REVIEW
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The Potential Impact of Probiotics on Neurodegenerative Diseases

ABSTRACT

Commensal microorganisms predominantly reside inside or on the human body. These organisms are collectively called the microbiome. The human intestinal tract harbors the most abundant and diverse collection of microbes. Probiotic products or supplements have been linked to particular health concerns. These products contain probiotic strains that exhibit beneficial characteristics tailored to address specific clinical conditions, primarily related to the gastrointestinal tract. Within these, the dysregulation of gut microbiota may contribute to the occurrence or development of Alzheimer's disease and Parkinson's disease through diverse mechanisms that are not yet fully understood but are believed to involve modulations in gut microbiome composition, strengthening of gut barrier integrity, and interactions with the host's immune system. Although the effectiveness of probiotics can vary depending on various factors and the process of choosing appropriate probiotic formulations through diverse strains with optimal effectiveness can be challenging, understanding the fundamental mechanisms and assessing the effectiveness of probiotics have the potential to provide potential treatment options for neurodegenerative diseases. Here we aimed to review the possible interaction between probiotics and neurological diseases.

Keywords: Neurological diseases, probiotics, microbiota, microbiome

INTRODUCTION

Neurodegenerative disorders such as Alzheimer's disease (AD) and Parkinson's disease (PD) are increasingly burdening healthcare systems as a result of the aging population.[1,2] These disorders not only cause progressive loss of cognitive and motor functions but also share other pathogenic similarities, including defective protein quality control and mitochondrial homeostasis. The characteristics of degenerative diseases also include the accumulation of aggregating proteins such as amyloid. The extensive overlap between age-related disorders and productive involution suggests that the two processes interact at multiple levels.[3] Although much progress has been made in understanding disease pathobiology, there are still no effective ways to develop treatment for the progression of such disorders.[4,5]

The complex community of the gut microbiota (GM) is influenced by several factors, including genetic components, age, diet, and lifestyle characteristics. Diet has an especially significant impact on the GM community composition, and its various components such as carbohydrates, proteins, fats, and polyphenols determine the pattern and diversity of the GM.[6,7] Given the crucial roles of the GM in metabolic pathways and its link to several diseases, it is suggested to intervene in GM signaling and its subsequent diseases. Probiotic administration might contribute to the restoration of commensal microbiota and repair the epithelium barrier.[8]

Probiotics are microorganisms that offer health advantages. Scientists have explored their potential for regulating the nervous system and treating nervous disorders, including AD and PD.[9,10] Probiotics operate through mechanisms that are not yet fully understood but are believed to involve alterations in gut bacteria composition, fortification of gut barriers, and interaction with the body's immune system. Ongoing studies indicate that probiotics have the potential to impact the gut–brain axis, potentially diminishing neurological vulnerabilities. Notably,

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probiotics such as *Lactobacillus* and other similar strains that serve as beneficial gut microbes have captured attention for their potential in managing neurological disorders such as AD and PD. The emerging therapeutic advantages of probiotics in addressing a range of health conditions have generated a surge of interest in these dietary supplements. Further research is needed to fully understand the potential of probiotics in treating nervous diseases and to identify the most effective strains and doses.[10]

GUT MICROBIOTA AND BRAIN CONNECTIONS

The complex environment of the human digestive tract comprises approximately 1000 distinct microbial species, predominantly belonging to the *Firmicutes* and *Bacteroidetes* phyla, with smaller populations from *Actinobacteria*, *Proteobacteria*, *Fusobacteria*, *Verrucomicrobia*, and Archaea. These microscopic residents thrive within the hospitable conditions provided by their host organism, flourishing and contributing to various essential functions. Notably, the GM plays a pivotal role in facilitating the circulation of numerous metabolites through the bloodstream to various tissues and organs, including the brain. The gut–brain axis serves as a communication network facilitating the relationship between the GM and the brain. Communication between the gut, the microbiota, and the brain is facilitated by various signals from neural, immune, and endocrine pathways.[11] The gut possesses its own distinct nervous system known as the enteric nervous system (ENS). In spite of the direct connection of the ENS to the brain nerves, the GM has no direct access to these neural networks. However, intestinal microorganisms can provide this access indirectly via immune cells causing inflammation in the intestine, as well as through secreted neurotransmitters and neuroactive metabolites that have the potential to communicate with various receptors of GABA, 5-HT, and DA.[12-14]

IMPACTS OF PROBIOTICS ON NEUROLOGICAL DISEASES

Compounds produced by a healthy gut microbiome support neurological and immunological function. Immune-related neurological diseases (NDs) have been connected to disruptions in the GM. The GM regulates gut–brain connections, which may lead to possible therapies for neurological disorders such as AD and PD.[10,15,16] Dysbiosis, altered immune responses can contribute to the inflammatory processes of multiple sclerosis (MS) in the central nervous system (CNS).[17,18] In this context, while chemical medications are employed in the treatment of NDs, there is growing interest in applied research and the utilization of natural substances like probiotics. Moreover, these alternatives have no discernible side effects and play a preventive role.

