Journal of Applied Pharmaceutical Research
Volume 12 Issue 5, Year of Publication 2024, Page 01 – 15
DOI: https://doi.org/10.69857/joapr.v12i5.648

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Review Article

JOURNAL OF APPLIED PHARMACEUTICAL RESEARCH | JOAPR
www.japtronline.com *ISSN: 2348 – 0335*

EXPLORING THE NEUROPROTECTIVE ROLE OF PROBIOTICS IN THE THERAPEUTIC INTERVENTIONS OF COGNITIVE DECLINE

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Article Information
Received: 7th June 2024
Revised: 23rd July 2024
Accepted: 6th September 2024
Published: 31st October 2024

Keywords
Cognitive decline, mitochondrial dysfunction, neuroinflammation, neurodegeneration, probiotics, tau protein.

ABSTRACT

Background: Cognitive decline is developing as a critical alarm in public health concerns initiated by neuroinflammation, an indispensable contributing factor in neurodegenerative diseases. Probiotics and postbiotics have evolved as key therapeutic factors in treating neuroinflammation by modulating neuroinflammatory pathways and therapeutically controlling cognitive decline by its influence on the gut-brain axis. **Methodology:** This comprehensive review integrates the current status of the insight into the molecular mechanisms of probiotics that promote cognitive health. The review explains their synergistic effects on gut microbiota and their influence on neuroinflammation, mitochondrial function, neurotransmitter levels, and insulin sensitivity. It also explores preclinical and clinical studies involving the neuroprotective benefits of specific probiotic strains. **Results:** Probiotics are reported to alter gut microbiota by supporting neuroinflammation, thus enhancing cognitive function. The key findings were their role in reducing plaque formation and controlling tau protein hyperphosphorylation, thus improving mitochondrial efficiency. Recent research reveals that strains such as Lactobacillus and Bifidobacterium have proven efficacy in reducing tau phosphorylation and amyloid β pathology in animal models. In addition, probiotics improve insulin sensitivity and neurotransmitter levels, leading to improved cognitive outcomes. **Discussion:** The microbiota-gut-brain axis is essential in studying the neuroprotective role of probiotics. Probiotics have been reported for their ability to reduce neuroinflammatory markers, leading to improved neurogenesis in the brain's hippocampus. Thus transforming these research findings to clinical therapies requires further research to support and to overcome the limitations and exploring the complete mechanism involved.

Conclusion: Probiotics thus being explored to develop as new therapeutic interventions in cognitive decline, with substantial preclinical evidence supporting their benefits. Still persistent research is essential to transform these findings in clinical trials in the development of probiotic-based therapies for cognitive health.

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INTRODUCTION

People across various age groups increasingly recognize cognitive decline as a significant public health concern [1]. Neuroinflammation significantly contributes to the development of cognitive disorders [2]. The upcoming research enlightens the ability of postbiotics and probiotics to alleviate cognitive decline and neurodegeneration through their interaction with the gut-brain axis [3]. By changing the composition of the gut microbiota and lowering neuroinflammation, probiotics can potentially protect cognitive function and prevent neurodegenerative diseases [4]. The transformation of these findings into effective clinical interventions necessitates future research to identify the present limitations and understand the detailed mechanisms. This review's goal is to condense knowledge on the role of probiotics in cognitive health, enlighten their therapeutic abilities, and explain their benefits.

NEUROINFLAMMATION

Neuroinflammation plays a vital role in the degeneration of neurons and cognitive decline. The inflammation in the neuron leads to a decrease in cognitive function. It alters the morphology of the brain, resulting in a reduction in the size of the hippocampus, a region crucial for memory. Critical brain areas experience a decrease in glucose utilization while the brain's fluid-filled cavities, known as ventricles, expand. The prolonged occurrence of neuroinflammation leads to the development of chronic degenerative disorders like dementia [5]. Neuroinflammation is a potent initiator that promotes neurodegeneration and the development of cognitive decline. This process is characterized by an inflammatory response in the central nervous system, which activates microglia and astrocytes, thus producing cytokines and chemokines [6]. The neuroinflammatory cascade will lead to brain cell death and neuronal dysfunction, which could ultimately lead to cognitive decline [7]. So, combining studies in neurology and cognitive neuroscience is essential for learning how neuroinflammation happens and coming up with ways to study this response [8]. Recent studies have proven probiotics as a promising avenue for alleviating inflammatory markers, suggesting a means of lowering neuroinflammation [9]. By influencing the gut-brain axis, probiotic treatments may correct neurotransmitter level imbalances, thus relieving cognitive disturbances. Prebiotics and postbiotics have the potential to change the gut microbiota, reduce neuroinflammation, and improve cognitive health. For instance, studies have found that prebiotic supplements, primarily galactooligosaccharides, improve postoperative cognitive dysfunction and lessen the impact of neuroinflammation during surgery. Postbiotics, also known as metabolic byproducts, cell-free supernatants (CFS), and other soluble factors resulting from live bacteria, play an essential role in probiotic research. Probiotic therapy can potentially alleviate neuroinflammation's behavioral and neurological impacts by establishing long-term immunoregulation in the central nervous system [10]. Probiotics may slow or even reverse cognitive deterioration in adults, but further high-quality research is necessary to draw definitive conclusions. Research has demonstrated that postbiotics shield neurons from neurodegenerative diseases by altering numerous pathways. These include increasing dopamine, decreasing α-synuclein, stopping inflammation and apoptosis, and increasing BDNF secretion and antioxidant activity [11]. Cognitive impairments are typically associated with disturbances in neurotransmitter systems, especially those involving cholinergic and glutamatergic pathways [12].

