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Review Article

Mycobiome–Brain Interactions: Emerging Role of Gut Fungi in Neurodegeneration

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Abstract

Neurodegenerative diseases, such as Alzheimer's and Parkinson's, are increasingly linked to disruptions in the gut-brain axis. While most research is focusing on bacterial microbiota, the gut mycobiome, or fungal population of the gastrointestinal tract, has emerged as a potentially essential but understudied contributor to neurological health. Gut fungi interact with human immunology, metabolic processes, and microbial networks, and an imbalance (fungal dysbiosis) can cause systemic inflammation, blood-brain barrier disruption, and neuroinflammatory reactions. Microglial activation, oxidative stress, and neuronal damage can be influenced by fungal metabolites and cell wall components, indicating ways in which the mycobiome may contribute to neurodegeneration. Patients with multiple sclerosis, Alzheimer's disease, Parkinson's disease, and several mental disorders have been shown to have altered fungal profiles, suggesting potential involvement in the course of the disease and the severity of its symptoms. The complexity of gut microbial control of brain function is further highlighted by interactions between fungal and bacterial communities. This review summarizes current evidence on gut mycobiome composition, mechanisms of mycobiome–brain communication, and associations with neurodegenerative diseases. Understanding these interactions may reveal novel biomarkers and therapeutic targets, emphasizing the need for longitudinal studies and mycobiome-focused interventions to clarify the clinical significance of gut fungi in neurodegeneration.

Keywords: Gut mycobiome, Gut–brain axis, Neurodegeneration, Fungal dysbiosis, Neuroinflammation

1. Introduction

Neurodegenerative diseases, particularly Alzheimer's disease (AD) and Parkinson's disease (PD), contribute to a significant and increasing global health burden, characterized by progressive dysfunction of the neurons and loss of cognitive or motor function. These disorders are linked to multifactorial pathologies such as protein aggregation, oxidative stress, neuroinflammation, and disruption of central nervous system (CNS) homeostasis (Chen et al. 2025; Kustrimovic et al. 2024). Traditionally, research has focused on intrinsic neural mechanisms; nevertheless, accumulated evidence indicates that peripheral systems, in particular, the gastrointestinal tract, play a significant role in neurodegenerative processes through complex bidirectional communication pathways collectively known as the gut–brain axis (GBA) (Chen et al. 2025). The GBA involves neural, immune, endocrine, and metabolic communication between the CNS and the gastrointestinal microbiome, allowing microbial communities to affect neuroinflammation, blood-brain barrier (BBB) function, and neuronal activity (Carabotti et al. 2015; Shah et al. 2024). Individuals with AD and PD have consistently reported

changes in gut microbial composition, or dysbiosis, supporting the idea that gut microbial conditions may influence disease susceptibility and progression (Kustrimovic et al. 2024). Changes in gut microbial communities have been linked to neurodegenerative markers and cognitive function changes, indicating that microbial signals may influence the onset and course of disease (Nagpal et al. 2020; Xi et al. 2021). While the majority of research has concentrated on the bacterial components of the gut microbiota, more recent studies have shown how the gut mycobiome, the fungal communities that live in the gastrointestinal tract, may play a significant but little-known role in influencing systemic inflammation, metabolic signalling, and host immune responses (Hadrich et al. 2025; Z. Liu et al. 2025).

According to preliminary research, individuals with mild cognitive impairment and AD markers have different gut mycobiome compositions, and these fungal signatures interact with bacterial communities and diet in ways that are associated with neurodegenerative processes (Nagpal et al. 2020). In PD cohorts, fungal profiling has revealed distinct faecal mycobiome and metabolome patterns, raising the possibility that fungal dysbiosis may contribute to disease pathophysiology (Gubert et al. 2022; De Pablo-Fernandez et al. 2022).

