influencing the progression of MS.

### Amyotrophic Lateral Sclerosis

Amyotrophic Lateral Sclerosis (ALS) is a chronic and progress-

ive disease with an unknown cause. ALS specifically targets the anterior horn cells of the spinal cord, the brainstem motor neurons, the cortical pyramidal cells, and the pyramidal tract in the brain[38]. Its clinical manifestation includes symptoms of dysfunctional upper and lower motor neurons, and is the most common form of motor neurone disease[39]. Several studies have found a significant increase in the abundance of *Escherichia coli* in ALS patients compared to control groups, while the significant decrease in the abundance of anaerobic bacteria, such as *Eubacterium rectale* and *Megamonas*[40,41]. Additionally, the dysbiosis of the gut microbiota in ALS patients worsens with symptom progression, indicating that alterations in gut microbiota could potentially be used as a diagnostic marker for ALS[42]. Blacher et al. explored the relationship between ALS severity in mice and their gut microbiota, finding that ALS mice had nearly no *Akkermansia muciniphila* or even lacked it in the gut, but restoration of *Akkermansia muciniphila* in the gut effectively slowed the progression of ALS in mice[43]. Another study also confirmed the pivotal role of *Ruminococcus torques* and *Parabacteroides distasonis* in exacerbating the progression of ALS in mice. According to a clinical study from 4 ALS patients, the ratio of Firmicutes/Bacteroidetes and the abundance of *Ruminococcus* in the ALS patients were lower than that in the healthy controls[44]. Similarly, other studies have come to similar conclusions, that is, as compared to healthy individuals, ALS patients have poorer abundance and evenness of gut microbiota and archaeal communities, with decreased relative abundance of Firmicutes/Bacteroidetes and methanogenic archaea, and a downward trend in the relative abundance of beneficial microbes (such as Faecalibacterium and Bacteroides)[45]. These discoveries enhance our comprehension of the connection between ALS and gut microbiota, offering new avenues for research in the treatment and prevention of this disease. (see Table 1).

**Table 1. The Changes in Gut Microbiota in Neurodegenerative Diseases.**

| Neurological Disease | Increased Bacteria | Reduced Bacteria | Ref |
|---|---|---|---|
| Alzheimer's disease | *Escherichia* | *Megamonas* | [41] |
| | *Lactobacillus*, *Dorea*, *Bifidobacterium* | *Parabacteroides*, *Alistipes*, *Alloprevotella*, *Haemophilus* | [46] |
| | *Bifidobacterium* | *Faecalibacterium* | [47] |
| | Actinobacteria<br>Bacilli | Negativicutes, Bacteroidia | [21] |
| Parkinson's disease | Actinobacteria | *Oscillospira*, *Roseburia*, *Ruminococcus* | [48] |
| | *Lactobacillus* | *Clostridium* | [49] |
| | *Collinsella* | *Rothia* | [50] |
| | *Bifidobacterium* | *Faecalibacterium* | [51] |
| Amyotrophic lateral sclerosis | *Methanobrevibacter*, Firmicutes | *Faecalibacterium*, *Bacteroides* | [44] |
| | *Dorea* | *Faecalibacterium* | [45] |
| | *Citrobacter* | *Prevotella* | [52] |
| | *Escherichia*, *Streptococcus* | *Roseburia* | [53] |
| Multiple Sclerosis | *Varibaculum* | *Lachnospira* | [54] |
| | *Bilophila*, *Desulfovibrio* | Bacteroidales, Clostridiales | [55] |
| | *Bifidobacterium*, *Streptococcus* | *Bacteroides*, *Prevotella* | [56] |

## The potential mechanism of gut microbiota in neurodegenerative diseases

Gut microbiota, a vast repository of bacteria residing in the gastrointestinal tract, establishes connections between intestine and the central nervous system (CNS) through fermentation of exogenous substances or stimulation of enterochromaffin cells (EC). Dysbiosis of the gut microbiota often leads to symptoms of various neurological diseases. The underlying machanisms are involved in the changes of neurotransmitter levels, the intestinal barrier, neuroimmune and so on (Fig. 1).

### Gut microbiota affects intestinal barrier permeability

The intestinal barrier is a dynamic system composed of epithelial cells, mucus-secreting goblet cells, and cytokines-secreting immune cells. It serves as a defensive structure against the invasion of pathogenic antigens from the intestinal lumen into the body, playing a crucial role in preventing infection and inflammation[57]. Maintaining the integrity of the intestinal barrier is essential for preserving intestinal homeostasis. The damaged intestinal barrier facilitates bacterial translocation, further leads to the exogenous endotoxins infiltration and bacterial amyloids of nervous system. These adverse effects prompt the immune system to become activated and stimulate the production of pro-inflammatory cytokines, which are significant contributors to neurodegenerative diseases.

In patients with Parkinson's disease (PD), there is a reduction in the levels of tight junction proteins, such as zonula occludens-1 (ZO-1) and occludin, in the colonic tissues when compared to the control group[58], indicating impaired intestinal barrier function. Increased intestinal permeability can expose intestinal neurons to microbial metabolites, some of which have pro-inflammatory effects, leading to local inflammation and oxidative stress, ulti-