A multi-strain probiotic formulation has a pro-neurogenic and neuroprotective effect against neuroinflammation in a mouse model [13]. Probiotics may be a treatment strategy for multiple sclerosis because they modulate the gut-brain axis and neuroinflammation. Gut dysbiosis and neuroinflammation contribute to depression, and probiotics may have therapeutic potential by modulating the gut-brain axis. The gut microbiome influences neuroinflammation through metabolites, immune cell trafficking, and the vagus nerve [14]. The change in gut microbiota composition caused by probiotics and postbiotics plays a critical role in the progression of cognitive decline. Emerging evidence from preclinical models indicates that probiotics can enhance neurogenesis, particularly in the hippocampus, a brain area crucial for learning and memory [15]. Researchers believe that the modulation of the gut microbiota and subsequent anti-inflammatory effects mediate this effect, providing a promising avenue for cognitive enhancement and neuroprotection. Researchers report that probiotics impact the microbiota, reducing plaque accumulation and influencing amyloid-protein pathology. Tau protein hyperphosphorylation influences neurofibrillary tangle formation, a critical neurodegeneration marker, and a hallmark signal for cognitive disorders [16]. Recent research looked into how well certain types of probiotics can help lower tau protein hyperphosphorylation by blocking glycogen synthase kinase (GSK-3b) [17]. Researchers have documented Lactobacillus and

Bifidobacterium as reducing tau protein phosphorylation in the Alzheimer's disease model [18].

MICROBIOTA GUT-BRAIN AXIS

The microbiota-gut-brain (MGB) axis is an intricate communication system that integrates the gut microbiota with cognitive and emotional centers in the brain. This axis is critical for maintaining neurological health and is involved in neurodegenerative disease pathogenesis. Recent research has shed light on understanding MGB with a cognitive and emotional center in the brain [19]. Dysfunction in the axis will impact the development of cognitive decline by affecting the CNS. Numerous studies confirm the strong correlation between gut dysbiosis and the onset of mental disorders [20]. Animal studies have shown that probiotics can help alleviate depression by modulating the axis. However, there is a need for further research to establish their clinical efficacy in humans [21]. Clinical studies have found that probiotics can improve mood, anxiety, and depression in patients. Preclinical studies show that some beneficial bacteria, also known as psychobiotics, impact treating some mental health difficulties. Giving mice different oligosaccharides as a long-term prebiotic has antidepressant and anxiety-reducing effects. They also lower the release of corticosterone, which changes gene expression in the brain's hippocampus and hypothalamus. The gut-brain axis mediates the cognitive-enhancing effects of probiotics in aged SAMP8 mice, while the LPS-TLR4/NF-B signaling pathway inhibits inflammation [22]. The interaction between genetic predispositions and the gut microbiota is an intriguing area of current research. Initial research has discovered that specific kinds of bacteria in the gut could impact the activation of genes associated with neurodegeneration, with the possibility of decreasing genetic susceptibility by interfering in this process [23]. Hormonal imbalances, particularly during critical periods such as menopause, can exacerbate cognitive decline [24]. The microbiota-gut-brain axis interacts closely with the endocrine system, influencing the secretion and regulation of hormones essential for brain health [25]. Researchers have explored the potential of probiotics to stabilize hormonal fluctuations, potentially protecting against hormone-related cognitive impairments. Research suggests impaired neurogenesis, the process of generating new neurons, is associated with cognitive decline. Factors such as aging, neuroinflammation, and alterations in the gut microbiota can influence this decline [26]. Researchers have proposed probiotics as a potential therapy for age-related cognitive impairment because they can modulate the gut microbiota.

