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FOOD & MEDICINE HOMOLOGY

ISSN 3006-6867 (print); 3006-4252 (online)
https://doi.org/10.26599/FMH.2027.9420172

Review Article

The potential of edible mushrooms to intervene neuroinflammation in neurological diseases by targeting gut microbiota

Shu-Jian Wu[1, 2, †] (✉), Shi-Jue Gao[3, †]

[1] *Department of Nutrition and Food Safety, Public Health School, Fujian Medical University, Fuzhou* 350108, *China*
[2] *Shenzhen Hospital of Southern Medical University, Integrative Microecology Clinical Center, Shenzhen Clinical Research Center for Digestive Disease, Shenzhen Key Laboratory of Gastrointestinal Microbiota and Disease, Shenzhen Technology Research Center of Gut Microbiota Transplantation, Shenzhen* 518100, *China*
[3] *National Key Laboratory of Intelligent Tracking and Forecasting for Infectious Diseases, National Institute for Viral and Prevention, Chinese Center for Disease Control and Prevention, Beijing* 102206, *China*
[†] *Shu-Jian Wu and Shi-Jue Gao contributed equally to this work.*

Received: 9 September 2024 / **Revised:** 18 September 2024 / **Accepted:** 21 September 2024

Abstract: Neurological disorders not only diminish the quality of life but also pose significant financial burdens on every patient. Presently, neurological disorders present a challenge to societal medical resources. Strategies to relieve and control neurological disorders are urgently required. Increasing studies have reported a close link among the gut microbiota, neuroinflammation, and neurological disorders. Diet plays a crucial role in influencing gut microbiota, suggesting that dietary supplements could be effective in intervening neurological disorders. Therefore, this review summarizes the relationship between neuroinflammation and neurological disorders, and the impact of gut microbiota on the neuroinflammation of neurological disorders is also discussed. Meanwhile, edible mushrooms, known for their multiple health benefits, have gained increasing attention as a valuable food resource. This highlights the pathways through which edible mushrooms modulate gut microbiota to alleviate neurological disorders by reversing dysbiosis and targeting microbial short-chain fatty acids (SCFAs) and tryptophan metabolism pathways. These findings provide robust support for developing therapeutic strategies and potential interventions based on the interactions between edible mushrooms and gut microbiota.

Keywords: edible mushroom; neurological disorders; neuroinflammation; bioactive components; gut microbiota

Citation: Wu S. J., Gao S. J.. The potential of edible mushrooms to intervene neuroinflammation in neurological diseases by targeting gut microbiota. *Food & Medicine Homology*, 2027, 4: 9420172. https://doi.org/10.26599/FMH.2027.9420172

1 Introduction

Neurological disorders are a wide range of diseases influencing the central and peripheral nervous system, which are classified into early-onset neurodevelopmental disorders and late-onset neurodegenerative disorders, including autism spectrum disorder (ASD), Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD), and others[1, 2]. Every patient with neurological disorders not only suffers from diminished quality of life but also poses significant financial and social burdens[3]. For instance, 1 in 54 children in the USA have ASD[2]. The costs associated with ASD may reach $46.1 billion by 2025, surpassing those related to stroke and hypertension[4, 5]. There are over 50 million AD patients worldwide, and annual costs for AD are $1 trillion[6]. Therefore, neurological disorders present a challenge to societal medical resources.

Increasing evidence indicates that neuroinflammation significantly impacts neurodevelopment and neuronal functions, such as neuron proliferation, apoptosis, plasticity, and functionality, leading to various tissue damage in neurodegenerative disorders[7]. Alleviating neuroinflammation may be an effective strategy for preventing and treating neurological disorders. Meanwhile, numerous studies have revealed the bidirectional communication between the gut microbiota and the brain, and the main pathways through which gut microbiota can affect brain health *via* the gut-brain axis by producing considerable amounts of neurotransmitters, modulating intestinal secretion, Sand affecting the central immune system[3]. Thus, gut microbiota and neuroinflammation could be two key targets for intervention in neurological disorders.