Studies employing transgenic mouse models of AD provide additional evidence that the fungal microbiota can affect neuroinflammation and cognitive impairment. *Saccharomyces boulardii*, is one of the probiotic fungal species that has been demonstrated to improve synaptic function and cognitive performance, suppress microglia-mediated neuroinflammation by blocking the Toll-like receptor (TLR) signalling pathway, and restore gut fungal balance. These results demonstrate how the gut mycobiome can be targeted therapeutically to alter neuroinflammatory processes through the GBA (Ye et al. 2022). These observations highlight the growing significance of gut fungi in gut–brain communication and suggest that changes in the mycobiome may contribute to the pathophysiology of neurodegenerative diseases. This review aims to provide an overview of the current understanding of the gut mycobiome, its influence on immune and neural pathways, and emerging implications for neurodegenerative diseases.

2. Gut Mycobiome: An Underexplored Microbial Component

Fungi constitute a unique microbial population within the gastrointestinal tract known as the gut mycobiome, even though the gut microbiome is frequently described primarily in terms of bacteria. Even though this community makes up a considerably smaller portion of the whole microbiota, it interacts with the immune system and other microbial communities to shape host physiology. Although the precise composition varies greatly between geographic populations, high-throughput sequencing studies have shown that the gut mycobiome of healthy individuals is mainly made up of fungi from the phyla *Ascomycota* and *Basidiomycota*, including genera like *Saccharomyces*, *Candida*, *Penicillium*, *Aspergillus*, and *Malassezia* (Huseyin et al. 2017; Lai et al. 2023).

The gut mycobiome shows more inter-individual variability but lower total diversity when compared to the bacterial microbiome. It also seems to interact with host immunity in novel ways that are still being discovered. For instance, in healthy people, gut mycobiota profiles have been linked to IgG responses against gut fungal commensals, indicating active immune recognition of fungal microbiota members (Moreno-Sabater et al. 2020). Despite their relatively low abundance, fungal species can affect immune modulation, metabolic interactions, and the structure of bacterial communities. This suggests that the gut mycobiome is an unexplored but functionally significant part of the gut ecosystem, with a potentially important role in host physiology, immune regulation, and disease

development.

3. Fungal Dysbiosis and Host Immune Dysregulation

Fungal dysbiosis is defined as an imbalance in the composition and function of the gut fungal community, which is frequently characterised by the overgrowth of opportunistic species like *Candida* spp. or alterations in relative abundance within the mycobiome (Kiran et al. 2025; Iliev and Leonardi 2017). Although fungi make up a lesser proportion of the gut microbiota than bacteria, variations in fungal populations have been associated with immune system modifications and higher inflammatory responses in both human and animal studies (Pérez 2021). Increased gut *Candida* abundance has been seen in people with gastrointestinal (GI) disorders such as colorectal cancer and inflammatory bowel disease, combined with alterations in fungal diversity (Huang et al. 2024; Catalán-Serra et al. 2024; Acar et al. 2024), indicating that mycobiome perturbations may affect host immune activation and barrier function. These alterations are linked to altered recognition by innate immune receptors, specifically the C-type lectin receptor Dectin-1, which binds β-glucans in fungal cell walls and starts downstream signalling that can cause pro-inflammatory reactions in host tissues (Zhang et al. 2025; Y. Wang et al. 2021).

Dectin-1 and TLRs are two pattern recognition receptors that the host immune system uses to identify fungal cells. When Dectin-1 is activated, spleen tyrosine kinase is phosphorylated, and signalling complexes are assembled, which sets off inflammatory pathways and the production of cytokines. The importance of immune sensing in preserving fungal homeostasis is shown by the fact that in mouse models lacking Dectin-1, compromised antifungal immunity leads to fungal overgrowth and increased vulnerability to inflammation (Zhang et al. 2025). In addition to compromising intestinal barrier integrity and facilitating the flow of pro-inflammatory cytokines and fungal metabolites into the bloodstream, chronic or unresolved immune activation brought on by persistent fungal dysbiosis may promote systemic inflammation. It has been proposed that these long-term inflammatory conditions have a role in distal organ consequences, such as altering neuroinflammatory pathways via the GBA, indicating a mechanism linking immunological dysregulation, gut fungal imbalance, and neurodegenerative processes (Fakharian et al. 2023; Fung, Olson, and Hsiao 2017).