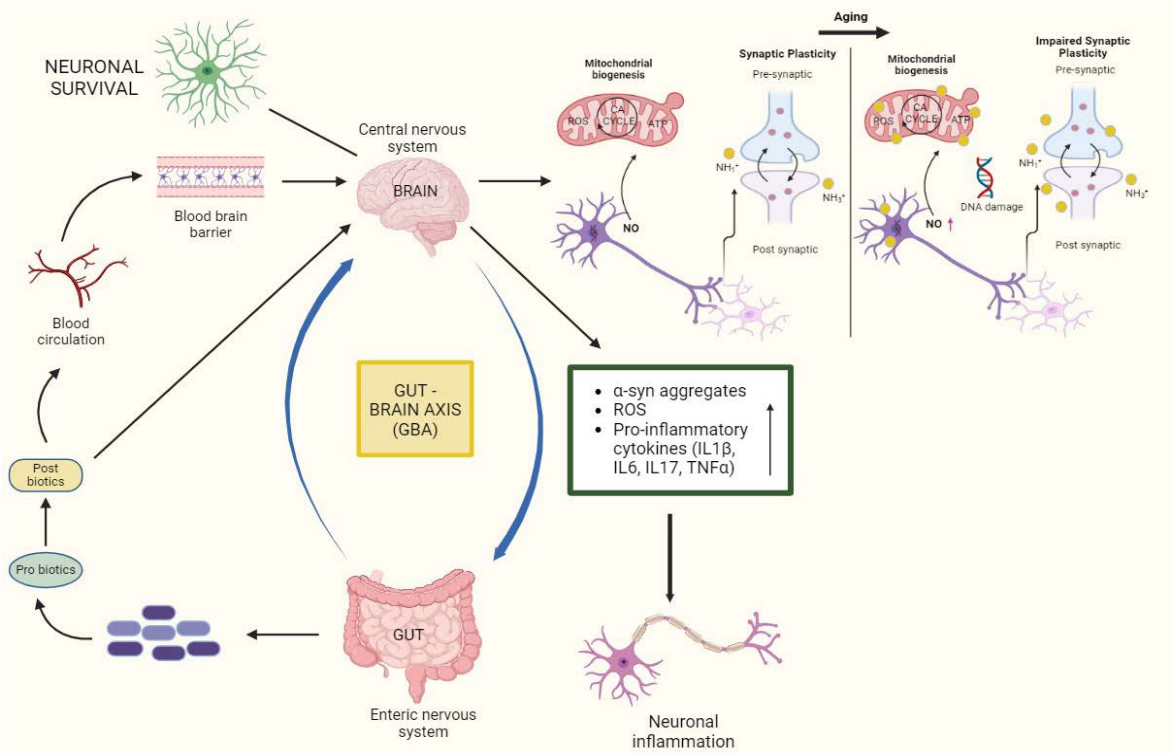

Figure 1: Mechanism involved in GBA (Gut-Brain Axis)

ROS: Reactive oxygen species; IL: Interleukin; TNF: Tumor necrosis factor; NO: Nitric oxide

MITOCHONDRIAL DYSFUNCTION

Mitochondrial dysfunction and neurotransmitter imbalances are prominent features of neurodegenerative diseases. Consuming probiotics and postbiotics can improve the efficiency of mitochondria and regulate the levels of essential neurotransmitters like gamma-aminobutyric acid (GABA) and serotonin [27]. Such regulation can have an impact on cognitive functions and help prevent neurodegeneration. We believe that the modulation of the gut microbiota and its subsequent anti-inflammatory effects mediate this effect, providing a promising avenue for cognitive enhancement and neuroprotection. Different neurological disorders note deficits in mitochondrial dysfunction, a signaling factor in synaptic integrity. This resulted in mitophagy during synapsis, leading to synaptic degeneration. Mitochondrial distribution and motility are essential for the maintenance and strength of dendritic spines, and they play a crucial role in synaptic plasticity in the cellular mechanism for learning and memory [28]. Probiotics and postbiotics have demonstrated the ability to restore cognitive function in insulin-resistant obese rats by enhancing insulin sensitivity, mitochondrial activity in the brain, and synaptic plasticity.

INSULIN RESISTANCE

One risk factor for developing cognitive disorders is insulin resistance [29]. Probiotics have been proven to improve insulin resistance in experimental models of Alzheimer's disease. Obesity and physical activity initiate insulin resistance, and its progression impacts the development of cognitive decline, according to recent research [30]. Probiotics can improve insulin resistance, according to studies [31]. Researchers reported that the treatments restored cognitive function in obese insulin-resistant rats by enhancing hippocampal activity and mitochondrial function. Brain-derived neurotrophic factor (BDNF) and butyrate levels increased when probiotics and synbiotics were taken together [32]. This improved spatial memory. According to further research, Probiotics improved disease markers such as lipid profiles, inflammatory markers, and microbiota composition. Future clinical studies are necessary to enhance the molecular pathways that underpin the potential connection between insulin resistance and cognitive decline [33]. Probiotic supplementation improves insulin levels and the MOMA-IR index, indicating an improvement in insulin resistance.

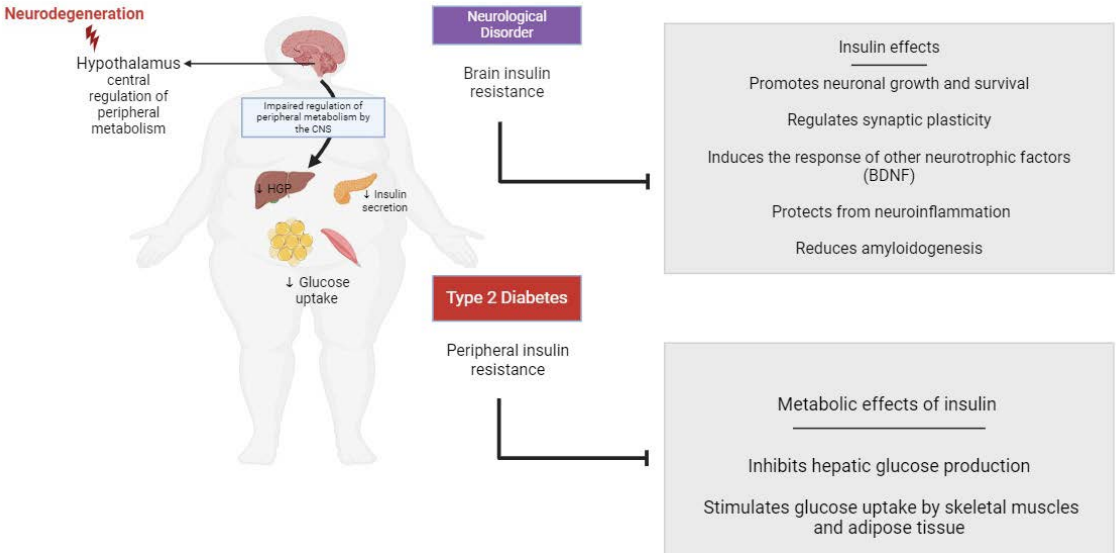

Figure 2: Neurodegeneration due to insulin resistance

CNS: Central nervous system; HGP: Hepatic glucose production; BDNF: Brain-derived neurotrophic factor