The key probiotics are primarily found within the genera *Lactobacillus* and *Bifidobacterium*. Probiotics play a crucial role as beneficial bacteria in maintaining the balance of homeostasis by influencing the microbiome, which refers to the community of microorganisms in the body. Recent research efforts have focused on exploring how probiotics can be utilized to manage the symptoms of NDs. Considering the proven effectiveness of specific probiotic strains in shaping the microbiome balance and the significant impact of the microbiome and the gut–brain axis on the severity of NDs, it is evident that probiotics have the potential to serve as valuable tools in the management of brain-related conditions, such as NDs.[16]

Recent research has highlighted the potential of probiotics in treating neurodegenerative diseases, particularly AD and PD. Bi et al.[19] and Ji et al.[20] both discussed the role of probiotics in modulating the gut microbiome and reducing neuroinflammation, which are key factors in the development of AD. Neuroinflammation is recognized as a significant pathophysiological factor in neurodegenerative conditions like PD alongside AD. The heightened loss of dopaminergic neurons due to this inflammation can exacerbate disease symptoms. Specific strains like *Lactobacillus* and *Bifidobacterium* have been shown to enhance cognitive function and memory, which are often impaired in neurodegenerative conditions.[18,21]

Probiotics are increasingly being explored as anti-inflammatory treatments for neurodegenerative disorders, showing promise in reducing oxidative stress and inflammation linked to lowering the risk of non-communicable diseases.[22] For instance, the Lab4b probiotic has been found to decrease disease pathology in mice with AD, fostering conditions that support anti-inflammatory cytokines.[23] Likewise, probiotics like *Acidophillus*-KAL4 have been proven to lower inflammation and reduce harm to the intestinal barrier in mouse models of AD, suggesting their potential as therapeutic options.[20,24,25] Mohammadi et al.[26] provide evidence of the beneficial effects of a specific probiotic formulation in reducing neuroinflammation and improving memory in a rat model of AD. These findings collectively suggest that probiotics could be a promising therapeutic option for neurodegenerative diseases.

The regulation of neurotransmitter levels, particularly the control of dopamine (DA) and serotonin (5-HT), plays a crucial role in managing neurodegenerative diseases. As probiotics release anti-inflammatory, antioxidant, or anti-pro-inflammatory cytokines, probiotics such as VSL#3, consisting of 8 bacterial strains, are complex supplements that aid in reducing neurodegeneration and inflammation. Without changing the effects of mesenchymal stromal cells (hMSCs), VSL#3 interacts with hMSCs to decrease neurodegeneration and inhibit NOD-like receptor protein-3, which triggers inflammation. Notably, individual probiotic strains like *Bifidobacterium longum* have been found to enhance cognitive function, while multi-strain probiotics can contribute to improved adult cognition.[27]

γ-Aminobutyric acid (GABA) and acetylcholine (ACh) are crucial neurotransmitters involved in the regulation

of cognitive functions, emotional control, and memory processes. Acetylcholine is specifically associated with cognitive abilities such as learning and memory, whereas GABA serves as the primary inhibitory neurotransmitter in the CNS, moderating excessive neural activity by controlling neuronal excitability.[28] Research suggests that certain probiotic strains, such as *Lactobacillus rhamnosus* JB-1, *Limosilactobacillus reuteri* PBS072, and *Bifidobacterium breve* BB077, may increase GABA production in the gut, potentially influencing mood and anxiety levels through the gut–brain axis. These strains have been shown to alter GABA receptor expression, reduce corticosterone levels, and decrease anxiety-related behaviors.[29,30] Additionally, GABA-producing probiotic candidates have been found to positively modulate the gut microbiome composition and metabolism, further supporting their potential role in gut health and mental well-being.[31] Research shows that some probiotics, like *B. longum*, may help brain function. Cui et al.[32] found that a prebiotic called lactulose increased *Bifidobacterium* levels in mice. Mills et al.[33] discussed how *B. longum* could affect brain activity. In a mouse model of Alzheimer's, a combination of *Bifidobacterium bifidum* and *B. longum* improved memory and cognition. This suggests that *B. longum*, either alone or with other strains, may enhance cognitive abilities.[34]

Studies reveal that certain probiotic strains, like *Lacticaseibacillus rhamnosus* HA-114, can positively impact energy levels and cholesterol regulation in animal models with Huntington's disease and other neurological disorders.[35] This strain was discovered to safeguard nerve cells and regulate fat levels and energy through a process called mitochondrial beta-oxidation. Similarly, other probiotic strains, including *L. rhamnosus* BFE5264[36], *L. rhamnosus* MTCC 5957, *L. rhamnosus* MTCC 5897, and *Lactobacillus plantarum* Lp09 and Lp45, have demonstrated cholesterol-lowering effects and improvements in cholesterol metabolism in animal models.[37] These findings suggest that probiotic supplementation may have potential therapeutic benefits for neurological conditions and metabolic diseases.