The role of dietary bioactive components has been severely underestimated in treatment for neurological diseases[3, 8-11]. Dietary bioactive components are not only significant factors influencing the gut microbiota, but also offer high safety and low side effects. Many dietary bioactive components can affect the composition of gut microbiota and its metabolites (such as short-chain fatty acids (SCFAs), acetylcholine, and serotonin), subsequently intervening brain health through the "gut-brain" axis[3, 12, 13]. Notably, edible mushrooms, as a rich source of carbohydrates, amino acids, proteins, fatty acids, vitamins,

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Address correspondence to Shu-Jian Wu, sjwu2024@fjmu.edu.cn

phenolic compounds, etc., have attracted significant attention from scientific community worldwide due to their nutritional importance and medicinal benefits[14, 15]. Numerous studies have found that different bioactive components from edible mushrooms have active effects on gut microbiota in different diseases[15]. This review aims to discuss the association between gut microbiota, neuroinflammation, and neurodegenerative diseases, and the potential of edible mushrooms in ameliorating neuroinflammation of neurodegenerative diseases by regulating the gut microbiota, providing a novel perspective on using edible mushrooms as dietary supplements in the treatment/prevention of neurological diseases.

2 Neuroinflammation, gut microbiota, and neurological diseases

Inflammation is a protective response to eliminate harmful substances in various cell and tissue injuries, thereby benefiting tissue repair[3, 9, 10, 12, 15-27]. However, persistent inflammation can cause excessive damage to cells and tissues, resulting in the destruction of normal tissues, chronic inflammation, and eventually disease[3, 28]. The neuroinflammation (the inflammation in the brain) caused by different pathways has been regarded as playing a key role in the pathogenesis of the various neurological disorders[29-31]. For example, CCR2 monocytes (pro-inflammatory) enter the late-embryonic brains to promote acute neuroinflammation and subsequently cause neonatal cerebral hypoxic-ischemic brain injury in mice by becoming pathological microglia[32]. Impaired autophagy in microglia leads to NLRP3 inflammasome activation, enhancing neuroinflammation, causing PD-like symptoms (impairment in motor coordination and cognitive learning) in mice[33]. Emerging evidence demonstrated that upregulation of some matrix metalloproteinase (MMP) in microglia (MMP-3 and MMP-9) augments the neuroinflammation by promoting pro-inflammatory cytokines, leading to neuroinflammation-induced brain damage in neurological diseases[34]. Ion channels, such as potassium channels, calcium channels, sodium channels, etc., are critical in the process of neuroinflammation by regulating microglial proliferation, chemotaxis, phagocytosis, antigen recognition and presentation, apoptosis, which have been linked to multiple neurodegenerative disorders, including AD and PD[30, 35]. It has been reported that several microRNAs contribute to exacerbated neuroinflammation by modulating the activation, polarization, proliferation, and apoptosis of microglia in PD and AD[36]. More importantly, numerous clinical studies have shown increased microglial activation (inflammation) and high levels of pro-inflammatory cytokines in the brains of AD patients[37]. In ASD patients, immune dysregulation can be observed, including high levels of pro-inflammatory mediators (NF-κB, IL-6, and TNF-α) and low levels of the anti-inflammatory mediator TGF-β1[38]. A recent study found that over 700 genes known to be associated with neuroinflammation were significantly altered in the postmortem brains of patients with six brain diseases, including AD, PD, ASD[39]. These findings in animal models and clinical studies indicate a close association between neuroinflammation and the occurrence and development of many neurological diseases, indicating the alleviation neuroinflammation in neurological diseases is a strategy for treating neurological disorders (Fig. 1).