Researchers have linked disruptions in neurodegeneration to the development of neurodegenerative illnesses [34]. The presence of the APOE e4 allele can significantly impact the likelihood of developing mental disorders [35]. Genetic factors, such as the APOE e4 allele, can play an important role in the development of mental disorders. The genetic makeup, particularly the presence of the APOE e4 allele, can substantially affect the risk of mental disorders [36]. Genetic factors significantly influence the likelihood of developing mental disorders, suggesting that probiotics and other interventions that enhance neurogenesis could be promising strategies for addressing cognitive decline. APOe4 alleles include APOE e2, APOE e4, APOE e3, and so on [37].

Table 1: Insulin resistance genes and their components

Component	ISR 1 /ISR 2	Amyloid Beta Protein	Tau Phosphorylated Protein	Reference
Purpose in Insulin Resistance	A fundamental role in the insulin signaling pathway influences insulin sensitivity and the metabolism of glucose	Related to accumulation in Alzheimer's disease, impacts of insulin signaling pathways.	Coordinated by insulin signaling, implicated in neurofibrillary tangles in Alzheimer's disease.	[38]
Gene Variants	Variants in genetics are connected with changes in insulin sensitivity, the risk of diabetes, and cognitive outcomes.	Variants related to the increased risk of deposition of amyloid and Alzheimer's disease.	Genetic factors are influencing tau phosphorylation and the risk of Alzheimer's.	[39]
Mechanism of action	Regulates insulin signaling, affects synaptic plasticity, and affects the survival of neurons.	Interlinked with insulin pathways affecting neurodegeneration and cognitive function.	Insulin resistance provokes tau pathology through kinase deregulation.	[40]
Involvement of Probiotics	It influences the gut microbiota, cognitive function, and insulin sensitivity.	Probiotic interventions may relieve neuroinflammation and the accumulation of amyloid.	It shows potential for changing tau phosphorylation and neuronal health.	[41]
Inflammation	Insulin resistance leads to chronic inflammation, affecting cognitive health and brain functions.	Inflammatory responses to amyloid beta proteins lead to cognitive impairment and neurodegeneration.	Inflammation mediates the formation of neurofibrillary tangles and tau hyperphosphorylation.	[42]
Mitochondrial function	Impaired mitochondrial function is due to insulin resistance, which affects cognitive function and neuronal energy metabolism.	Amyloid beta protein destroys mitochondrial function and provokes neurodegeneration.	Tau pathology affects mitochondrial dynamics and neuronal health.	[42]

NEUROGENESIS

Neurogenesis relies on tightly controlled molecular signaling pathways; mitochondrial dysfunction lowers the number of adult neural stem cells (NSCs) and stops brain development [43]. Neurodevelopmental and neuropsychiatric disorders are associated with defects in neurogenesis. Mitochondrial dysfunction links brain problems like neuroinflammation, oxidative stress, neurofibrillary tangles, and the formation of amyloid plaques. This dysfunction affects energy production, calcium ion buffering, and free radical management, leading to cognitive decline, neuronal degeneration, and malfunction [44]. Pathogenic fragments build-up, and when amyloid precursor protein (APP) is processed incorrectly, it causes cognitive impairment by slowly destroying neurons and synapses [45]. Mitochondria that don't work properly affect neural differentiation, cell cycle exit, neural progenitor cell (NPC) proliferation, and NSC self-renewal [46]. Age-related mitochondrial dysfunction in CNS cells is marked by decreased density, decreased membrane potential, and slowed mitochondrial biogenesis [47]. Because of their high ammonia content, aged neurons produce more ROS, NO, and fragmentation of DNA [48]. Neurotransmitter secretion and receptor expression affect synaptic plasticity, which is necessary for memory, learning, and brain maintenance [49]. Dietary interventions focusing on mitochondrial function have appeared as potential strategies to reduce the effect of cognitive decline in late adulthood [50]. In addition to that, physical activity like exercise and supplementation have shown promising results in enhancing mitochondrial function and memory activities in Alzheimer's disease in vivo models [51]. Exercise alters the NF-kB signaling pathway, while postbiotics reduce the expression of the APP gene, disrupt amyloid plaques, and enhance the

quality of mitochondrial proteins [52]. These treatments, when combined with aging and Alzheimer's disease, will benefit mitochondrial function in cognitive decline. Increased levels of ammonium affect synaptic plasticity by suppressing the TCA cycle in glia and neurons, which lowers mitochondrial ATP synthesis [48]. Disruptions in synaptic plasticity, observed in diseases like Alzheimer's, autism, and intellectual disabilities, lead to cognitive impairment [53]. Cognitive decline is also associated with reduced synapse density with aging, mental health issues like schizophrenia and depression, and traumatic brain injuries [54]. Medication, dietary changes, and brain stimulation are some of the treatments. Neurotransmitters, receptors, and signaling molecules regulate synapse function [55]. Probiotics can impact by generating neurotransmitters like GABA and serotonin, adjusting the gut-brain axis, and changing the gut flora. Probiotics can have an impact on this. They improve synapse function and may enhance synaptic plasticity by reducing oxidative stress and inflammation, thereby mitigating cognitive deficits resulting from aging, mental health disorders, and neurodegenerative diseases [56]. Probiotics mitigate oxidative stress, inflammation, and DNA damage by boosting neurotransmitters and promoting synaptic and mitochondrial biogenesis [57]. They enhance immune system function, digestion, and nutrient absorption and possibly even lessen the symptoms of digestive disorders like IBS by maintaining a healthy gut flora, all of which contribute to better overall health [25]. Recent research emphasizes the critical role of mitochondrial dysfunction in cognitive decline due to aging and Alzheimer’s disease. For example, Lactobacillus reuteri produces GABA, an important inhibitory neurotransmitter in the brain and spinal cord. Lower levels of stress reactivity and depressive symptoms are associated with GABA's capacity to decrease neuronal excitability [58].

