Exploring the Effects of the Gut Microbiome on Alzheimer's Disease

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Abstract

Alzheimer’s disease is a progressive neurodegenerative disorder that is exacerbated by neuroinflammation linked to gut microbiome imbalances. Dysbiosis has been shown to increase neuroinflammation and facilitate the infiltration of lipopolysaccharides (LPS) into the brain, worsening Alzheimer's pathology. Key approaches discussed include ketogenic and Mediterranean diets, as well as multi-strain probiotics like Bifidobacterium breve A1, which may reduce oxidative stress and inflammation while enhancing short-chain fatty acid (SCFA) levels. Given the growing prevalence of Alzheimer's disease and the limited value of current treatments, understanding the role of the gut-brain axis offers a promising avenue for novel therapeutic interventions. By targeting gut microbiome imbalances, it may be possible to mitigate neuroinflammation and slow disease progression, providing new hope for patients and their families.

Keywords: Alzheimer’s disease, Gut microbiota, Neuroinflammation, Nutrition, Probiotics

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The gut microbiome, a diverse community of microorganisms residing in the gastrointestinal tract, plays a crucial role in maintaining overall health through its interaction with the brain, through the gut-brain axis (Newcombe et al., 2018). This intricate network has recently been recognized for its significant impact on neurodegenerative diseases, particularly Alzheimer's disease. Alterations in gut microbiota composition, or dysbiosis, have been associated with heightened neuroinflammation– a hallmark of this disease. Evidence suggests that dysbiosis can lead to the production of gut-derived metabolites and inflammatory mediators that affect brain function and contribute to Alzheimer's pathology by promoting the infiltration of lipopolysaccharides (LPS) into the central nervous system (Newcombe et al., 2018). Historically, Alzheimer's research has predominantly focused on genetic factors and neurotoxic proteins, with the role of the gut microbiome remaining relatively underexplored. However, emerging studies that will be discussed in this review have illuminated how shifts in gut microbiota influence systemic inflammation and cognitive decline, suggesting that dietary interventions and probiotics could offer novel therapeutic strategies.

Literature Review

Mechanisms of the Gut-Brain Axis in Alzheimer's Disease

The gut-brain axis is a complex communication network between the gastrointestinal tract and the central nervous system that plays a pivotal role in maintaining homeostasis and influencing neurological health (Singh et al., 2023). This system operates through hormonal, neural, and immunological pathways, each playing a role in brain function and overall health. Understanding these pathways is essential as disruptions in these systems can contribute to disease progression (Singh et al., 2023).

Hormonal pathways involve the release of gut-derived hormones, such as cortisol and serotonin, which can modulate stress responses and mood, further illustrating the bidirectional nature of gut-brain communication. Imbalances in cortisol or serotonin levels can affect synaptic plasticity and promote amyloid-beta plaque formation. Synaptic plasticity is the brain's ability to adapt by strengthening or weakening connections between neurons. Moreover, amyloid-beta plaques are protein clumps that disrupt communication between neurons (Stampanoni et al., 2019). These disruptions in communication and neural plasticity contribute to the cognitive decline and memory loss characteristic of Alzheimer's disease.

In the neural pathway, the vagus nerve serves as the primary neural link that transmits signals between the gut and brain, affecting brain function and modulating activity through gut-derived hormones and immune signals (Govindaraju, 2022). Altered vagus nerve signaling can lead to increased neuroinflammation and the release of pro-inflammatory cytokines, which are known to contribute to the pathology of Alzheimer's disease (Govindaraju, 2022). Additionally, immunological pathways are associated with the alterations in gut microbiota composition that trigger systemic inflammation (Zhao et al., 2023). This paper will primarily focus on the immunological pathways to highlight how changes in gut microbiota can cause systemic inflammation and potentially contribute to Alzheimer's disease.

Gut Microbiota Characteristics Commonly Found Among Alzheimer's Patients

Dysbiosis, an imbalance in gut microbiota, is commonly observed in Alzheimer's patients and is linked to increased intestinal permeability, often referred to as "leaky gut", which permits bacterial endotoxins like lipopolysaccharides (LPS) to enter the bloodstream and reach the brain (Cattaneo et al., 2017). Studies have confirmed the presence of LPS in the hippocampus of Alzheimer's patients, indicating that these microbial components can cross the blood-brain barrier (BBB), contributing to neuroinflammation (Zhao et al., 2024). Once in the brain, LPS activates microglia, the brain's immune cells, leading to chronic neuroinflammation that aggravates neuronal damage and promotes amyloid-beta plaque formation (Pourahmad et al., 2024).