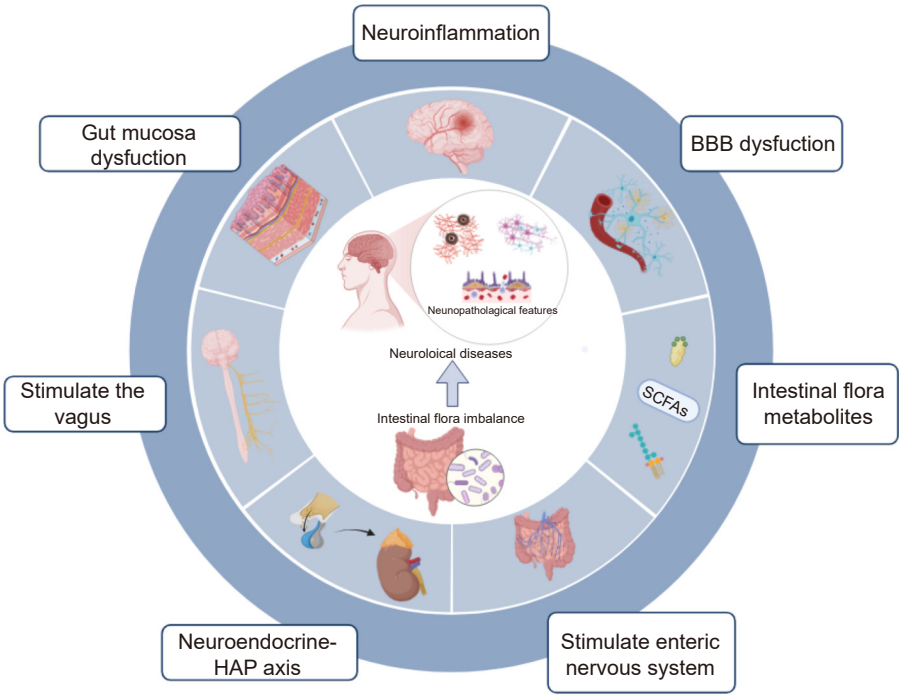


**Fig. 1. Pathogenesis of neurological diseases caused by the gut microbiota in accordance.**

mately contributing to the aggregation of pathological α-synuclein and the onset of PD[59]. The gut microbiota is also able to regulate the expression and distribution of proteins responsible for forming intestinal tight junctions, while also promoting the production of cytokines like tumor necrosis factor (TNF), interleukin (IL)-1β, and IL-6. These cytokines can directly impact intestinal barrier proteins, leading to an increase in intestinal permeability[60]. Recent research has discovered that the levels of lipopolysaccharide (LPS) in the frontal cortex and hippocampus of Alzheimer's disease (AD) patients is significantly higher than that in normal individuals[61], indicating severe damage to the barrier protective system in AD. Additionally, some specific gut microbiota can release large amounts of neurotoxic amyloids, and then enter the nervous system with the weakened intestinal barrier function. These bacterial amyloids may participate in the aggregation and spread of amyloid proteins, activating microglia and triggering inflammatory immune responses, thus playing an important role in early AD[62]. In a study on amyotrophic lateral sclerosis (ALS) model mice[63], it was found that before the onset of ALS symptoms, a noteworthy decline in the levels of expression of ZO-1 protein responsible for maintaining tight junctions in the intestinal tissues of SOD1G93A ALS model mice, accompanied by irregular distribution. Calcium-binding proteins also showed a decreasing trend, exacerbating the progression of ALS. Meanwhile, the increased intestinal barrier permeability has also been observed in relapsing-remitting multiple sclerosis (MS) patients[64]. Studies on experimental autoimmune encephalomyelitis (EAE) mice have also shown increased intestinal barrier permeability[65], with overexpression of the tight junction protein Zonulin, a protein leading to significant changes in intestinal morphology. In the early stages of EAE, dysbiosis in the gut microbiota leads to the increased intestinal barrier permeability, and invasion of various pathogenic bacteria and their metabolites. Partially activated immune cells and inflammatory mediators will penetrate the blood-brain barrier, resulting in central nervous system disorders like Multiple Sclerosis (MS) and inflammatory harm. Studies have found that taking probiotics can help maintain the integrity of the intestinal and blood-brain barriers, thereby slowing the onset and progression of neurodegenerative diseases[66]. For example,[67], Clostridium mainly exerts beneficial effects of probiotics through metabolites such as butyrate, secondary bile acids, and indolepropionic acid, which stimulate intestinal epithelial cells and strengthen the intestinal barrier, which can effectively reduce inflammation and allergic disease reactions. Probiotics are also able to increase the adhesion of intestinal mucosal cells by interacting with the surface of intestinal mucosal cells. This helps to maintain the structural integrity of mucosal cells, reduces voids in the intestinal mucosa, and slows the penetration of harmful substances[68]. Overall, these findings highlight the critical role of the gut microbiota in modulating intestinal barrier function and its implications in the pathogenesis of neurodegenerative diseases.

## Gut microbiota regulates neurotransmitter and hormone levels

The gut microbiota can produce and generate a multitude of neurotransmitters or precursor-like neurotransmitters, such as acetylcholine, γ-aminobutyric acid (GABA), histamine, and serotonin[69]. These substances can directly or indirectly transmit diverse signals to the central nervous system (CNS) via the enteric nervous system or alternative pathways, influencing brain activity states. For instance, *Lactobacillus* and *Bifidobacteria* can synthesize GABA, while *Escherichia coli*, *Bacillus spp*., and yeast can produce norepinephrine, and *Bacillus spp*. can also synthesize dopamine[70].

Neurotransmitters have diverse functions in organisms, including regulating neural impulses and signaling, inhibiting patholo-

gical activation of neurons, reducing the expression of pro-inflammatory factors, and modulating the activity patterns of astrocytes[71]. These functions play crucial roles in emotional control and the regulation of neurodegenerative diseases. Prolonged neurotransmitter deficiency can lead to neuronal and synaptic degeneration, thereby triggering neurodegenerative diseases such as AD and PD[72]. For example, the decrease of serotonin (5-HT) in the brain is a prevalent pathological characteristic of anxiety disorders, depression, AD, and PD patients[73,74]. Supplementation with probiotics, such as *Lactobacillus plantarum* PS128, can increase the concentrations of dopamine (DA) and 5-HT in the prefrontal cortex and striatum of newborn mice, offering a new direction for the treatment of PD[75]. Commendamide and other acylethanolaminesalso plays an important role in the gut-brain axis. Commendamide is an agonist of G protein-coupled receptor G2A/132, It may affect G2A/132 receptors through brain-gut axis function, thereby affecting inflammation, pain, and central nervous system diseases, among others[76]. Truini A et al.[77] evaluated the effect of n-Palmitoylethanolamide (PEA) on neurotoxicity in patients with chemotherapy-induced painful neuropathy. The results showed that PEA treatment could significantly improve pain and neurological function, suggesting that it may have neuroprotective effects. In patients who continue chemotherapy, PEA treatment can maintain the therapeutic dose while not further deteriorating neurological function, which has a positive effect on the survival of patients. Rousseaux C[78] findings suggest that Lactobacillus may influence intestinal pain by modulating intestinal pain and inducing the expression of opioid and cannabis receptors, providing a potential mechanism for the treatment of related diseases. Cannabinoids are thought to play an important role in soothing inflammation, reducing pain, and protecting the central nervous system, and interactions with cannabinoid receptors may enable these functions. Generally, 5-HT is considered a major neurotrophic factor during development and also acts as a promoter of growth and an inhibitor of inflammation in the intestinal mucosa. The existence, formation, and possible biological activity of N-acyltryptophan, a novel fatty acid-derived mediator, in the intestinal tract were studied. Studies have found that N-acyltryptophan is present in the gut and may play an important role in regulating intestinal function and the nervous system. This provides a new research direction for further research on the role of N-acyltryptophan in gut health and related diseases[79]. Similarly, studies have found that there is a strong link between tryptophan metabolism and the gut-brain axis, and gut microbes can influence tryptophan metabolism and, in turn, nervous system function. The importance of gut microbiota in regulating the function of gut-brain axis is emphasized, which provides new possibilities for the use of gut microbiota in the treatment of neurological diseases[80]. The transfer of gut microbiota from normal mice to germ-free mice prompt the mature of intestinal nerves and the enhancement of transit rate of the small intestine. These findings indicate that the gut microbiota can promote the development and maturation of intestinal nerves by producing serotonin (5-HT) or stimulating serotonin receptors. Studies on germ-free animals have shown that the gut microbiota in anxiety-related mice stimulates the production of neurotransmitters such as 5-HT and dopamine, thereby regulating the development of their brain circuits[81]. Another evidence have also proved that treatment with *Lactiplantibacillus plantarum* elevates the concentrations of the key neurotransmitter 5-HT in the brain and serum. Additionally, heat-inactivated probiotics and metabolites from the gut microbiota have been found to promote the generation of 5-HT in the colon[82].