It also enhances vagal mesenteric nerve signaling, playing a role in the parasympathetic regulation of the gut-brain axis. Clinical studies have shown that Lactobacillus reuteri supplementation can reduce anxiety-like behavior in animal models and improve mood in humans [59]. Age, demographic status, concomitant medication, risk factors, and genetic predisposition may vary for the individuals in the assimilation of probiotics. Personalized nutrition medicine using probiotics may be tailored in the near future by focusing on the integration of these approaches [60]. Similarly, Bifidobacterium bifidum generates brain-derived neurotrophic factor (BDNF), a protein essential for neuron survival, growth, and differentiation. BDNF decreases enteric neuron excitability and reduces depression manifestation levels by promoting neuronal plasticity and cognitive function [61]. Supplementation with Bifidobacterium bifidum has been associated with increased BDNF levels in the brain, potentially leading to improved memory and reduced symptoms of depression in clinical trials [62].

IMMUNOREGULATION IN INSULIN RESISTANCE

Immunoregulation in the CNS is a controlling factor in neuroinflammation development. Postbiotics have neuroprotective effects by elevating dopamine levels, reducing α-synuclein, inhibiting neuroinflammation, and promoting neurofactor secretion [63]. Researchers have reported the effects of probiotics like Bifidobacterium and Lactobacillus on neuroinflammatory signaling [10]. Research on probiotics focuses on the distinctions between normal and altered immune function in the intestines. The intestinal epithelium, mucus layer, and intestinal lumen maintain their integrity in a normal immunological function. This environment promotes healthy immune cell function, characterized by effective interactions between dendritic cells, naive T cells, and Th17 cells, as well as the production of IL-17, a cytokine critical for mucosal immunity [64].

Additionally, short-chain fatty acids (SCFAs), metabolic byproducts of dietary fiber fermentation by the gut microbiota, play a pivotal role in maintaining intestinal health [65]. Studies have demonstrated that probiotics like Lactobacillus rhamnosus GG and Bifidobacterium animalis boost the production of SCFAs, promoting gut health and immune function [66]. IgA (immunoglobulin A) is also critical, as it binds to antigens and pathogens in the gut, preventing their translocation and maintaining mucosal immunity. Research indicates that probiotic strains like Lactobacillus casei can increase IgA levels, further supporting immune defense. On the other hand, factors like antibiotic use, poor diet, or chronic stress often lead to an impaired intestinal barrier and reduced mucus integrity, indicating altered immunological function [67]. This disruption leads to compromised immune cell function, adversely affecting dendritic cells, naive T cells, IL-17, and Th17 cell production [68]. An imbalance in the gut microbiota, known as dysbiosis, ensues, characterized by an increase in pathobionts (potentially harmful microbes) and a reduction in beneficial microbes. For example, decreased Lactobacillus and Bifidobacterium

populations can reduce SCFA production, impairing gut health and immune function. Studies have shown that probiotics like *Saccharomyces boulardii* can help restore microbial balance by promoting the growth of beneficial microbes and inhibiting pathobionts. Changing the way the gut's metabolism works can also cause less production of SCFAs, which are needed to feed colonocytes, control inflammation, and keep the barrier intact [69]. Research has demonstrated that probiotics, such as Bifidobacterium longum, can enhance SCFA levels and improve intestinal barrier function. Probiotics have been shown in clinical trials to change the gut microbiota's composition, strengthen the mucus layer, and boost the production of antimicrobial peptides. These effects lower the risk of infections and inflammatory diseases [70]. For instance, studies have found that Lactobacillus plantarum strengthens the mucus barrier and reduces gut inflammation. Thus, the visual representation underscores the critical role of probiotics in maintaining a healthy intestinal environment, supporting immune function, and preventing dysbiosis and its associated health issues.