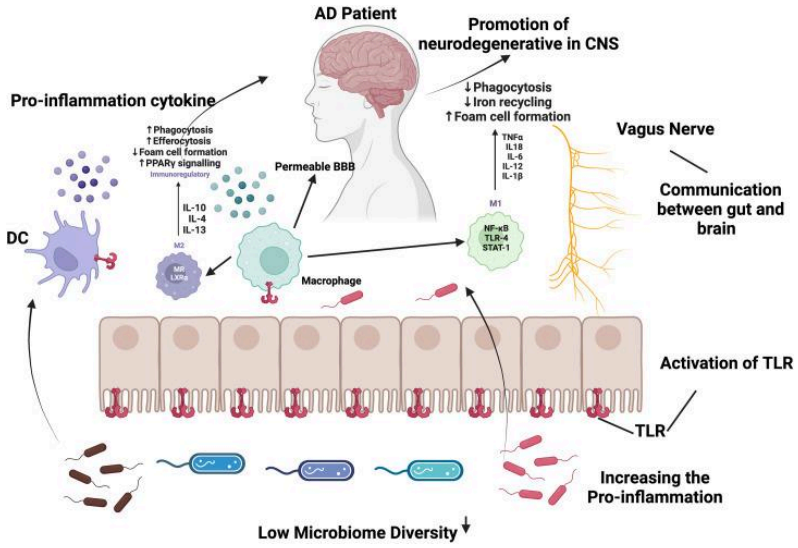
Dysbiosis often also leads to a reduced production of gut-derived metabolites such as short-chain fatty acids (SCFAs) (Shabbir et al., 2021). Additionally, it has been shown that Alzheimer's patients often have a reduced production of SCFA's. SCFA's, like butyrate, are beneficial because they have been shown to exert anti-inflammatory effects by inhibiting histone deacetylases (HDACs), enzymes that regulate gene expression linked to neuroinflammation (Pourahmad et al., 2024).

Healthy vs. Alzheimer's Gut Microbiota Composition Comparison

In recent years, several studies have explored the differences in gut microbiota composition between Alzheimer's disease patients and healthy controls, revealing significant alterations that may contribute to disease progression (Figure 1.) (Seo et al., 2023). These studies show that Alzheimer's patients exhibit a distinct gut microbiome profile, characterized by reduced diversity and specific changes in bacterial groups compared to healthy individuals. For instance, Alzheimer's patients had decreased levels of Bifidobacterium and Lactobacillus, which are known for their anti-inflammatory properties (Seo et al., 2023). Conversely, there was an overrepresentation of pro-inflammatory bacteria like Escherichia/Shigella and Proteobacteria, which are associated with increased gut permeability and inflammation (Pourahmad et al., 2024). Additionally, Alzheimer's patients were also shown to have increased activation of TLR's, or toll-like receptors, and permeability of the blood-brain barrier (BBB). These processes promote neurodegeneration in the central nervous system through interaction between the gut and brain, involving immune cells like macrophages and dendritic cells, and signaling through the vagus nerve (Pourahmad et al., 2024). Similarly, the reduction of Firmicutes and an increase in Bacteroidetes in Alzhiemer's patients, suggests that these shifts in bacterial populations may exacerbate neuroinflammatory processes through the production of harmful metabolites like LPS (Kowalski and Mulak, 2022).

Figure 1

Impact of the Gut Microbiota on the Development of Alzheimer's



Note. This figure illustrates how low gut microbiome diversity leads to increased inflammation and neurodegeneration in Alzheimer's disease through interactions between the gut, immune system, and the brain. Pourahmad, R., saleki, K., Zare Gholinejad, M., Aram, C., Soltani Farsani, A., Banazadeh, M., & Tafakhori, A. (2024a). Exploring the effect of gut microbiome on Alzheimer's disease. Biochemistry and Biophysics Reports, 39, 101776. https://doi.org/10.1016/j.bbrep.2024.101776

In a study investigating the gut-brain connection, researchers used germ-free mice– mice that were raised in a sterile environment without any gut microbiota or immune system– to understand how the absence of a microbiome affects brain function and behavior (Foster et al., 2010). These mice were compared with a control group of mice that had a normal, healthy gut microbiota. Initially, the germ-free mice were kept in a completely sterile environment to prevent any exposure to external microbes. The researchers then measured anxiety-like behaviors and levels of neurotransmitters, such as serotonin and norepinephrine, which are vital for mood regulation and cognitive processes. To further explore the role of the microbiome, the researchers introduced a standard microbial community into the guts of the germ-free mice and repeated the behavioral and biochemical assessments. They observed that the germ-free mice initially exhibited reduced anxiety-like behavior and changes in neurotransmitter levels. However, once their gut microbiota was restored, these changes were partially reserved, indicating that the gut microbiome has a significant influence on brain function and behavior. The key takeaway from this study is not that the absence of a microbiome is beneficial. Rather, the study underscores the critical role that a healthy gut microbiome plays in maintaining normal brain function and emotional well-being. The disruptions in the microbiome, as seen in

conditions like Alzheimer's disease, could potentially affect neurochemical pathways that contribute to cognitive decline (Foster et al., 2010).

Conducting similar studies in humans presents ethical and practical challenges. Removing or severely altering the human microbiome could have unpredictable and harmful effects on overall health, making it unethical to replicate the germ-free conditions on humans. This highlights the importance of animal models in studying complex biological systems like the gut-brain axis, while also emphasizing the need for careful consideration when translating these findings to potential treatments for human diseases.