Except for 5-HT, γ-aminobutyric acid (GABA) can also be produced by specific gut microbiota such as *Lactobacillus* and *Bifidobacteria*. It has a crucial role in controlling synaptic transmission, intestinal motility, and inflammation in the enteric nervous system. A recent study indicated that the levels of GABA in the hypothalamus of PD patients are lower than that in the control group, suggesting that GABA dysfunction in the brainstem could be a pivotal factor in the progression of PD[83]. Altogether, alterations of the gut microbiota in patients with neurodegenerative diseases might change the circulating levels of neurotransmitters, further exacerbate the severity of the diseases.

**Gut microbiota participates in neuroinflammation**

Microglia, as crucial immune players in the central nervous system, play a key role in protecting the body against damage and disease invasion. Nonetheless, hyperactive microglia can result in a range of problems, including increased levels of pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), as well as the production of substances like nitric oxide (NO), which then participate in neurodegeneration-related inflammatory processes, causing damage to brain neurons[84]. In samples of the substantia nigra from PD patients, it has observed the aggregation of activated microglia and infiltration of pro-inflammatory cytokines[85]. Meanwhile, various neurotransmitters secreted by gut microbiota may also play a role in regulating the development and activation of microglia. For instance, substances like acetylcholine produced by *Lactobacillus* and γ-aminobutyric acid (GABA) produced by *Lactobacillus* and *Bifidobacteria* can modulate the activation state of microglia directly or indirectly. Another microbial metabolite influencing microglial activity is serotonin[86]. Activated microglia metabolize serotonin to produce the neurotoxin quinolinic acid, which is associated with various neurodegenerative diseases such as Huntington's disease and depression[87]. In mice with experimental autoimmune encephalomyelitis (EAE), a model for multiple sclerosis (MS), it was shown that metabolites produced by dietary tryptophan by gut microbiota could inhibit the activation of microglia, and inhibit the generation of pro-inflammatory cytokines in astrocytes, thereby mitigating the disease[88]. Dysregulation of intestinal mucosal immune function triggers inflammatory responses, leading to an increase in microglia and astrocyte numbers, stimulating the generation of free radicals and the release of pro-inflammatory cytokines, ultimately resulting in systemic chronic inflammation, disruption of the blood-brain barrier, and structural rearrangement, ultimately leading to cognitive impairment[89]. Actually, the intestinal barrier and intestinal mucosal immune are inseparable. Once the intestinal mucosal structure is disrupted, the function of the intestinal barrier is compromised, leading to increased permeability of the intestinal epithelium. This situation may lead to bacterial translocation (a process known as translocation) or the infiltration of toxic substances into the bloodstream, thereby triggering intestinal inflammation. By observing the content of calprotectin in feces, it can indirectly assess the severity of intestinal inflammation. Lebl-

huber et al. measured the calprotectin content in stool samples from 22 AD patients and found that approximately 70% of AD patients had significantly elevated fecal calprotectin concentrations[90]. Furthermore, intestinal inflammation may also lead to an increase in the quantity of S100 calcium-binding protein A8/A9, further exacerbating the trend of AD development. These results suggest that gut microbiota dysbiosis can directly or indirectly affect various inflammatory mediators, further induce central nervous system inflammation responses, ultimately lead to pathological damage of the central nervous system.

## Gut microbiota-derived metabolites influence the development of neurodegenerative diseases

Inflammation plays a key role in triggering various central nervous system diseases, with its occurrence rate reaching up to 25%[91]. Several diseases, such as stroke, Alzheimer's disease, and autism, are often accompanied by severe inflammation[92,93]. A wealth of evidences suggest that gut microbiota and their metabolites can trigger host neuroimmune responses, thereby influencing the functioning of the host central nervous system[94]. For instance, gut microbiota metabolites such as lipopolysaccharides (LPS)[95], short-chain fatty acids (SCFAs)[96], bile acids (BAs), amino acids, trimethylamine oxide (TAMO), etc. can affect the occurrence of chronic neuroinflammation through various molecular mechanisms (Fig. 2). Hence, comprehending the significance of gut microbiota-derived metabolites in the onset and progression of neurodegenerative diseases is vital and essential.

### Effect of short-chain fatty acids on neurodegenerative diseases

Short-chain fatty acids (SCFAs) are the primary metabolites produced through the breakdown of dietary fiber by the gut microbiota, primarily including acetate, propionate, and butyrate[97]. Studies have shown that various gut microbiota, such as genera of *Bacteroides*, *Lactobacillus*, *Clostridium*, *Bifidobacterium*, *Roseburia*, *Ruminococcus*, *Prevotella*, and *Fusobacterium,* possesses ability to generate SCFAs[98]. In the human gastrointestinal tract, SCFAs can transmit signals via binding to G protein coupled receptor (GPCR) on the surface of intestinal epithelial cells, and they can also enter the circulatory system through passive or active transport to exert further effects. Notably, SCFAs can cross the blood-brain barrier to exert anti-inflammatory functions in the brain[99-101]. Furthermore, SCFAs can promote the restoration of normal function of activated microglia by attenuating their overactivation and inducing phenotypic switching, thereby controlling inflammation[102]. SADLER et al. found that the addition of mixed SCFAs (such as acetate, propionate, and butyrate) can convert the pro-inflammatory M1 phenotype of microglia to the anti-inflammatory M2 phenotype, thereby improving cortical remodeling and synaptic plasticity in late-stage stroke recovery to ameliorate motor dysfunction[103]. Similarly, in an Alzheimer's disease (AD) mouse model, acetate could alleviate neuroinflammation by inhibiting the transformation of microglia into the pro-