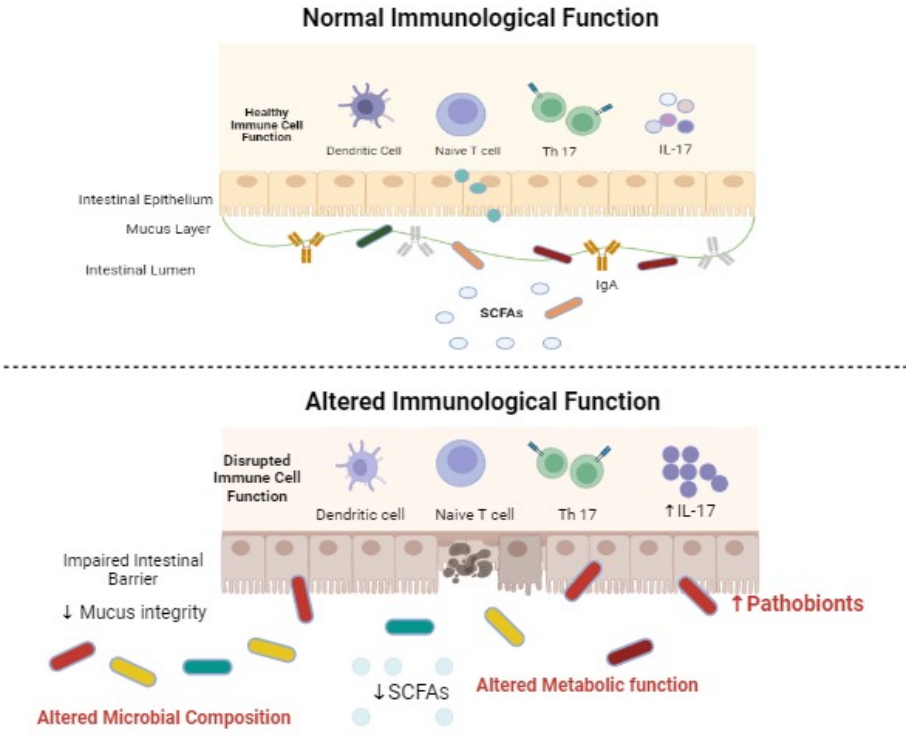

Figure 3: SCFA (Short Chain Fatty Acid) in immunoregulation
Th: T-helper cell; IL: Interleukin; SCFA: Short Chain Fatty Acid; Ig: Immunoglobulin

One of the risk factors linked to the development of cognitive disorders is insulin resistance. We also outline the metabolic effects of insulin, which are crucial for maintaining glucose homeostasis. Insulin inhibits hepatic glucose production and stimulates glucose uptake by skeletal muscles and adipose tissue. Insulin resistance impairs these actions, causing a rise in blood glucose levels and the metabolic dysfunctions associated with type 2 diabetes [71]. The image highlights the bidirectional relationship between brain and peripheral insulin resistance. Brain insulin resistance contributes to neurodegeneration and neurological disorders, while peripheral insulin resistance leads to type 2 diabetes. This interconnected pathway underscores the importance of holistically addressing insulin resistance to mitigate neurological and metabolic diseases. Insulin's vital role in maintaining outside energy is a significant protective role for neurons and a neurotrophic role in the central nervous system, promoting neuron survival, growth, and sustainability while influencing cognitive functions, memory development, and synaptic plasticity [72]. In addition to neuronal recovery and regrowth, IGF-1 is required for neural stem cell growth, lipid synthesizing, and synapse buildup. Insulin resistance outside the body lowers glucose uptake and raises glucose production in the liver. This, in turn, leads to brain insulin resistance, dementia, and cognitive decline. Interfering with insulin signaling is a key molecular mechanism linking type 2 diabetes and Alzheimer's disease [73]. Insulin controls the breakdown of glucose in the

brain, synaptic flexibility, and the production of the genes and neurotransmitters that regulate memory consolidation. Insulin also triggers responses to other neurotrophic substances, such as Brain-derived neurotrophic factor (BDNF), which support neural stem cells' survival, differentiation, and growth [74].

Insulin's neuroprotective qualities support the survival of neurons and guard against neuroinflammation, oxidative damage, and excitotoxicity. It also regulates cell glial function, cell survival, and myelin production. Insulin plays an essential role in the brain and has the potential to serve as an effective treatment for people with type 2 diabetes and dementia. Alterations in insulin and signaling levels in the brain can cause neuron death, synapse dysfunction, and dementia. According to studies, probiotics can improve insulin resistance. Moreover, if its neuroprotective effects extend to other neurodegenerative conditions, insulin may play a larger role in preserving neuronal health and averting neurodegeneration. BDNF and butyrate levels increased when probiotics and synbiotics were taken together, improving spatial memory [75].

Probiotics have been proven to improve insulin resistance in experimental models of Alzheimer's disease. Obesity and physical activity initiate insulin resistance, and its progression impacts the development of cognitive decline, according to recent research. Thus, researchers reported that the treatments restored mental performance in insulin-resistant, overweight mice. By enhancing hippocampal activity and mitochondrial function, Probiotics improved disease markers such as lipid profiles, inflammatory markers, and microbiota composition, according to further research composition were enhanced. Shortly, we need to conduct clinical studies to further explore the molecular pathways that could link insulin resistance and cognitive decline. The interconnected pathways between neurodegeneration, neurological disorders, and type 2 diabetes highlight that insulin resistance plays a crucial role in these conditions. The central nervous system (CNS) depicts the hypothalamus as the central regulator of peripheral metabolism. The hypothalamus's impaired regulation of peripheral metabolism leads to a cascade of metabolic dysfunctions. On the neurological side, brain insulin resistance is a critical factor. Insulin does many things in the brain that help neurons grow and stay alive. It controls synaptic plasticity, activates neurotrophic factors like BDNF, stops neuroinflammation, and lowers amyloidogenesis. These functions are essential for maintaining cognitive function and neuronal health. Insulin resistance in the brain disrupts these processes, contributing to neurodegeneration and the development of neurological disorders.

Simultaneously, the image depicts the peripheral effects of insulin resistance, which are central to the pathophysiology of type 2 diabetes. Resistance to insulin in tissues outside the central nervous system, including skeletal muscle and fat, decreases glucose uptake. Additionally, the liver increases hepatic glucose production (HGP), further exacerbating hyperglycemia. The pancreas responds with increased insulin secretion, but over time, this compensatory mechanism fails, leading to hyperinsulinemia and, eventually, type 2 diabetes.

