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Gut–brain Axis Modulation by Probiotics: Insights into Natural Remedies for Neurodegeneration

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Abstract

Neurodegeneration is mainly caused due to neuronal loss; gut microbiota plays an important role in the human body. There is some new evidence which indicates there is bidirectional communication between the gut and brain, *i.e.*, "Gut-Brain Axis". The main pathways for this are Humoral, immunological, endocrine and neuronal pathways. Probiotics are live microorganisms that improve cell-signalling and Blood -Brain Barrier Interaction and improve cognitive function. This gut microbiota is capable of synthesizing neurotransmitters and other signalling molecules responsible for the regulation of brain functioning and development. Probiotics produce numerous metabolites such as Short-chain Fatty acids, Bacteriocins, Serotonin, Gamma-Amino Butyric acids, Bacteriocins Vitamins, *etc.*, which are major players in the delivery of therapeutics to neurodegenerative diseases. There is increasing evidence that gut microbiota dysbiosis is not just a contributing factor but also a potential therapeutic target for individuals with neurodegenerative disorders.

Major Findings: Fermented food–derived probiotic isolates are expected to exhibit functional resilience and produce neuroactive metabolites capable of modulating the gut–brain axis. These metabolites will be evaluated for their potential to attenuate neurodegenerative processes. The study aims to establish probiotics as safe, natural therapeutic candidates for future neurodegenerative disease management.

Keywords: Bioactive Metabolites, Cognition, Gut-brain Axis, Neurodegeneration, Probiotics, Short Chain Fatty Acid

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1. Introduction

Probiotics are live bacteria that impart a beneficial effect on the host when they are taken in suitable quantities. Probiotics are microbes of many genera and species and have been investigated for their effects on different diseases and health outcomes. Contemporary probiotics consist of bacteria, *e.g.*, *Lactobacillus*, *Streptococcus*, and *Enterococcus* spp., yeast *(Saccharomyces cerevisiae)*, *Bifidobacterium*, *Propionibacterium*, *Bacillus*, and *Escherichia coli*[1]. The "Gut-Brain Axis" (GBA) term is used to describe the

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sophistication of such interactions. Gut dysbiosis, a significant underlying cause of various gastrointestinal diseases, can also increase pro-inflammatory cytokines, monocytes, lipopolysaccharides, and T helper cells through the microbiota-gut-brain axis, enhancing the intestine and the blood-brain barrier permeability. Bidirectional communication between the GIT and brain is well established[2]. Direct neural impulses, along with indirect enzymatic and hormonal impulses, are continuously sent to the GIT lumen to control and regulate movement, secretion, and transmission of sensory impulses. But the same impulses are sent from the GIT to the brain, affecting its function and the control and regulatory function of the brain. In fact, the brain and GIT have 200–600 million interconnected neurons[3].

Neurodegenerative diseases are a collection of disorders that involve progressive nerve cell degeneration, mostly in the brain. They include a variety of disorders, including Alzheimer's disease, Parkinson's disease, Dementia with Lewy bodies, Vascular Dementia, Huntington's disease, Frontotemporal Dementia, and Motor Neuron disease. They have combined clinical symptoms, with few presenting with pure syndromes and the majority having mixed features. Successful therapy of these disorders has also been challenging, despite the large amount of research put into medicinal and surgical treatment[4]. Many neurodegenerative diseases are age-related, and their incidence increases with the ageing population of the world. The following are some examples of neurodegenerative disorders: ALS, which impacts breathing and movement; Parkinson's disease, which impacts movement and coordination; Huntington's disease, which results in motor and cognitive impairment; and frontotemporal dementia, which has the ability to change behaviour and personality. Despite the pathophysiological features of each of these diseases being distinct from one another, they all have underlying pathways which result in progressive neuronal dysfunction and death. It is also true that ageing poses a serious threat to neurological diseases[5]. Individuals become more prone to these debilitating conditions with ageing. Ageing is a typical and inescapable process in itself, yet it is also closely associated with the occurrence and progression of neurological diseases. Globally, neurodegenerative disorders affect millions of people. Although age still stands as the leading risk factor for the onset of Non-Communicable Diseases (NCDs), recent studies show that a person's genetic makeup and environment can both heighten the risk for NDs[6].