4. Mechanisms of Mycobiome–Brain Communication

The gut mycobiome interacts with the brain primarily via the BBB, immunological modulation, microbial metabolites, and neurotransmitter regulation. The BBB regulates brain homeostasis by preventing harmful substances from entering the CNS. However, gut mycobiome dysbiosis can impair BBB integrity, leading to neuroinflammation and neurological diseases (Mou et al. 2022; Zeng et al. 2024).

Mycotoxins and other fungal metabolites have the capacity to enter the bloodstream and disrupt the BBB's tight junctions, increasing permeability and activating neuroinflammatory reactions (Nyúl-Tóth et al. 2016). Mycotoxins are all secondary metabolites of different fungi (IARC 1986) and have the ability to harm brain cells, cause inflammation, and alter the balance of neurochemicals (Ehsanifar et al. 2026). Dysbiosis can also cause systemic endotoxemia and enable inflammatory mediators such as lipopolysaccharides (LPS) to enter the brain, resulting in microglial activation, neuronal injury, and cognitive loss (Blake et al. 2024; Arnesen et al. 2023; Kalyan et al. 2022).

BBB function is further influenced by interactions between the bacterial microbiota and the gut mycobiome. Indirectly affecting the integrity of the BBB and immunological modulation, changes in fungal communities can disrupt microbial balance and decrease the synthesis of short-chain fatty acids (Yetgin 2024; L. Wang et al. 2024). Innate immune receptors, such as TLRs