PSYCHOLOGICAL WELL-BEING BY PROBIOTICS AND METABIOTICS

Bacteroides fragilis is notable for producing acids with a short carbon chain, including butyrate, acetate, and propionate. These SCFAs have anti-inflammatory properties and support gut barrier integrity, crucial for maintaining a healthy gut-brain axis. They contribute to reduced stress reactivity and depression levels by crossing the blood-brain barrier and modulating brain function. Research has shown that butyrate, a specific SCFA, can enhance memory and learning in mice and has potential therapeutic effects in treating neurodegenerative diseases [76].
Lastly, Lactobacillus rhamnosus produces exopolysaccharide (EPS), a polymer that influences gut microbiota composition and immune responses. EPS has been linked to decreased anxiety and compulsive behaviors, possibly by modulating the gut-brain axis. Studies show that taking Lactobacillus rhamnosus supplements can lower the amount of stress-related corticosterone in the body and make animals act more like they are anxious. This suggests that it might be useful for treating anxiety disorders [77]. The diagram emphasizes the profound impact of specific probiotics on the nervous system by producing various bioactive compounds. By modulating the gut-brain axis, these microorganisms can significantly influence mental health, offering potential therapeutic strategies for managing conditions such as depression, anxiety, and cognitive decline. Understanding these interactions provides a foundation for developing targeted probiotic therapies to enhance psychological well-being.

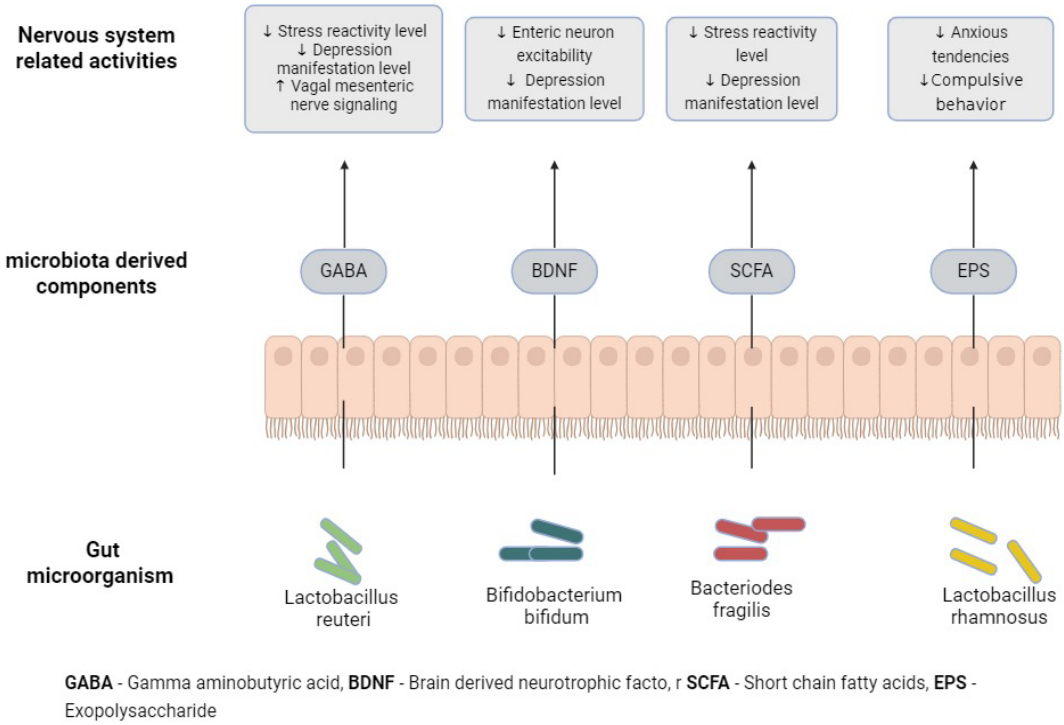

Figure 4: Gut microorganism and their microbiota-derived components

Table 2: Microorganisms based on pro/post/metabiotics and their functional properties related to cognitive decline

SNo	Pro/Post/Metabiotics	Microorganism	Functional properties	Reference
1.	Postbiotics	*Lactobacillus plantarum*	Inhibited the reduction of short-chain fatty acids caused by Salmonella infection	[78]
2.	Probiotics	*Lactobacillus reuteri* ATG-F4	Increase of cytokine IL-10 and serum dopamine level in Alzheimer's disease	[79]
3.	Metabiotic	*Bifidobacterium bifidum, Bifidobacterium longum*	Protection of dopamine-releasing neurons Decrease of motor dysfunctions	[80]
4.	Probiotics	*Bacteroides fragilis* NCTC 9343	Reduction of autistic behavior in Alzheimer's disease	[81]
5.	Probiotics	*Lactobacillus rhamnosus, Lactobacillus reuteri*	Regulation of anti-inflammatory pathways in Alzheimer's disease	[82]
6.	Probiotics	*Lactococcus* sp., *Enterococcus* sp., *Streptococcus* sp.	Regulation of emotions, sleep, and cognitive function (anxiety and depression, cognition)	[79]
7.	Probiotics	*Bacillus adolescentis* SPM0212	Inhibition of cancer cell growth (colorectal cancer)	[83]
8.	Probiotics	*Saccharomyces cerevisiae* CNCM I 3856	Modification of pro-inflammatory cytokine production (colorectal cancer)	[84]
9.	Metabiotic	*Lactobacillus paracasei* D3-5	Anti-inflammatory effect by regulation of the nuclear factor-kB(NF-κB) ssignaling	[79]
10.	Postbiotics	*Lactobacillus casei*	Inhibition of IL-6 synthesis by inhibiting NF-κB	[85]
12.	Probiotics	*Bifidobacterium breve* A1	Reduction of neuroinflammation in Alzheimer's disease	[86]