Most neurodegenerative conditions, including Alzheimer's Disease (AD), Parkinson's Disease (PD), Huntington's Disease (HD), and Frontotemporal Lobar Dementia (FTD), have been associated with ageing as a primary risk factor. The aged are at higher risk of experiencing these neurodegenerative diseases. There are a few established treatments for these common neurological emergencies. Neurodegenerative diseases incur substantial economic and individual costs[7,8] (Figure 1).

2. Key Factors Contributing to Neurodegenerative Diseases: Insights into Mechanisms and Risk Factors

Neurodegenerative diseases are evolving rapidly, with recent studies immensely expanding our understanding of their pathogenic processes and emphasising as much as ever before the classical pathological processes, as well as newly discovered cellular dynamics and systemic mechanisms. Protein misfolding and aggregation remain the signature, but cryo-electron microscopy research has revealed the ultrastructure of fibrillar aggregates such as β-amyloid in AD and α-synuclein in PD. These findings suggest that some structural conformations are more toxic, enhancing synaptic dysfunction and neurotoxicity. Oxidative stress has also come into prominence, and recent omics-based studies have shown that oxidative damage represents an early alteration in neuronal metabolic pathways[9]. Redox proteomics, for example, identified oxidatively modified proteins in the brains of AD and ALS patients to indicate the insufficiency of antioxidant response. Parallelly, mitochondrial dysfunction has increasingly been associated with mitochondrial DNA and nuclear gene mutations that regulate mitochondrial dynamics. Research on mitophagy autophagy directed against mitochondria revealed its primary failure in early stages of neurodegeneration, as specifically observed in PD[10]. Further, the neuroinflammatory hypothesis has emerged into view with single-cell RNA sequencing of human brain tissues establishing microglial subtypes associated with disease development. These glial cells

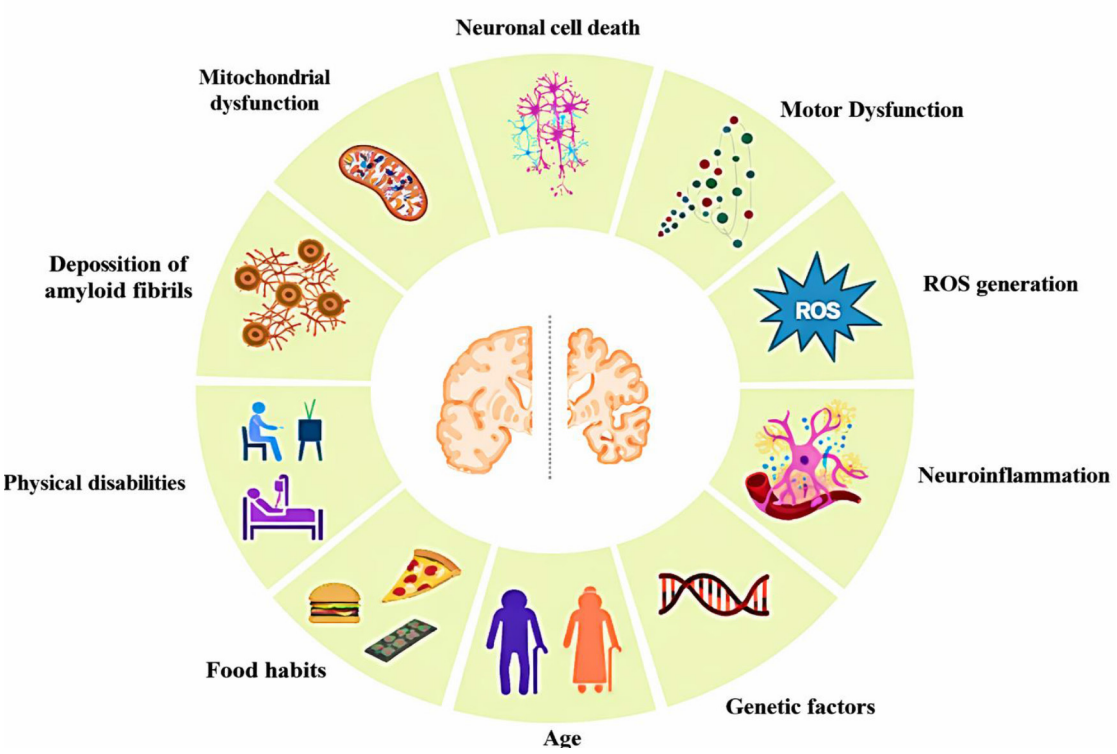


Figure 1. Neurodegenerative disorders entail progressive neuronal loss, protein misfolding and aggregation, mitochondrial dysfunction, oxidative stress, neuroinflammation, and cellular homeostasis disruption, ultimately leading to cognitive and motor dysfunction.