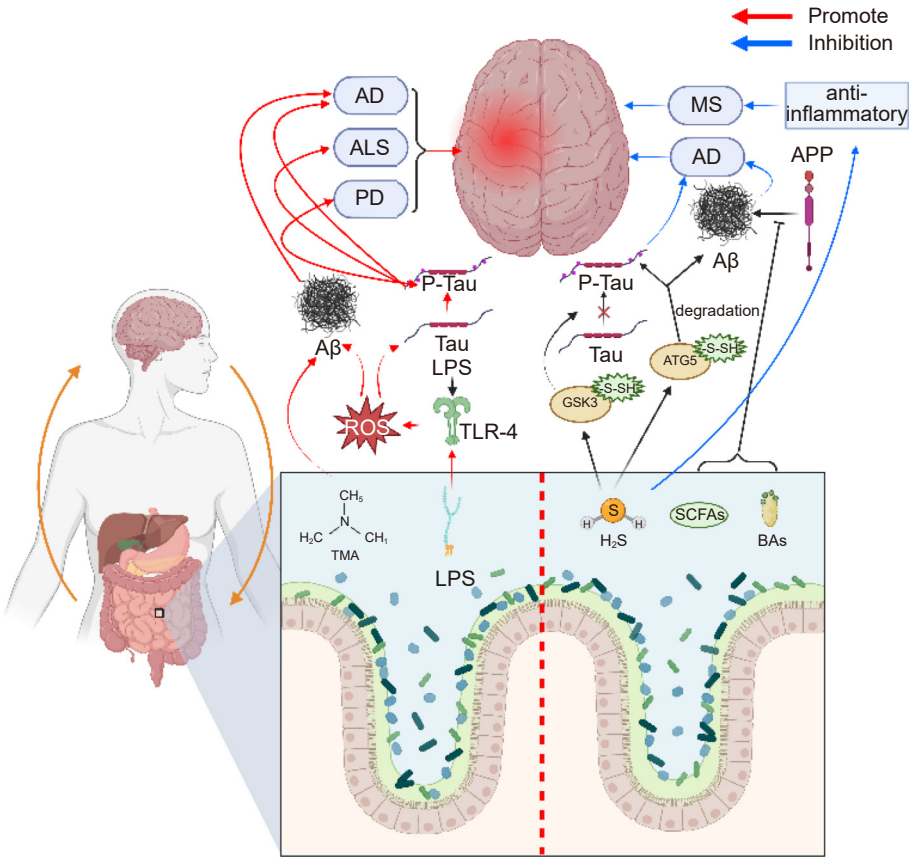


**Fig. 2. The impact of gut microbiota metabolites on neurodegenerative diseases.**

inflammatory M1 type, thereby significantly relieving memory impairment and other disease symptoms[104]. This may be because butyrate can promote the expression of leukocyte antigen-1 and is related to the secretion of IL-4, TNF, and ICAM-1, which in turn is involved in the immune response of cells. In addition, butyrate can also promote the proliferation of regulatory T cells by inducing the PD-1/PD-L1 signaling pathway, and regulate the number balance of M1/M2 macrophages in colon tissue. These effects suggest that butyrate plays an important role in PD disease[105,106]. In addition to AD, the SCFAs levels were also influenced the development of Parkinson's disease (PD) in MPTP-induced mice[107]. The application of SCFAs obviously ameliorates the mobility disorder caused by PD[108]. This could be because butyrate is able to penetrate the substantia nigra pars compacta (SNpc) of the midbrain, then slow down and inhibit the overactivation of microglia and various signaling pathways such as NF-κB pathways, thus decreasing the concentrations of crucial pro-inflammatory cytokines IL-6, IL-1β, and TNF-α. Overall, as endogenous ligands of GPCRs, SCFAs could attenuate neuroinflammation and regulate the activity of microglia to influence the development of neurodegenerative diseases.

**Effect of trimethylamine N-oxide (TMAO) on neurodegenerative diseases**

Trimethylamine oxide (TMAO) is a major metabolite produced by the gut microbiota and is primarily derived from dietary nutrients such as phosphatidylcholine, choline, and L-carnitine. Gut microbiota usually metabolizes dietary choline into, a gas that is then absorbed into the bloodstream and further processed by flavin-containing monooxygenase 3 (FMO3) to form TMAO[109,110]. Currently, TMAO is recognized as a negative metabolite that lead to the occurrence and onset of neurodegenerative disorders like Parkinson's disease (PD) and Alzheimer's disease (AD)[111]. Specifically, TMAO can penetrate the intestinal epithelial barrier and enter the bloodstream, affecting synaptic plasticity and thus influencing central nervous system and cognitive function[112]. Studies have shown that the concentrations of TMAO in the CSF (cerebrospinal fluid) were differed among individuals with mild cognitive impairment, AD patients, and normal individuals[113]. The concentration of TMAO in the cerebrospinal fluid of AD patients and mild cognitive impairment patients is higher than that in normal individuals. Importantly, there is a positive correlation between TMAO concentration and AD biomarkers such as t-Tau, neurofilament light chain (NFL), p-Tau, and p-Tau/Aβ42. Therefore, TMAO may promote AD pathology. Reshaping the gut microbiota can effectively inhibit TMA generation and reduce the concentration of TMAO produced, thereby alleviating the impaired cognitive functions[114]. It is reported that the combination of *Lactobacillus plantarum* and metformin can boost the efficacy of metformin on AD mice by regulating the gut microbiota, inhibiting TMAO formation, and reducing amyloid levels[115]. To further investigate the relationship between TMAO, neuroinflammation, and age-related cognitive impairment, researchers conducted a six-month TMAO intervention experiment on young mice. The results showed that TMAO stimulation promotes a significant increase in the number of inflammatory factors and expression of astrocyte activation markers, along with severe cognitive impairment, as compared to the healthy control group[116]. Another animal experiments confirmed a strong association between the concentrations of TMAO and AD-like pathological features and age-related cognitive impairment in amyloid precursor protein/presenilin 1 mice. Moreover, the decline of TMAO levels is conducive to alleviate age-related cognitive impairment, which emphasizing the crucial role of TMAO in controlling neuroinflammation and affecting cognitive functione. In summary, TMAO is associated with cognitive impairment diseases, and reducing TMAO levels may be beneficial for preventing cognitive impairment diseases, providing a new direction for the clinical treatment of age-related cognitive impairment.