PROBIOTICS IN COGNITIVE DECLINE

- **The gut-brain axis:** This is a bidirectional communication channel through which the gut microbiome affects the CNS. Probiotics are important in this pathway.
- **Neuroactive Molecules:** The intestinal bacteria create neuroactive molecules, such as serotonin, GABA, and short-chain fatty acids (SCFAs), that influence brain function and help lessen neurological illnesses [87].
- **Alzheimer's disease**: Research suggests that probiotic metabolites, such as SCFAs, modulate anti-inflammatory and cholinergic neuronal signaling pathways, which may reduce the symptoms of Alzheimer's disease [88].
- **Parkinson's disease**: Research has shown that probiotics like Lactobacillus plantarum PS128 can reduce motor dyskinesia and neuronal apoptosis in Parkinson's disease models [89].
- **Depression and anxiety**: According to the paragraph on anxiety and depression, probiotic metabolites may play a role in treating depression and anxiety by regulating the synthesis of neuroactive chemicals involved in mood regulation, such as serotonin and GABA [90].
- **Autism Spectrum Disorder**: Certain probiotic strains, such as Lactobacillus reuteri and Bacteroides fragilis, have demonstrated promise in reducing the behavioral symptoms connected to the condition [91].
- **General Neuroprotection**: Certain probiotic strains and their metabolites have been associated with neuroprotection through mechanisms such as anti-inflammatory actions and neurotransmitter level modulation [92].

All of these factors—gut health, neuroactive molecule synthesis, and neuroinflammation reduction—showcase probiotics' therapeutic potential in treating cognitive decline. These conditions are critical in neurological disorders such as Parkinson's and Alzheimer's disease, mood disorders, and autism spectrum disorder.

METABIOTICS IN COGNITIVE DECLINE

- **Short-chain fatty acids, or SCFAs**, are essential because they regulate immunity by decreasing pro-inflammatory cytokines like TNF-α and IL-6 and promoting anti-inflammatory cytokines like IL-10. Examples of SCFAs include butyrate, propionate, and acetate [93].
- **Histone Deacetylase Inhibition:** Studies have shown that certain metabiotics, such as folate, acetate, propionate, and butyrate, inhibit histone deacetylases and modify histone acetylation. This can affect the expression of genes linked to inflammation and possibly neuroprotection [94].
- **Effects that reduce inflammation**: Parts of probiotics like lipoteichoic acid (LTA) from Lactobacillus species reduce inflammation by controlling pathways like NF-κB signaling, linked to neurodegenerative disorders and inflammation [95].
- **Potential Neuroprotective Effects:** Although not mentioned specifically in the text, the capacity of SCFAs and other metabiotics to control inflammation and maybe affect epigenetic modifications raises the possibility of a neuroprotective effect. Chronic inflammation exacerbates neurodegenerative diseases like Alzheimer's disease, and reducing inflammation with metabiotics may slow down cognitive deterioration.

RECENT ADVANCEMENTS & FUTURE DIRECTIONS

There is a need for greater investigation to find novel forms of metabiotics and their components that may effectively prevent a range of illnesses, including cancer. A recent meta-analysis of randomized control studies in Alzheimer's disease and mild cognitive impairment patients reported that there is no difference in efficacy between single and multiple species [96]. A Pohang University of Science and Technology research team devised a novel strategy for reporting beneficial bacteria with anticancer effects. IMB001 is a Live Biotherapeutic Product (LBP), as Lactobacillus plantarum IMB19 (LpIMB19) with solid proof of activity from preclinical studies with different types of cancers [97]. A personalized approach termed precision nutrition based on individual properties has shown promise with a direct impact on the composition of the gut microbiome [98]. Large-scale clinical trials are yet to be completed to support and reveal the facts mentioned above to overcome different factors like demographic status, nutrition style, metabolic pattern, etc

CONCLUSION

Probiotics and postbiotics hold significant promise as interventions for neurodegeneration and cognitive decline, and a growing body of evidence supports their role in modulating the neuropathological mechanisms involved. However, translating this potential into effective clinical interventions requires further research to overcome current limitations and fully understand the mechanisms of action. As the population ages and the incidence of neurodegenerative diseases rises, exploring innovative and complementary therapeutic approaches such as probiotics and postbiotics becomes increasingly essential. This

discussion section critically analyzes the review's findings and summarizes them. It highlights the potential of probiotics and postbiotics in treating neurodegeneration, but it also acknowledges the need for more thorough research to translate these findings into real-world clinical applications.

FINANCIAL ASSISTANCE
NIL

CONFLICT OF INTEREST
The authors declare no conflict of interest.

AUTHOR CONTRIBUTION
J Renukadevi, R Velmurugan, and G Nandhinidevi contributed equally in drafting the manuscript's content, articulating the research findings and discussions, and contributing to technical coherence and quality. V S Karthikha and V Sri Vaishnavi contributed equally in formatting and editing the manuscript**.**

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