Increasing scientific evidence supports that gut microbiota intervene the pathogenesis and/or progression of many neurological diseases by modulating neurotransmission and biological process pathways[3, 40, 41] (Fig. 2A). Several clinical studies have proposed that there is gut microbiota dysbiosis in neurological diseases (ASD, PD, AD, HD, etc.), which impacts the immune system and inflammatory responses in the pathogenesis and development of these diseases[40, 42-46]. For example, the decrease of butyrate-producing bacteria (such as *Faecalibacterium*) is linked to the immune disturbances in AD[46]. *Bacteroides* and Lachnospiraceae were reduced to regulate pro-inflammatory signaling cytokines IFN-γ and IL-6 in ASD[42]. Eight inflammation-associated microbiotas (*Parabacteroides*, *Akkermansia*, *Coprococcus*, *Bilophila*, *Collinsella*, *Methanobrevibacter*, *Eggerthella*, *Adlercreutzia*) were associated with PD progression[43]. *Intestinimonas* and *Bilophila* were correlated with IL-4 and IL-6 in HD, respectively[45]. Moreover, it has been reported that abnormalities in microbial metabolites, such as SCFAs and tryptophan (Trp), are frequently observed in various neurological diseases. These abnormalities may play a role in the development of conditions like AD, ASD, and PD[40, 47]. This evidence suggests that it is possible to target the regulation of gut microbiota and thereby attenuate neuroinflammation in neurological disorders. Notably, the fecal microbiota transplantation (FMT) treatment significantly relieved cognitive deficits and neuroinflammation in *APP/PS1* transgenic mice by reversing the changes in gut microbiota and SCFAs[48]. Microbial diversity and ASD-related behavioral symptoms in children with ASD were improved by FMT, and the improvements were sustained for eight weeks after treatment[49]. FMT can attenuate neuroinflammation in PD mice by reversing changes of gut microbiota and SCFAs to reduce TLR4/TNF-α signaling[50]. These studies demonstrated that FMT targeting restoration of gut microbiota dysbiosis can be an effective treatment strategy for neuroinflammation in neurological diseases (Fig. 2B).

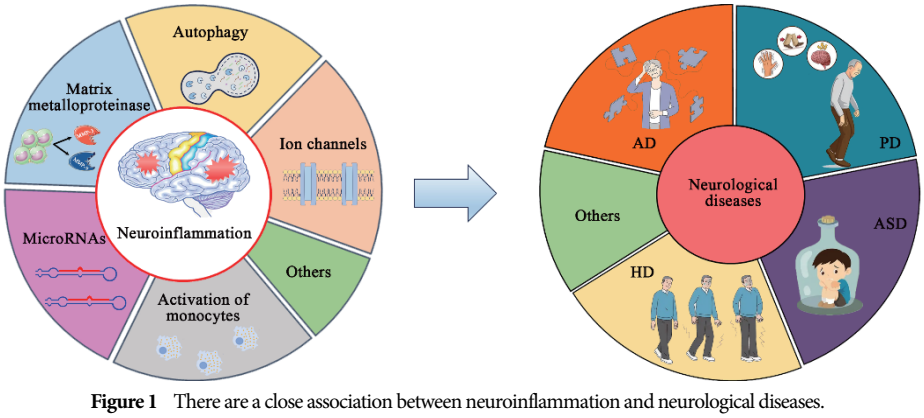


Figure 1 There are a close association between neuroinflammation and neurological diseases.