Therapeutic Potential of Modulating the Gut Microbiome

Modulating the gut microbiome through dietary interventions presents a promising avenue for both prevention and treatment of Alzheimer's disease. Dietary interventions, particularly the Mediterranean diet, have been shown to prompt beneficial gut flora and elevate SCFA levels, which has the potential to reduce the risk of Alzheimer's by 41% (Liang et al., 2024). Additionally, the ketogenic diet, characterized by high fat and low carbohydrates can offer relief and improve the course of Alzheimer's. The ketogenic diet has been shown to selectively diminish the population of Bifidobacterium in the gut and reduce pro-inflammatory cells (Liang et al., 2024).

Table 1

Therapeutic Intervention of Alzheimer's through Gut Microbiota Manipulation

Category	Drug	Effect
Dietary ways	Ketogenic diet	Minimizing bifidobacteria abundance; reducing pro-inflammatory cell levels; improving cerebral vasculature and BBB functionality
	Mediterranean diet	Attenuating the risk of AD onset
Probiotic	Bifidobacterium breve strain A1	Diminishing the expression of inflammation and immune response genes in the hippocampus

Note. This table lists dietary approaches and a probiotic treatment and highlights their effects on Alzheimer's disease. Liang, J., Wang, Y., Liu, B., Dong, X., Cai, W., Zhang, N., & Zhang, H. (2024). Deciphering the intricate linkage between the gut microbiota and Alzheimer's disease:

Elucidating mechanistic pathways promising therapeutic strategies. CNS Neuroscience & Therapeutics, 30(4). https://doi.org/10.1111/cns.14704

Probiotics also present a promising therapeutic approach. Recent studies have primarily focused on the administration of multi-strain probiotics and specific strains like Bifidobacterium breve A1 to Alzheimer's patients, providing a comprehensive understanding of how probiotics can influence the disease's progression (Liang et al., 2024). One such study conducted a trial involving 60 elderly patients diagnosed with Alzheimer's. The participants were divided into two groups: one receiving a multi-strain probiotic supplement and the other a placebo. Over a 12-week period, the group receiving probiotics showed significant improvements in cognitive functions, as measured by Mini-Mental State Examination (MMSE) scores, compared to the placebo group. MMSE is a widely used test that assesses cognitive impairment through tasks involving orientation, recall, attention, calculation, language, and visual construction, compared to the placebo group. Additionally, the probiotic groups exhibited favorable changes in metabolic profiles, including reduced markers of oxidative stress and inflammation, which are factors known to intensify the processes of Alzheimer's (Akbari et al., 2016). However, one limitation of the study is that it did not control for dietary differences between the groups, which could have influenced the results.

Another study further supported these findings by examining the effects of multi-strain probiotics on Alzheimer's patients over a similar duration. Like the previous study, it demonstrated improvements in cognitive function and memory. However, it also showed positive changes in serum neopterin and tryptophan breakdown, two metabolic markers associated with oxidative stress and inflammation. The study suggested that these improvements might contribute to the overall cognitive benefits observed in the probiotic group (Leblhuber et al., 2018).

Despite the promising potential of dietary interventions and probiotics in modulating the gut microbiome for Alzheimer's disease treatment, their feasibility as widespread solutions is still under investigation. These approaches are generally non-invasive making them attractive for patients, especially when compared to more conventional treatments like pharmaceuticals, which often come with significant side effects. However, the effectiveness of gut microbiome interventions may vary based on individual factors such as genetics, lifestyle, and the baseline health of the microbiome, making personalized treatment plans necessary. While these gut-focused interventions show considerable promise, they may be most effective when used in conjunction with existing treatments. In comparison, pharmacological approaches targeting amyloid plaques may offer more direct mechanisms of action, but also pose higher risks and uncertainties. Thus, the best therapeutic strategy might involve a combination of gut modulation and other treatments, capitalizing on the benefits of both approaches (Singh et al., 2023).

Conclusion

The gut-brain axis and its influence on Alzheimer's disease remains a critical area of scientific inquiry, with growing evidence pointing to the significant role of gut microbiota composition in the progression of this neurodegenerative disorder. Dietary interventions, such as the Mediterranean and ketogenic diets, along with probiotic supplementation have emerged as promising strategies to modulate gut microbiota, offering potential benefits in reducing cognitive decline and inflammation in Alzheimer's patients. However, the current body of evidence, largely derived from animal studies, highlights the necessity for more extensive human clinical trials to \validate these findings and establish the safety of these interventions in the broader populations. As research continues to advance, a deeper understanding of the gut-brain connection could pave the way for novel, integrative approaches to Alzheimer's disease prevention and treatment.

Importantly, the impact of the gut-brain axis is not limited to Alzheimer's disease. Similar mechanisms have been observed in other neurological conditions. For instance, in Parkinson's disease, changes in gut microbiota composition are thought to contribute to the accumulation of alpha-synuclein, in both the gut and the brain. This suggests that therapeutic strategies targeting the gut microbiota may have broader implications beyond Alzheimer's, offering potential benefits across a range of diseases characterized by gut-brain axis dysfunction (Santos et al., 2020).

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