**Effect of bile acids on neurodegenerative diseases**

Bile acids (BAs) exhibit a close bidirectional regulatory relationship with gut microbiota, laying the foundation for understanding how gut microbiota modulate host metabolism[117]. Bile acids are the end products of cholesterol metabolism in the liver, with primary bile acids synthesized mainly in the liver and secondary bile acids produced predominantly through the action of gut microbiota. In the liver, cholesterol is metabolized into primary bile acids via two distinct pathways. One pathway involves the classical route, guided by cholesterol 7α-hydroxylase (CYP7A1), resulting in the formation of cholic acid (CA) and chenodeoxycholic acid (CDCA)[118]. The other pathway, known as the alternative pathway, is catalyzed by sterol 27-hydroxylase (CYP27A1), yielding CDCA. BAs not only link the interactions between liver and intestines through enterohepatic circulation but also transmit signals to the central nervous system directly or indirectly via systemic circulation. The BAs levels in healthy individuals are different from patients with neurodegenerative diseases. For example, the blood levels of primary BAs in AD patients are decreased, while the levels of microbiota-derived secondary BAs, deoxycholic acid and its glycine and taurine conjugates, are increased[119]. Graham SF et al. suggested that alterations in bile acid levels could be utilized as a potential biomarker for forecasting Parkinson's disease (PD) and may indicate the advancement of PD.

The rise in secondary conjugated BA concentration is closely associated with cognitive decline. TUDCA exhibits anti-inflammatory properties in the central nervous system, alleviating glial cell activation and the release of pro-inflammatory cytokines, holding significant value for central nervous system diseases[120]. TGR5 (G protein-coupled receptor 5) is expressed in neurons and astrocytes, and activation of TGR5 by bile acids can reduce astrocyte activation and suppress the generation of pro-inflammatory cytokines IL-1β, IL-6, and TNFα, thereby reducing neuroinflammation[121]. It has been found that secondary bile acid tauroursodeoxycholic acid could bind to the TGR5, leading to the inhibition of neuroinflammatory factors (TNF-α, IL-6), nitrosative stress and endoplasmic reticulum stress. The intervention of these signaling molecules can ameliorate depressive behavior in mice subjected to chronic unpredictable stress treatment[122]. Studies have demonstrated that in an experimental animal model of hepatic encephalopathy-induced cognitive impairment using azoxymethane (AOM), the TGR5 agonist betulinic acid effectively mitigates cognitive decline, increases cAMP concentration in the cortex, reduces astrocyte activation, and diminishes pro-inflammatory cytokine secretion[123]. This further improves the prognos-

is of AOM-treated mice, attenuates neuroinflammation, thereby affecting cognitive function, and facilitating the treatment of neurodegenerative diseases.

### Effect of lipopolysaccharides (LPS) on neurodegenerative diseases

Lipopolysaccharide (LPS) constitutes the primary element of the outer membrane of Gram-negative bacteria and is also an endotoxins[124]. Composed of lipids and polysaccharides, LPS is a metabolic byproduct of gut microbiota, primarily originating from genera such as *Escherichia* and *Klebsiella* within the Enterobacteriaceae family. LPS is a metabolite involved in regulating inflammation and can trigger innate immune responses by activating toll-like receptor 4 (TLR4)[125]. Microglia, innate immune cells widely distributed in the brain, primarily function to monitor changes in the brain microenvironment and identify potential pathogens[126]. Binding of LPS to TLR4 on microglia activates nuclear transcription factor κB (NF-κB), leading to microglial activation and the release of a series of inflammatory factors such as NO, TNF-α, and IL-1β, ultimately resulting in systemic and neurological inflammatory responses, neuronal apoptosis, and cognitive impairment[127]. Villarán et al. induced midbrain inflammation by injecting LPS into an ulcerative colitis rat model to investigate whether peripheral inflammation affects midbrain inflammation. They found increased levels of nitric oxide synthase (iNOS), intercellular adhesion molecule-1 (sICAM-1), microglia, and astrocytes in the substantia nigra after LPS injection, exacerbating disease severity in ulcerative colitis rats[128]. Existing study indicates that LPS triggers TLR4-CD14/TLR2 receptors in the immune system, leading to increased expression levels of inflammatory cytokines such as TNF-α and IL-1β regulated by NF-κB, finally resulting in central nervous system inflammation and promoting the development of AD[129,130]. Once LPS disrupts the blood-brain barrier, it releases inflammatory mediators and neurotoxins into the brain, activating microglia-mediated inflammatory responses and oxidative stress, further exacerbating blood-brain barrier damage, neuronal injury, and even apoptosis, thus worsening the pathology and progression of neurodegenerative diseases. Kitazawa et al. observed that intraperitoneal injection of LPS,into 3xTg-AD mice induced microglial activation, enhancing CDK5 activity and promoting tau protein phosphorylation, accelerating the AD pathological process[131]. WANG et al. observed significantly elevated levels of LPS and peripheral inflammatory markers in individuals with post-stroke cognitive impairment (PSCI) compared to those without PSCI[132]. This may be due to a substantial rise in Enterobacteriaceae bacteria and a substantial decrease in butyrate levels in the intestines of PSCI patients, possibly resulting in intestinal barrier damage, allowing LPS to leak into the bloodstream, triggering chronic peripheral inflammatory responses and further releasing peripheral LPS and inflammatory cytokines into brain tissue, promoting apoptosis of neurons in the hippocampal CA1 region and amyloid-β deposition in the thalamus, ultimately accelerating the progression of neurodegenerative diseases.