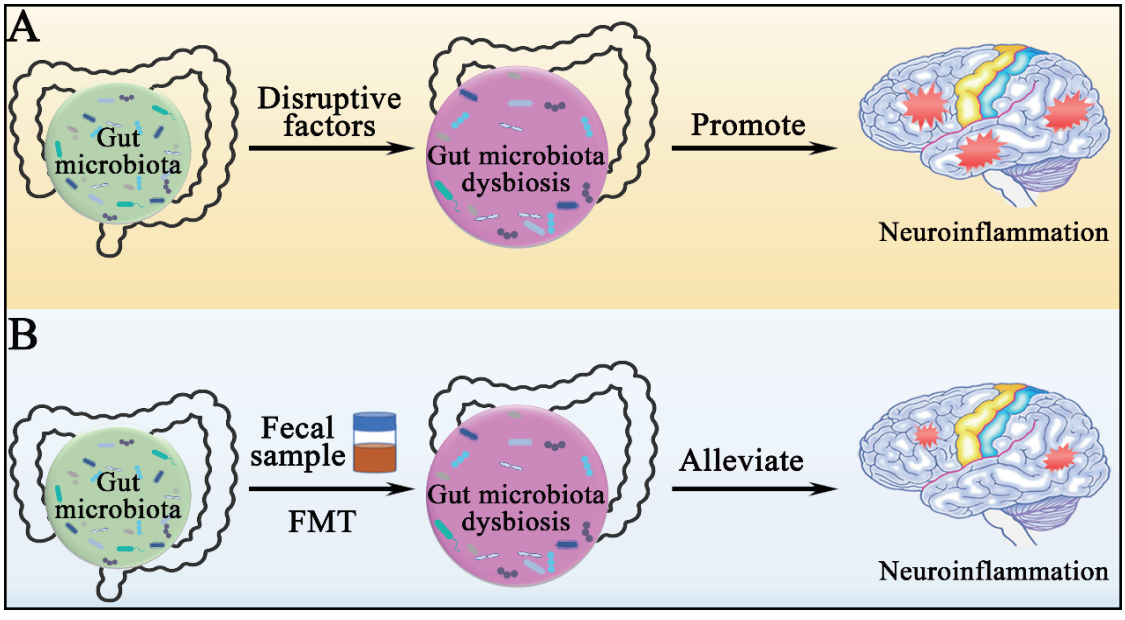


Figure 2 Gut microbiota may be a potential target to intervene neuroinflammation of neurological diseases. (A) Gut microbiota dysbiosis caused by disruptive factors may promote neuroinflammation. (B) Gut microbiota dysbiosis can be reversed by fecal microbiota transplantation from a healthy donor to alleviate neuroinflammation.

Overall, neuroinflammation and gut microbiota dysbiosis are closely associated with the pathogenesis and development of neurological diseases. Targeted modulation of gut microbiota, which in turn mitigates neuroinflammation *via* the gut-brain axis, is one of the pathways for intervening in neurological disorders.

3 Edible mushrooms regulate gut microbiota to intervene neurological diseases

Most edible mushrooms are rich in a variety of bioactive compounds that have beneficial effects on improving human biological functions, such as polysaccharides, proteins, polyphenols, vitamins, and others[9, 10, 17-22]. These bioactive compounds have a profound impact on the gut microbiota[3, 12, 15, 23, 24, 51]. Thus, edible mushrooms could be a potential dietary supplementary to intervene in neurological diseases by regulating the microbiota-gut-brain axis (Table 1). For example, diets supplemented with 5% (*w*/*w*) of *Agaricus bisporus* or *Agaricus bisporus brunnescens* can increase SCFA-producing bacteria (*Akkermansiaceae* and *Tannerellaceae*), and subsequently microbiota-derived SCFAs provide a link between the microbiota and the brain, reducing brain oxidative stress and the levels of IL-6, Nox-2 and Hmox-1 expression in mice with neurological diseases[25]. *Hericium coralloides* exerts anti-AD effects by activating the Nrf2 signaling pathway and regulating gut microbiota (increasing *Akkermansia*, *Alistipes*, and *Helicobacter*, and decreasing *Anaerotruncus* and *Ruminococcus*) to prevent oxidative damage and delaying AD progression[26]. *Pleurotus* powder increased the abundance of *Bifidobacterium* (beneficial bacteria) and the level of butyrate in a fermentation model using fecal sample from autistic child *in vitro*, indicating *Pleurotus. eryngii* and *Pleurotus. ostreatus* to the diet may have a positive effect on children with ASD[27].