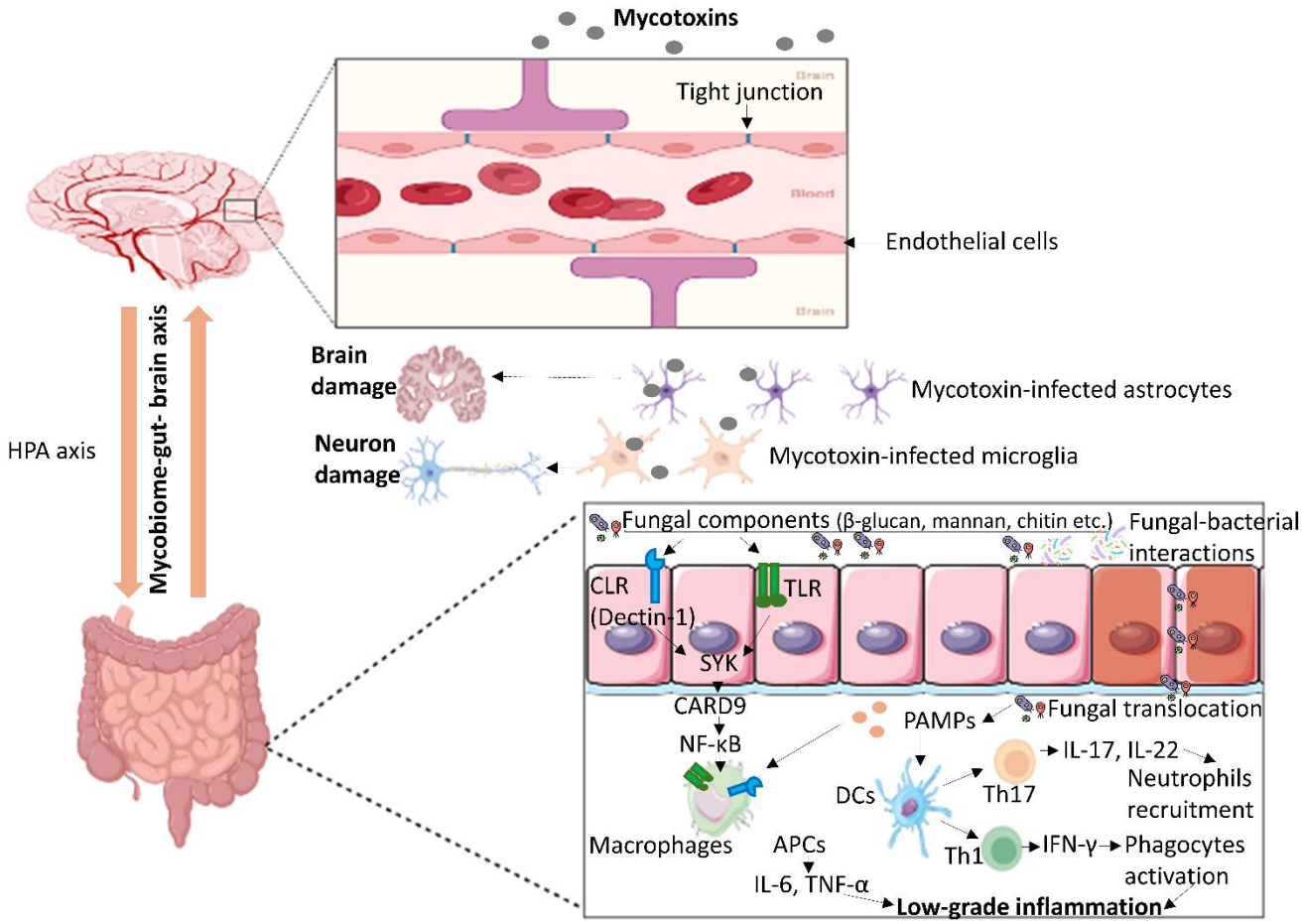

Figure 1: The role of the gut mycobiome in gut–brain axis communication and neuroimmune modulation.
Mycotoxins (e.g., aflatoxins, ochratoxin A, fumonisin) and its metabolites can easily cross the blood-brain barrier and infect astrocytes and microglia, which eventually leads to neuronal damage and brain damage.
The intestinal mycobiome contributes to bidirectional communication between the gut and the brain through immune, metabolic, and neuroendocrine pathways. Pattern recognition receptors (PRRs) of the host immune system, including CLRs and TLRs, recognize fungal cell wall components such as β-glucan, chitin, and mannan. This recognition activates downstream signalling cascades involving SYK, CARD9, and NF-κB, resulting in the production of proinflammatory cytokines and systemic immune activation, which may influence CNS function. Interactions between fungi and bacteria shape the intestinal microecosystem; disruption of these interkingdom relationships contributes to dysbiosis, altered barrier integrity, and increased intestinal permeability, facilitating fungal translocation and peripheral inflammation that can impact the brain.
The gut mycobiome forms an integral component of the gut–brain axis. The CNS modulates fungal composition via the HPA axis and stress-related pathways, while fungal metabolites, immune mediators, and neuromodulatory substances influence neuronal signalling, behavior, and cognitive function. Abbreviations: CLRs, C-type lectin receptors; TLRs, Toll-like receptors; SYK, spleen tyrosine kinase; CARD9, caspase recruitment domain family, member 9; NF-κB, nuclear factor-kappa B; CNS, central nervous system; HPA, hypothalamic-pituitary-adrenal; PAMPs, pathogen-associated molecular patterns; DCs, dendritic cells; APCs, antigen-presenting cells; IL, interleukin; TNF, tumor necrosis factor; Th, T helper cell; IFN-γ, interferon gamma (Gu et al. 2019).

and dectin-1, interact with mannan and β-glucans found in fungal cell walls, influencing dendritic cells and macrophages and causing neuroinflammatory disorders, including AD and PD (Batbayar, Lee, and Kim 2012). Another gut-brain pathway for communication is the activation of the vagus nerve by fungal species such as *Saccharomyces* and *Candida* (Han et al. 2022). BBB tight connections are further disrupted and CNS inflammation is encouraged by immune

dysregulation induced by mycobiome imbalance (Obermeier, Daneman, and Ransohoff 2013).