### Effect of hydrogen sulfide ($H_2S$) on neurodegenerative diseases

Hydrogen sulfide (H2S) is recognized as the third gasotransmitter following nitric oxide (NO) and carbon monoxide (CO). In mammalian cells, endogenous $H_2S$ is primarily generated through enzymatic pathways and non-enzymatic pathways[133,134]. Similar with mammalian cells and tissues, gut microbiota can also produce $H_2S$ gas[135]. The main source of $H_2S$ production is from the fermentation and metabolism of inorganic sulfates and sulfites in undigested food residues by sulfate-reducing bacteria in the intestines[136]. $H_2S$ is typically accumulated in large quantities in the central nervous system[137]. This is primarily attributed to the effect of $H_2S$ produced by cystathionine-β-synthase (CBS) and 3-mercaptopyruvate sulfurtransferase (3-MST) on neurons and glial cells, contributing to the maintenance and improvement of brain function and exerting a self-protective effect[138,139]. Impaired generation of $H_2S$ is considered a significant factor in the occurrence and development of Alzheimer's disease (AD)[140]. Studies have shown that plasma and brain levels of $H_2S$ in AD patients are significantly lower than those in healthy individuals, and plasma levels of $H_2S$ are negatively correlated with the severity of AD, indicating an important regulatory role of $H_2S$ in neurological diseases[141]. $H_2S$ has been found to alleviate neuroinflammation in AD mice by suppressing the overexpression of IL-1β and TNF-α, as well as the proliferation of astrocytes and microglia induced by Aβ1-40 in the hippocampus[142]. In LPS-induced bilateral ventricular neuroinflammation rat model, exogenous administration of sodium hydrosulfide (NaHS) can alleviate the decline of learning and memory function and hippocampal CA1 neuronal ultrastructure damage. This may be because the NaHS treatment could inhibit the NF-KUB pathway in rats, reduce the excessive production of pro-inflammatory mediators, and thus weaken LPS-induced cognitive impairment[143]. This finding may be used to prevent or slow down the progression of neurodegenerative disorders like Alzheimer's disease (AD). It is widely known that AD patients may produce excessive levels of pro-inflammatory cytokines such as interleukin-1α (IL-1α), IL-1β, IL-6, IL-8, IL-12, and tumor necrosis factor-α (TNF-α)[144]. In contrast, $H_2S$ has been shown to significantly inhibit the release of TNF-α, IL-1β, and IL-6, and exerts its effects by inhibiting the upregulation of cyclooxygenase-2 (COX-2) and the activation of NF-κB[145]. Given that elevated levels of TNF-α may impede the clearance of Aβ in the brain of AD, leading to cognitive impairment[146], the inhibitory effect of $H_2S$ may help to slow the progression of AD. Additionally, Hu et al. found that NaHS could reduce the release of products from LPS in microglia and astrocytes, as well as decrease the release of nitric oxide (NO) and TNF-α. Overall[147], this indicates that $H_2S$ has important implications for the management of neuroinflammatory-related conditions and could be a promising strategy for treating neurodegenerative diseases.

## Treatment of neurodegenerative diseases based on targeted gut microbiota

### Probiotics

Probiotics, as beneficial active microorganisms, can positively impact host health by rebuilding or improving the gut microbiota. It has been reported that the intake of specific probiotics can ef-

fectively prevent and ameliorate neurological diseases through the gut-brain axis[148,149]. For instance, Huang et al. discovered that *Lactobacillus plantarum* PS128 prevented cognitive decline in a mouse model of Alzheimer's disease induced by d-galactose, through the regulation of propionic acid levels, glycogen synthase kinase-3 (gSK-3) activity, and gliosis[150]. Tan et al. demonstrated that *Lactobacillus plantarum* DR7 notably reduced harmful bacteria (*Enterobacter*), whereas increased beneficial bacteria (*Lactobacillus* and *Acetobacter*) to alleviate AD-related symptoms in drosophila model[151]. Ekwudo M N et al.[152] investigated how probiotics can improve cognitive function in rats with Huntington's disease through anti-inflammatory mechanisms. The findings suggest that probiotics can improve cognitive function through anti-inflammatory effects, providing new evidence for the potential role of probiotics in the treatment of Huntington's disease. A systematic review and meta-analysis of the role of probiotics in Huntington's disease were conducted. The review of studies shows that probiotics may play a role in the treatment of Huntington's disease, which provides a certain basis and direction for the application of probiotics in the treatment of Huntington's disease[153]. Sun et al. investigated the therapeutic effect of *Clostridium butyricum* (CB) on AD mice. They found colonization with CB altered the gut microbiota composition in AD mice, increased the level of the SCFA metabolite butyric acid, significantly slowed β-amyloid deposition and cerebellar gray matter activation, and suppressed the secretion of pro-inflammatory cytokines TNF-α and IL-1β, thus preventing neuroinflammation and improving cognitive dysfunction in AD mice[149]. Except for AD, it is also recognized that *Bifidobacterium breve* CCFM1067 could improve motor impairment in Parkinson's disease (PD) mice by increasing neurotrophic factor and short-chain fatty acid levels, reducing glial cell overactivation, inhibiting oxidative stress damage and inflammatory responses, as well as protecting dopaminergic neurons[154]. Hence, both animal experiments and clinical studies have confirmed that intervention with probiotics can regulate the gut microbiota structure, which can effectively mitigate the central nervous system diseases through regulating nervous system, endocrine system, immune system, and host metabolism, (see Table 2).

**Table 2. Mechanistic Approach to Probiotics in Neurological Applications.**

| Probiotics | Disease | Mechanism | Ref |
|---|---|---|---|
| *Lactobacillus rhamnosus* | Anxiety and depression | vagus | [155] |
| *Lactobacillus Bifidobacterium* | Anxiety and depression | Secretion of γ-aminobutyric acid neurotransmitter | [156] |
| *Lactobacillus reuteri* | Autism spectrum disorder（ASD） | Improve gastrointestinal permeability | [157] |
| *Lactobacillus*、*Bifidobacterium* | Memory impairment | Inhibits the nuclear factor-κB pathway | [158] |
| *Lactobacillus rhamnosus* | Autism spectrum disorders neuropsychiatric disorders in infancy | Enhances intestinal epithelial integrity, protects the intestinal barrier, regulates the immune system of the gastrointestinal mucosa | [159] |
| Probiotics for *Lactobacillus* and *Bifidobacterium* | Alzheimer's disease（AD） | Reduces β amyloid deposition in the brain and reduces serum inflammatory factor content | [107] |
| *Lactobacillus rhamnosus* | Anxiety and depression | Modulates expression of central A-type GABA α2 receptors | [160] |
| Milk fermented with Lactobacillus helveticus IDCC380 | Alzheimer's disease（AD） | Reduces levels of beta-amyloid in brain cells and serum | [161] |
| *Lactic acid bacteria* | Experimental perverted reactive encephalitis (EAE) | Plugs and conversion growth factor-β (TGF-β) increase, auxiliary T cell 1 (TH1) and auxiliary T cell 17 (TH17) decrease | [162] |
| *Eosinophils* | Autism spectrum dysfunction（ASD） | Activate the vagus neural pathway at the level of the intestinal nervous system | [163] |