3.1 Edible mushrooms are rich proteins and polysaccharides to change gut microbiota composition

Edible mushrooms can change gut microbiota composition. It has been reported that edible mushrooms are rich in protein (the average of 23.80 ± 9.82 g/100 g dry weight)[20] and carbohydrates (range between 32 g/100 g and 61.4 g/100 g)[52], indicating that edible mushrooms are good resource to obtain proteins and polysaccharides. One the one hand, the gut microbiota composition can be altered by different source and content of protein/peptides, and consequently influence human health[12]. The bioactive peptides from edible mushrooms have been gradually reported in recent years, including *Cordyceps militaris*, *Ganoderma Lucidum*, *Agaricus bisporus*, and others[9, 10, 20, 53, 54]. It has been reported that *Cordyceps militaris* or its protein hydrolysates (mainly VQNVGNGVLLGFHGR, GAGVDVTVPFTPGR, and HQTSGDQVTSSTQHSFR) had a growth-promoting effect on *Lactobacillus*[55, 56]. Moreover, *Cordyceps militaris* peptides (VPRKL(Se)M and RYNA(Se)MNDYT) exert an AD-related neuroprotective effect by regulating gut microbiota (increasing *Lactobacillus* and decreasing *Akkermansia*) and modulating amino acid metabolic pathways to alleviate neuroinflammation and oxidative stress in the brain[9, 10, 54] (Table 1). This suggests that edible mushrooms are a good source of proteins with regulatory properties on gut microbiota in neurological diseases. On the other hand, the complex carbohydrates (e.g. β-glucan, cellulose, and lignin) cannot be digested and absorbed in the upper gastrointestinal tract, and finally reach the large intestine to be utilized by gut microbiota[57]. Research on polysaccharides of edible mushroom to promote human health by regulating gut microbiota and microbial metabolites has been increasing[58]. For instance, *Lentinula edodes*-derived (1→3)/(1→6)-β-glucan alleviates cognitive impairments through improving gut microbiota dysbiosis (increasing *Bacteroides*), intestinal barrier impairment (enhancing tight junction proteins), and neuroinflammation (inhibiting the pro-inflammatory macrophage) in mice[59] (Table 1). *Armillariella tabescens*-derived polysaccharides improved cognitive impairments by reversing gut microbiota dysbiosis (increasing SCFA-producing bacterial) and SCFAs deficiency, and reducing the levels of IL-6, IL-1β, TNF-α, oxidative stress, and neurotoxic protein content *via* activating the Keap-1/Nrf2 pathway to

Table 1 Edible mushrooms with a potential function in regulating the microbiota-gut-brain axis to intervene neurological diseases

Edible mushroom	Bioactive compounds	Model	Function	Reference
Agaricus bisporus or *Agaricus bisporus brunnescens*	Dry powder	Mouse (C57BL/6J, six-week-old, male)	● Reduced oxidative stress markers in the brain ● Reduced IL-6, Nox-2 and Hmox-1 expression ● Increased the abundance of Verrucomicrobia and *Akkermansiaceae* ● Reduced the abundance of Cyanobacteria and *Prevotellaceae*	[25]
Pleurotus eryngii and *Pleurotus ostreatu*	Dry powder	*In vitro* fermentation model using fecal sample from autistic child and typically developing child (male, aged 3.5–10 years old)	● Increased the abundance of *Bifidobacterium* ● Increased the levels of butyrate	[27]
Hericium coralloides	Dry powder	Mouse (transgenic *APP*/*PS1*, NA, male)	● Improved AD-like symptoms ● Reduced the levels of Aβ, p-tau, and oxidative stress ● Increased the abundance of *Akkermansia*, *Alistipes*, and *Helicobacter* ● Decreased *Anaerotruncus* and *Ruminococcus* ● Improved the microbial metabolites	[26]
Lentinula edodes	Polysaccharides	Mouse (C57BL/6J, nine-week-old, male)	● Prevented recognition memory impairment ● Ameliorated the alteration of gut microbiota, synaptic ultrastructure, neuroinflammation and brain-derived neurotrophic factor deficits ● Increased the abundance of *Bacteroides* ● Decreased the level of lipopolysaccharide and the proinflammatory macrophage accumulation ● Decreased the abundance of Firmicutes ● Increased the mucosal thickness and the expression of tight junction protein	[59]
Armillariella tabescens	Polysaccharides	Mouse (BALB/c, NA, male)	● Improved cognitive impairment ● Inhibited neuroinflammation, neurotoxic protein content, and oxidative stress ● Increased the abundance of *Lactobacillus*, *Bacteroides*, and *norank_f__Muribaculaceae* ● Promoted SCFAs catabolism	[60]
Oudemansiella raphanipes	Polysaccharides	Mouse (C57BL/6J, NA, male)	● Rescued age-related the deficits in social, learning and memory ability ● Increased the abundance of *Dubosiella*, *Clostridiales*, and *Prevotellaceae* ● Reduced the abundance of *Desulfovibrio* ● Enhanced tight junction and mucin 2 proteins expression for intestinal barrier integrity ● Reversed memory- and synaptic plasticity-related proteins levels	[79]
Cordyceps militaris	Peptide	Mouse (ICR, six-week-old, male)	● Restrained hyperactivation of microglia-mediated synapse engulfment and neuroinflammation ● Alleviated cognitive impairment, neuroinflammation and oxidative stress in the brain ● Increased the abundance of *Lactobacillus* and *Alistipes* ● Decreased the abundance of *Akkermansia* and *Bacteroides* ● Modulated the inflammatory-related metabolic pathways including histidine metabolism, lysine degradation, and purine metabolism	[9, 10, 54]
Hericium erinaceus	Extracts (contained hericenone, erinacine, and ergothioneine)	Mouse (C57BL/6J, 11 months old, male)	● Reverted cognitive frailty ● Decreased crucial markers of inflammation and cellular senescence (CD45, GFAP, IL6, p62, and γH2AX) in the dentate gyrus and *Cornus Ammonis* hippocampal areas ● Reduced the abundance of *Odoribacter*, *Clostridia vadinBB60*, and *Muribaculaceae* ● Increased the abundance of g *Clostridia UCG-014*, Lachnospiraceae_*NK4A136*, and *Eubacterium xylanophilum*	[80]