Neurotransmitter systems are also modulated by the gut mycobionts. Fungi may produce and release a wide range of bioactive compounds, including metabolites, neuromodulators, and molecules that mimic neurotransmitters. These compounds, which are generated by fungi, can interact with neural receptors and change the way neurotransmitters function and balance. For instance, several fungal species have been shown to create compounds that mimic neurotransmitters such as gamma-aminobutyric acid (GABA), serotonin, and dopamine. By directly interacting with gut neurotransmitter receptors or even breaching the BBB, these compounds generated from fungi can influence the amounts of neurotransmitters in the CNS (T. Liu et al. 2020; Yetgin 2024). Dysbiosis has been connected to conditions including anxiety and depression and may change the metabolism of bacterial neurotransmitters, impacting mood, behaviour, and cognition (Anand, Gorantla, and Chidambaram 2022). Tryptamine derivatives and other bioactive substances with serotonin-like characteristics are produced by certain fungi and have the potential to modify mood, cognition, and neural signalling (Ortega et al. 2023).

Fungal metabolites with neurotoxic qualities, such ochratoxin A and aflatoxins, have been connected to PD-related oxidative stress, mitochondrial dysfunction, and dopaminergic neuronal damage (Sava et al. 2006; Wu, Groopman, and Pestka 2014).

Modulation of gut fungal communities has been demonstrated to impact neuroinflammatory, microglial activation, and behavioural performance in animal models, suggesting that chemicals generated from fungi can impact cognition and motor function. Immune-mediated pathways, increased intestinal permeability, and systemic dissemination of fungal components that trigger inflammatory cascades are likely to be responsible for these effects (Fasano 2020; Brand et al. 2019). The mechanisms by which the gut mycobiome influences neuroimmune signalling and brain function are illustrated in **Figure 1**.

Mechanistically, prolonged fungal dysbiosis may increase peripheral and central immune activation by promoting chronic systemic inflammation, compromising the integrity of the epithelial barrier, and facilitating the translocation of fungal products into circulation. This process becomes more complicated by interactions between the bacterial and fungal communities, as microbial dysbiosis may have a synergistic effect on the progression of neurodegeneration (Riehl et al. 2023; Morais, Schreiber, and Mazmanian 2021). A growing body of experimental and clinical data indicates that gut fungal imbalance may play a role in the development and progression of disease through immunological, metabolic, and GBA-mediated processes, even if causality remains to be fully established (Zheng, Liwinski, and Elinav 2020; Yetgin 2024). These findings highlight gut mycobiome as a source of biomarkers and a therapeutic target in neurodegenerative diseases, although the molecular pathways are still being determined, suggesting the need for more longitudinal and interventional research.

5. Fungal Metabolites and CNS Dysfunction

A range of metabolites and toxins produced by gut fungi may affect the function of the CNS. Aflatoxin B1 (AFB1), ochratoxin A (OTA), T-2 toxin, deoxynivalenol (DON), 3-nitropropionic acid (3-NPA), zearalenone (ZEN) and fumonisin B1 (FB1) are the most common mycotoxins found in human food and animal feed (Richard et al. 2003). These substances are secondary metabolites of *Aspergillus*, *Penicillium*, and *Fusarium* species and can directly cause neurotoxicity by crossing the BBB (Wu, Groopman, and Pestka 2014; Sava et al. 2006; Ehsanifar et al. 2026; Pei et al. 2021).

These compounds have been shown to cause oxidative stress, mitochondrial dysfunction, DNA damage, and apoptosis in glial cells in vitro. They also activate astrocytes and microglia, which increases the production of pro-inflammatory

Table 1: Fungal species associated with neurological disorders and their potential roles in disease mechanisms.