**Fecal microbiota transplantation (FMT)**

Fecal microbiota transplantation (FMT) has been proposed as a novel treatment strategies for several diseases, including neurodegenerative diseases. FMT aims to rectify the equilibrium of the gut microbiome by transferring fecal bacteria from a healthy donor into the gastrointestinal tract of a patient, thereby addressing associated diseases[164]. Studies have shown that transplanting fecal bacteria from healthy mice to AD mice can effectively improve cognitive function and reduce brain β-amyloid (Aβ) deposition in APPswe/PS1dE9 transgenic (Tg) mice. This process modifies the structure of gut microbiota and elevates the fecal levels of short-chain fatty acids (SCFAs), which positively impacts cognitive impairment in AD mice[165]. Additionally, FMT treatment also ameliorates PD-related symptoms. On one hand, FMT reduces gut microbiota dysbiosis in PD mice, alleviating weight loss, restoring gut microbiota diversity, and increasing the abundance of Firmicutes phylum. On the other hand, FMT increases neurotransmitter content in the striatum, suppresses activation of microglia and astrocytes in the substantia nigra, decreases levels of inflammatory cytokines and lipopolysaccharides (LPS), and blocks the TLR4/TNF-α/NF-κB/MyD88 signaling pathway activation to ameliorate symptoms in PD mice[166]. Through successfully establishing a model of transgenic mice overexpressing human α-synuclein (ASO), Sampson et al. monitored the changes of PD related symptoms such as α-synuclein inclusion bodies, motor impairments, and reduced microglial activation in these mice. As compared to the healthy control group, ASO mice transplanted with PD microbiota exhibited more severe PD symptoms[26]. Similarly, Sun et al. demonstrated that PD mice experienced significant improvement in motor impairments, increased brain neurotransmitters, and elevated dopaminergic neuron counts after receiving FMT, with gradual normaliza-

tion of the microbiota composition[107]. These findings suggest that FMT not only improves gut microbiota in PD mice but also provides certain neuroprotective effects. By reconstructing the gut microbiota and adjusting the gut microbial ecosystem, FMT allows healthy gut microbiota to re-establish a stable ecological environment in the diseased body. In the further study, FMT may emerge as an effectapproach for treating neurodegenerative diseases.

**Diet**

Dietary interventions are the most effective and commonly applied methods of improving health. Generally, ingredients from diet can provide energy for both host and gut microbiota, then regulate the makeup and activity of the gut microbiota[167], promoting signaling between the enteric nervous system and the central nervous system[168], thereby aiding in the improvement of neural function and cognition[169]. The healthy dietary approaches can reduce disease morbidity, while the unhealthy diet can exacerbate the progression of the disease. For example, the excessive intake of saturated fatty acids may exacerbate oxidative stress and lipid peroxidation, thereby worsening neurodegenerative lesions in Alzheimer's disease (AD)[170] and Parkinson's disease (PD)[171]. Guida F et al.[172] investigated the role of PEA-OXA in restoring cognitive impairment caused by altered gut microbes associated with vitamin D deficiency. The results of the study showed that PEA-OXA can improve cognitive impairment, suggesting that it has a possible therapeutic effect. This effect may be related to changes in the gut microbiome caused by vitamin D deficiency, providing a new perspective for the treatment of related diseases. High-calorie intake has been correlated with early onset of Huntington's disease (HD). Additionally, excessive consumption of high-fat diets may also trigger intestinal oxidative stress reactions, thereby inhibiting Nrf2 signaling pathways to induce neuronal apoptosis, ultimately leading to cognitive impairment. A study found that high-fat diets significantly increased amyloid deposition, greatly increasing the risk of AD occurrence[173]. Furthermore, a high-fat diet can induce cognitive impairment and activation of gut neuroinflammation by regulating the gut microbiota[174]. Experimental evidence shows that a high-fat diet can lead to more anxiety-like behavior and decreased cognitive levels in mice, increasing the abundance of Firmicutes while decreasing that of Bacteroidetes[175]. Therefore, high-fat diets may cause changes in the gut microbiota, further exacerbating anxiety states and impairing cognitive abilities. On the contrary, the ketogenic diet (KD) significantly improves AD, PD, and HD, among other neurodegenerative diseases[176,177]. Both animal experiments and clinical trials have confirmed the effectiveness of KD in improving neurodegenerative diseases. KD may alleviate symptoms of neurological diseases by inhibiting mitochondrial damage [178,179]. Similarly, the Mediterranean diet (MD) also has an ability to enhance health and reduce the risk of multiple diseases. Many studies suggest that consuming an MD is an effective way to improve and treat neurodegenerative diseases. Meta-analyses have shown significant improvements in cognitive ability test scores in individuals consuming MD[180]. Clinical studies also indicate that long-term adherence to the Mediterranean diet can reduce the risk of AD or PD[181]. This may be because the Mediterranean diet is rich in healthy monounsaturated and polyunsaturated fatty acids, which helps reduce the risk of AD and PD. Thus, intervention methods such as the ketogenic diet and Mediterranean diet can affect the microbiota-gut-brain axis to improve cognitive function and alleviate neurodegenerative diseases. However, further studies are needed to elucidate how various dietary patterns impact the diversity of gut microbiota, as well as investigate the relationship between regulated-bacteria and cognitive abilities and neurodegenerative diseases, thus providing guidance for prevention and treatment strategies for neurodegenerative diseases.

**Prebiotics**

Prebiotics are non-digestible oligosaccharides or components, which are selectively fermenting in the intestine, and enhancing the beneficial bacteria to promote health[182]. Prebiotics include fructooligosaccharides (FOS), xylooligosaccharides, galactooligosaccharides (GOS), inulin, and oligofructose[183]. These compounds possess various beneficial properties, such as stimulating beneficial gut microbiota, enhancing the synthesis of short-chain fatty acids (SCFAs), regulating immune responses, controlling bacterial gene expression, and enhancing colonic absorption of micronutrients[184]. The supplementation of prebiotic can attenuate the symptoms of central nervous system diseases via increasing the brain activity of anti-inflammatory and antioxidant enzymes and enhancing the expression of neurotrophic factors[185]. For instance, fructooligosaccharides (FOS) derivatives can enhance the expression of brain antioxidant enzymes, reduce the expression of pro-inflammatory cytokines (such as TNF-α and IL-1β) to exert antioxidative, immunomodulatory, and neuroprotective effects, thus improve memory in AD mouse models[186]. Moreover, prebiotics can promote the colonization of beneficial bacteria while inhibit the growth of harmful bacteria. Feeding 5 × FAD transgenic AD mice with mannan oligosaccharide (MOS) for 8 weeks significantly increased the abundance of butyrate-producing bacteria and *Lactobacillus*. These alterations of gut microbiota composition effectively improved cognitive function and spatial memory, reduced Aβ accumulation in the cerebral cortex, hippocampus, and amygdala, maintained brain redox balance, and inhibited neuroinflammatory responses, thereby improving AD symptoms[187]. Orally administration of FOS for 6 weeks significantly improved cognitive deficits and pathological changes in Tg mice, with significantly upregulated expression of synapsin I, PSD-95[188], and downregulated phosphorylation of JNK, further exerting beneficial effects on AD by modulating the gut microbiota-GLP-1/GLP-1R pathway[189]. Due to the fact that prebiotics are mainly obtained from fruits, vegetables, and medicinal herbs, it is easy to obtain and suitable for large-scale industrial production. Therefore, prebiotics may serve as an adjunct therapy for improving cognitive impairment. Nonetheless, additional investigation is necessary to comprehensively grasp the alterations in gut microbiota and the precise mechanisms through which prebiotics and probiotics impact neurological disorders. Further clinical studies are essential to validate the potential effectiveness of prebiotics in managing neurodegenerative diseases.