"NA", not available; *APP*/*PS1* transgenic mice, transgenic mice expressing mutant human amyloid precursor protein (*APP*) and presenilin-1 (*PS1*) genes.

mitigate neuroinflammation in D-Gal-injury mice[60] (Table 1). These studies indicate that edible mushroom polysaccharides have great potential in modulating gut homeostasis to intervene in neuroinflammation. In summary, proteins and polysaccharides are the bioactive compounds of edible mushroom to regulate the abundance and diversity of gut microbiota to improve the development of neurological diseases.

3.2 Bioactive compounds of edible mushroom can regulate microbiota-mediated metabolism of SCFA and Trp

Edible mushrooms can regulate the levels of microbial metabolites. Increasing evidence has shown that microbial metabolites play a critical role in the communication networks

between the gut and brain through the blood-brain barrier[61]. Among them, SCFAs can be produced by gut microbiota from dietary proteins/peptides and polysaccharides *via* fermentation[62-64]. SCFAs can be utilized by epithelial cells and cross the blood-brain barrier into the nervous system, where they can directly interact with SCFAs receptors to affect neurological function in the brain[3,65]. For example, sodium butyrate, one of the histone deacetylase inhibitors, facilitates learning and re-establishes access to long-term memories in CK-p25 Tg mice by increasing histone acetylation[66]. SCFAs have the ability to interact with a variety of immune cells, including influencing the structural and functional integrity of microglia and participating in microglia activation to regulate brain functions[67,68]. It is well established that changes of microbial SCFAs play a key role in the development of neurological diseases. There is increasing research showing that many edible mushrooms and their bioactive componence, such as *Pleurotus eryngii*, *Pleurotus ostreatu*, *Armillariella tabescens* polysaccharides, *Cordyceps militaris* peptide, enhanced the abundance of SCFA-producing bacteria and the level of SCFAs, resulting in the alleviation of neurological diseases, including neuroinflammation, AD, and ASD (Table 1). Hence, edible mushrooms with rich in proteins and polysaccharides, not only increase the abundance of SCFA-producing bacteria but also serve as substrates that can be utilized by the gut microbiota to produce SCFA, which in turn intervene in neurological diseases.