Fungal Species	Associated Neurological Conditions	Mechanistic Category	Potential Contribution to Neurological Dysfunction	References
Candida albicans	AD; Autism spectrum disorder; Schizophrenia	Amyloid-associated overrepresentation; Opportunistic fungal overgrowth	Aβ aggregation, APP accumulation, neuroinflammation; Enhanced immune activation and altered gut barrier signalling influencing neurobehavioural regulation	(Strati et al. 2017; Jungbauer et al. 2022; Pisa et al. 2015; Yuan et al. 2021; 2024)
Malassezia spp.	AD; MS	Immune-mediated inflammation; Inflammation-associated fungal alteration	Th1/Th17 activation, neuroinflammatory responses; Immune-mediated CNS inflammation	(Yadav et al. 2022; S. Shah et al. 2021; Phuna and Madhavan 2022)
Alternaria, *Cladosporium* spp.	AD	Neuroinflammation-associated fungi	Neuroinflammation, possible cholinergic dysfunction	(Phuna and Madhavan 2022)
Aspergillus spp.	AD	Amyloid-associated fungal detection	Possible involvement in amyloid beta deposition and cognitive decline	(Fujihara et al. 2023; Yetgin 2024)
Cryptococcus neoformans	Cognitive dysfunction	Cognitive impairment association	Reduced cognitive performance, systemic immune effects	(Y. Liu et al. 2022)
Penicillium spp.	Depression	Mood-related fungal imbalance	Interaction with microbiota and inflammatory pathways	(Hao et al. 2023)

Note: AD= Alzheimer's disease; APP= Amyloid Precursor Protein; MS= Multiple sclerosis, PD= Parkinson's disease.

cytokines such as TNF-α, IL-1β, and IL-6 (Pei et al. 2021). Previous investigations have shown that reactive oxygen species (ROS) and lipid peroxidation gradually accumulated in the cytoplasm of human astrocytes treated with aflatoxin B1. Oxidative stress reduces mitochondrial permeability and DNA molecule integrity. *In vivo* and *in vitro* testing findings indicated that aflatoxin decreases the number of glial cells and neurons in the frontal cortex. AFB1 has been shown to trigger the NLRP3 inflammasome in microglia, promote ROS production, and enhance pro-inflammatory cytokine release, all of which are key cellular events linked to neuroinflammation and neuronal injury (Shi et al. 2015; Ashton et al. 2012).

Components of the fungal cell wall, such β-glucans, also interact with macrophages and microglia's innate immune receptors, such as Dectin-1, to modify immune activation and exacerbate CNS inflammation. This immune modulation is believed to be crucial for neuroinflammatory disorders and could worsen diseases like AD and PD (Han et al. 2022). These interactions can prepare microglia to adopt a pro-inflammatory phenotype that promotes oxidative stress and disturbs neuronal homeostasis. Oxidative stress caused by mycotoxin exposure causes excessive ROS buildup, inhibits mitochondrial function, and affects neuronal signalling pathways, contributing to synaptic dysfunction and cell death, which are strongly linked to neurodegenerative disorders (Mishra et al. 2024; Pei et al. 2021). Together, these fungal metabolites and immune-modulating factors collectively represent mechanisms by which the gut mycobiome may contribute to oxidative stress, microglial activation, and subsequent neuronal injury.

6. Mycobiome in Neurodegenerative Diseases

Emerging clinical evidence suggests that gut fungal communities are altered in patients with neurodegenerative disorders. Among the most

frequently identified fungi species in AD patients' brains are *Candida, Malassezia, Cladosporium,* and *Alternaria*. *Candida albicans* is more abundant in AD patients than in healthy controls, and fungal amyloid production has been linked to amyloid beta (Aβ) aggregation in the brain (Jungbauer et al. 2022; Pisa et al. 2015). *Candida* species have been postulated to cause fungal glial granulomas with amyloid precursor protein (APP) accumulating within once they reach the brain. Aβ can be produced as a result of APP cleavage. By triggering the immunological responses of helper T-cells (Th) 1 and Th17, *Malassezia* species can cause neuroinflammation. *Alternaria* and *Cladosporium* species are associated with neuroinflammation; the brain's acetylcholinesterase inhibitor synthesis may be influenced by these two fungal species (Phuna and Madhavan 2022).