**Traditional Chinese herbal medicine**

Traditional Chinese herbal medicines are characterized as multi-pathway and multi-target[190]. Increasing evidences suggest that traditional Chinese medicine (TCM) can exert its effects by mod-

ulating gut microbiota and its metabolites[191], thereby demonstrating beneficial effects. Therefore, the treatment and prevention of neurodegenerative diseases through modulating gut microbiota has become one of the hot topics[192]. Traditional Chinese herbal medicine plays a certain role in restoring gut microbiota imbalance and improving central nervous system function. It has been found that the extract of Liuwei Dihuang Decoction can reduce anxiety and improve cognitive function in AD mice by metabolizing glutamate into gamma-aminobutyric acid through gut microbiota[193]. Another study showed that salidroside restores intestinal barrier integrity, reverses the ratio of Bacteroidetes to Firmicutes, eliminates *Clostridium* and Streptococcaceae associated with cognitive impairment, restores gut microbiota to normal levels, regulates central nervous system and peripheral circulation inflammation response, and thus alleviates memory difficulties in SAMP8 mice[194]. TCM compound may also inhibit inflammation in neurodegenerative diseases by modulating gut microbiota. For example, Foshou San can ameliorate memory deficits, attenuate systemic inflammation and oxidative stress (MDA) caused by LPS in APP/PS1 mice, along with increase the abundance of *Lactobacillus* but reduce the number of *Escherichia coli*[195], indicating that Foshou San can improve pathological symptoms of AD by modulating gut microbiota. In a fisetin and LPS-induced PD rats, Huafengdan (HFD) significantly improved rat motor behavioral disorders, decreased the degeneration of dopaminergic neurons and the activity of microglial cells, and posed a protective effect on neurotoxicity induced by LPS + rot[196]. In addition, traditional Chinese herbs such as *Scutellaria baicalensis* Georgi[197], *Rheum officinale* Baill.[198], and *Tripterygium wilfordii* Hook. f.[199] can alleviate demyelination, inflammatory cell infiltration, and related symptoms of multiple sclerosis by regulating neuroinflammatory factors, demonstrating potent neuroprotective effects. A large number of experimental results indicate that Chinese herbal medicine can affect the progression of neurodegenerative diseases through the gut microbiota, providing a new perspective on the treatment of neurodegenerative diseases with TCMs. Based on the rich experience, we can further explore how various functional molecules of Chinese herbal medicine exert positive effects in improving neurodegenerative diseases through multi-target modulation, which holds significant implications for the prevention and management of neurological disorders.

## Conclusion and prospect

In conclusion, the close relationship between gut microbiota and neurodegenerative diseases has been clearly established. The critical role of gut microbiota and their metabolites in the bidirectional communication of the gut-brain axis cannot be ignored. Currently, understanding how gut microbiota influence neurodegenerative diseases, such as AD, PD, etc, isgradually becoming a hot research topic domestically and abroad. This review mainly updates the relationship between gut microbiota or microbiota-derived metabolites and neurodegenerative diseases, showing that microbial metabolites like SCFAs and BAs can effectively inhibit neuroinflammation, while metabolites like TMAO and LPS may trigger or exacerbate neuroinflammation. Therefore, modulating gut microbiota and their metabolites to treat neuroinflammation-induced neurodegenerative diseases is a feasible strategy. However, further research is needed to deepen our understanding of how gut microbiota and their metabolites participated in neurodegenerative diseases. This includes identifying and determining specific microbial communities and metabolites relevant to particular neurological diseases, elucidating the mechanisms of specific gut microbiota affecting the development of central nervous system diseases, and exploring the interactions between regulated bacteria or their metabolites in neurological diseases and the host immune system. Therefore, it is crucial to comprehensive understand the regulatory mechanisms governing the relationship between the central nervous system and gut microbiota. Precise modulation of gut microbiota not only holds significant value for human health, but also offers more possibilities to prevent the occurrence of central nervous system-related diseases. With the advancement of scientific technology and the development of research, it is reasoned to believe that the treatment of neurodegenerative diseases via adjusting gut microbiota will become feasible and effective, thus promising a new hope for patients.

### Abbreviations

3-MST, 3-mercaptopyruvate sulfurtransferase; AD, Alzheimer's Disease; ALS, Amyotrophic Lateral Sclerosis; AOM, azoxymethane; ASO, α-synuclein; Bas, bile acids; CBS, cystathionine-β-synthase; CDCA, chenodeoxycholic acid; CNS, central nervous system; CO, carbon monoxide; COX-2, cyclooxygenase-2; EC, enterochromaffin cells; FMO3, flavin-containing monooxygenase 3; FMT, Fecal microbiota transplantation; FOS, fructooligosaccharides; GABA, gamma-aminobutyric acid; GOS, galactooligosaccharides; GPCR, G protein coupled receptor; gSK-3, glycogen synthase kinase-3; H2S, Hydrogen sulfide; HD, Huntington's disease; HFD, Huafengdan; IL-1β, interleukin; LPS, lipopolysaccharide; IL-6, interleukin-6; KD, ketogenic diet; MD, Mediterranean diet; MOS, mannan oligosaccharide; MS, Multiple Sclerosis; NaHS, sodium hydrosulfide; NFL, neurofilament light; CA, cholic acid; NO, nitric oxide; NO, oxide; PD, Parkinson’s Disease; SCFAs, short chain fatty acids; SNpc, substantia nigra pars compacta; TCM, traditional Chinese medicine; TGR5, G protein-coupled receptor 5; TLR4, toll-like receptor 4; TMA, trimethylamine; TMAO, Trimethylamine oxide; TNF, tumor necrosis factor; TNF-α, tumor necrosis factor-alpha; ZO-1, zonula occludens-1; α-syn, α-synuclein.

## Funding

This work was supported financially by the National Natural Science Foundation of China (81973217).

## Authors' contributions

YFW: Wrote the manuscript. JG and YYL: Assisted the manuscript revision. YF: Prepared all tables and figures. CMW: Conceptualized the study and acquired the funding, as well as reviewed and edited the manuscript.

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