Moreover, Trp plays a key role in the production of serotonin (5-HT), kynurenine, and indole derivatives by gut microbiota, which have notable effects on neurological diseases[69-72]. Pathways of Trp metabolism through the 5-HT and kynurenine are related to neuroinflammatory processes in AD progression[73]. An experimental survey in ASD patients reported that a higher ratio of kynurenine to kynurenic acid and a lower level of Trp was observed in the ASD[74]. Indole-3-propionic acid, one of the Trp metabolites produced by the gut microbiota, has been shown to have a potential neuroprotective effect on neurological diseases-induced social and cognitive memory deficit disorders such as AD and ASD[71]. Surprisingly, Fijałkowska *et al.* reviewed that 15 edible mushrooms have high content of Trp, especially *Pleurotus*[72]. This indicates that edible mushrooms are a good source for Trp metabolism pathway. Furthermore, *Sanghuangporus* extract (mainly polyphenol compound) and Ganoderic acid A from *Ganoderma lucidum* (mainly lanostane triterpenoid compound) potently exerted anti-inflammation by regulating gut microbiota to produce indole derivatives (5-hydroxyindole-3-acetic acid and indole-3-aldehyde, respectively)[75,76]. The alcohol extract of *Ganoderma lucidum* mycelia increased the levels of the sleep-promoting neurotransmitter 5-HT and regulated the serotonergic synapse pathway in mice, which were dependent on the presence of gut microbiota[77]. Moreover, recent studies have revealed that *Lactobacillus* not only a SCFA-producing bacterium[3], but also could modulate multiple enzymes to metabolize dietary Trp[78]. Montgomery *et al.* reported that *Lactobacillus reuteri* in gut microbiota produce a wide array of Trp-derived metabolites by using dietary Trp, including indole acetate, indole-3-glyoxylic acid, tryptamine, p-cresol, and diverse imidazole derivatives, which activate the aryl hydrocarbon receptor and enhanced T cell production of IL-17 to suppress disease activity and inflammatory T cell responses in the central nervous system[78]. Notably, *Armillariella tabescens* polysaccharides and *Cordyceps militaris* peptides enhance the abundance of *Lactobacillus* and influence the metabolites pathway of Trp (Table 1). Taken together, these data suggest that edible mushrooms can serve as a source of Trp for the Trp metabolic pathway, and their bioactive compounds also can modulate the microbiota-mediated Trp metabolism for neurological diseases.

4 Conclusion

Based on the key role of gut microbiota in the gut-brain axis, targeted regulation of gut microbiota to alleviate neuroinflammation may be an effective strategy for intervening in neurological diseases. Edible mushrooms, containing various bioactive substances, have a significant effect on regulating gut microbiota. In the field of nutrition, edible mushrooms, as dietary supplements, has great potential for alleviating neurological diseases through the microbiota-gut-brain axis. There is no doubt that the research on the interaction between edible mushrooms and gut microbiota is conducive to the development of drugs for the treatment of neurological diseases. However, there are some questions that need to be further explored in the future. (1) what are the specific bioactive compounds in edible mushrooms that exert these effects? (2) Does the structure of the bioactive compounds correlate with the regulatory capacity of the gut microbiota? (3) What is the key microbiota targeted by edible mushrooms? (4) What is the specific pathway in the microbiota-metabolite axis that relieves neuroinflammation? Future studies should aim to address these questions.

Data availability

Not applicable.

Conflicts of interest

The authors declare that there are no conflicts of interest in this work.

Acknowledgments

None.

Funding

The authors would like to acknowledge the financial supports of Shenzhen Science and Technology Program (RCBS20231211090537063, JCYJ20230807142310022, and JCYJ20230807142310023), China Postdoctoral Science Foundation (2023M741594).

Author contribution statement

Shu-Jian Wu: Conceptualization, data curation, formal analysis, investigation, software, writing-original draft, editing, visualization, project administration. Shi-Jue Gao: Conceptualization, data curation, writing-review & editing.

Informed consent

Not applicable.

Ethics statement

Not applicable.

Use of AI statement

None.

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