Dysbiosis of the gut mycobiome has been reported in neurodegenerative diseases such as PD, AD, and multiple sclerosis (MS) (Tremlett et al. 2017). *Malassezia* spp. has also been shown to be more abundant in people with MS. Patients with relapsing-remitting MS have a different and altered fungal microbiome when compared to healthy controls (Yadav et al. 2022; S. Shah et al. 2021). MS has been associated with changes in the gut mycobiome, which are marked by a decrease in fungal richness and variety (Yetgin 2024).

Certain fungal taxa have also been linked to various neurological and neuropsychiatric conditions in addition to traditional neurodegenerative diseases. Studies have found a connection between gut mycobiota dysbiosis and conditions including depression, bipolar disorder, autism spectrum disorders, schizophrenia, and AD. Research suggests that some fungi species, such as *Saccharomyces* and *Candida*, may affect immunological responses, gut permeability, and neuroinflammation, all of which might have an impact on mental health outcomes (Hadrich et al. 2025).

When compared to healthy controls, individuals with autism spectrum disorder (ASD) have been found to have higher levels of *Candida albicans*, which may be related to disruption of the GBA (Strati et al. 2017). Psychiatric and cognitive disorders have also been linked to changes in fungal profiles. Depressive symptoms and potential interactions with the wider gut microbiota have been linked to changes in the number of *Penicillium* spp. Children and adolescents suffering from depression have altered gut microbiomes (Hao et al. 2023). Schizophrenia is associated with gut mycobiome dysbiosis, especially increased *Candida albicans*, which may affect immune regulation and is linked to more severe symptoms, chronic inflammation, and GBA disturbances (Yuan et al. 2024; 2021).

Additionally, people with a greater incidence of *Cryptococcus neoformans* have been linked to cognitive impairment (Liu et al. 2022). Together, these results broaden the range of neurological disorders linked to the mycobiome and support the idea that fungal imbalance may cause neuroinflammatory and neurobehavioural changes via immune and GBA-mediated pathways. **Table 1** summarizes the fungal species associated with neurological disorders.

7. Challenges and Research Gaps

Methodological limitations, such as challenges in precisely sequencing fungal communities, low fungal biomass in samples, and small cohort sizes, continue to restrict research on the gut mycobiome in neurodegeneration. Most available studies are cross-sectional, with a lack of longitudinal and clinical investigations to establish causality. Furthermore, there are still no established procedures for sampling, analyzing, and interpreting data. To elucidate the functional role of gut fungi in neurodegenerative disorders, tailored mycobiome-based therapies and carefully planned clinical trials are required.

8. Future Perspectives and Therapeutic Implications

Future strategies to restore fungal balance in the gut could involve probiotic or symbiotic methods,

dietary modification, and antifungal therapies. Modulating the gut mycobiome may offer a new way to treat or prevent neurodegenerative disorders. The use of gut fungal signatures as non-invasive biomarkers for early disease identification, prognosis, and treatment response monitoring may be made possible by developments in multi-omics and precision medicine.

9. Conclusion

The gut mycobiome has emerged as a previously neglected yet critical component of the gut-brain axis. Fungal dysbiosis has been shown to affect metabolic signalling, immunological responses, and neuroinflammatory pathways associated with neurodegenerative disorders. Future research that combines multi-omics techniques and controlled interventions is required to evaluate whether targeting gut fungi can prevent or reduce neurodegeneration. Increasing our understanding of mycobiome-brain interactions may lead to new routes for early detection, biomarker development, and novel therapy techniques for neurological disorders.

Conflict of Interest

The authors declare no conflict of interest.

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Consent Forms

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Author Contributions

MH conceptualized the study and wrote the final manuscript; NHK critically reviewed and edited the manuscript.

Data Availability

NA

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