In relation to AD, Webberley et al.'s study[38] in 3xTg mice shows that the lack of IL-10 reduces disease pathology in AD animals and that the Lab4b probiotic functions as a neuroprotective agent through an anti-inflammatory cytokine. In a similar vein, Yang et al.[39] address the significance of ProBiotic-4 (composed of *Bifidobacterium lactis*, *Lacticaseibacillus casei*, *B. bifidum*, and *Lactobacillus acidophilus*) in lowering levels of LPS and γ-H2AX, 8-OHdG, TLR4, RIG-I, and NF-κβ nuclear translocation in the brain, as well as in reducing gut barrier degradation and inflammation in aged senescence-accelerated prone 8 (SAMP8) animal models. Regarding PD, Sun et al.[40] generated male C57BL/6 (MPTP initiated) mice and examined the possibility of reversing gut microbiome dysbiosis. Colic GLP-1, colonic GPR41/43, and cerebral GLP-1 receptor levels were decreased in MPTP-induced rodents after 4 weeks of *Clostridium butyricum* therapy. By elucidating the fundamental processes of these ailments and evaluating the effectiveness of probiotics in vertebrate models, medications may be created to combat the diseases.[41,42]

Recent clinical research has shown promising outcomes for probiotic treatments in PD. Studies have demonstrated that various probiotic capsules can lead to amelioration of PD symptoms, as measured by the Movement Disorder Society Unified Parkinson's Disease Rating Scale.[42] Furthermore, investigations indicate that *Lactobacillus* and *Bifidobacterium* species may impact the levels of pro- and anti-inflammatory cytokines in individuals with PD. These findings suggest that probiotics could be a potential adjunct treatment for PD, although further research is needed to confirm these outcomes.[43]

Changes in microbiota observed in diseases such as PD and MS involve similar species, including *Akkermansia*, *Bifidobacterium*, *Butyricicoccus*, *Coprococcus*, *Dorea*, *Faecalibacterium*, *Parabacteroides*, and *Prevotella*. The discovery that *Bifidobacterium*, a bacterium aiding lactose breakdown, is present in higher levels in both AD and PD is significant. This elevation may be connected to lifestyle choices. Moreover, the abundance of Enterococci and Lactobacilli might affect drug efficacy and overall well-being.[44,45] Notably, alterations in *Bacteroides*, impacting immune responses and amyloid metabolism, are evident in both conditions. Remarkably, the comparable microbiome changes observed in AD and PD underscore shared underlying mechanisms.

Studies suggest a possible connection between changes in gut bacteria and epilepsy.[46,47] Treatments such as fecal transplants and probiotics have shown positive results. These approaches seem to improve imbalances in gut bacteria and reduce seizures. This indicates that they may help treat epilepsy.[48] However, the reliability of these findings is limited due to small study sizes and short durations. Even so, fecal transplants appear promising for various brain disorders, including epilepsy.[49] More research is needed to confirm these findings and explore using gut bacteria treatments for epilepsy.

Investigations based on the model organism *Caenorhabditis elegans* shed light on how gut bacteria influence neurological disorders. Researchers found that certain bacterial proteins, like curli, can trigger protein clumping and brain cell damage.[50] Diverse strains of bacteria in humans play a role in clumping proteins linked to neurological disorders, suggesting an interaction between gut microbes and these diseases.[50] The gut microbial ecosystem influences the gut–brain connection and can be modified through diet to release protective microbial compounds.[51] Certain protein clusters from bacteria disrupt the host's protein processes, revealing the intricate relationship between gut flora and NDs.[52]

New research shows that probiotics could help restore movement and disturb protein aggregates in invertebrate animal models. These aggregates are linked to brain diseases like PD.[53] Some probiotics, including *L. plantarum* and *Bifidobacterium dentium*, were found to control the endocytic pathway and disturb alpha-synuclein aggregates, a key problem in PD. *L. plantarum* was also related to reduced anxiety behavior and protection from stress-induced dysbiosis in adult zebrafish.[54] Together, these results suggest that probiotics may help manage brain diseases and immune responses in invertebrate animal models.

CONCLUSION

In conclusion, the GM is intricately involved in NDs, as an analysis of microbial imbalances and disruptions can help improve the treatment strategies for these disorders. Probiotics and microbiota in ND research seem to be a new perspective in the search for effective therapeutic approaches. Probiotic intervention has numerous benefits, including regulating neurotransmitter levels, enhancing anti-inflammatory pathways, and restoring balance to the brain–gut axis. Since such research keeps moving deeper into understanding these relationships, specific probiotic treatments could serve as an effective solution to manage these complex chronic diseases, helping patients achieve better quality-of-life outcomes. Studies on invertebrate and vertebrate models demonstrate that probiotics have the potential to reduce neuroinflammation, oxidative stress, and protein aggregation associated with AD and PD. The integration of probiotics into ND management appears to be highly promising, given the positive results reported in animal models and human trials. With more research to uncover how these microorganisms function and to improve formulations, it is possible that personalized probiotic treatments could be developed for patients suffering from NDs. The therapeutic potential of probiotics offers a chance to reduce the burden of neurodegenerative diseases globally and improve quality of life.

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