were formerly secondary responders but are now recognised as dynamic contributors to neuronal death through cytokine secretion and synaptic pruning. Disruption of proteostasis is another region of vigorous research[11]. Recent reports emphasize that autophagy and the ubiquitin-proteasome pathway are differentially impaired across brain regions and disease states. To illustrate, autophagic flux is drastically reduced in AD, but mutations of the E3 ligase parkin severely impair proteasomal activity in familial PD. In addition, axonal transport impairments that were once largely thought to result from structural disruption have recently been shown to involve defective motor proteins and misbehaving microtubule dynamics, as revealed by live-cell imaging experiments. Increasing evidence is also investigating the role played by systemic factors such as gut microbiota, vascular function, and systemic inflammation in modulating such central processes[12]. The gut-brain axis, for example, is now linked to neurodegeneration by microbial metabolites, systemic inflammation, and vagus nerve signalling. Overall, the synergy between multi-omics technologies, high-resolution imaging, and advanced genetic models is uncovering a more nuanced and integrated neurodegenerative disease mechanisms landscape, unfolding new prospects for early diagnosis and focused treatment[13].

2.1 Genetic Mechanisms in Neurodegenerative Disorders

Genetic factors have a significant influence on the process and development of the majority of NDs, and certain mutations of specific genes are directly implicated in the pathogenesis of the diseases. APP, PSEN1, and PSEN2 gene mutations are well established for familial Alzheimer's disease, whereas SNCA and LRRK2 mutations have been linked to Parkinson's disease. Similarly, Huntington's disease is caused by an expansion of a trinucleotide repeat of the HTT gene. Explaining the genetic aetiology of NDs is crucial not just for accurate and timely diagnosis but also for the formulation of gene-targeted, individualised therapies[14]. However, it is important to realise that neurodegeneration is likely

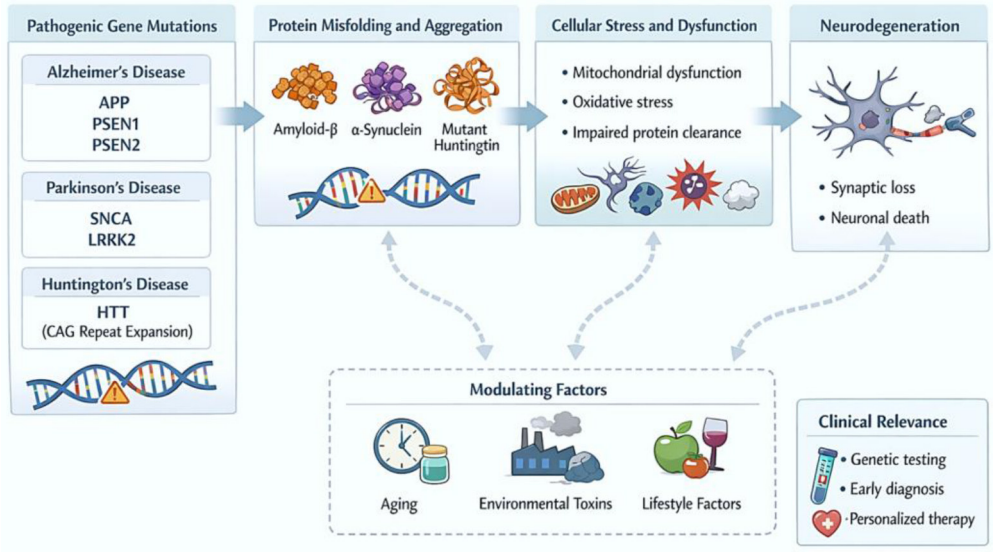


Figure 2. The schematic depicts the genetic factors involved in the development of neurodegenerative diseases. Mutations in genes associated with these diseases (APP, PSEN1, PSEN2, SNCA, LRRK2, and HTT) cause misfolded proteins, including amyloid-beta, alpha-synuclein, and mutant huntingtin. Accumulation of these misfolded proteins results in mitochondrial dysfunction, disrupted autophagy processes, and disrupted calcium homeostasis in cells. The cellular stress caused by this accumulation leads to neuroinflammation and progressive neuronal degeneration that results in cognitive deficits and movement deficits[16,17].

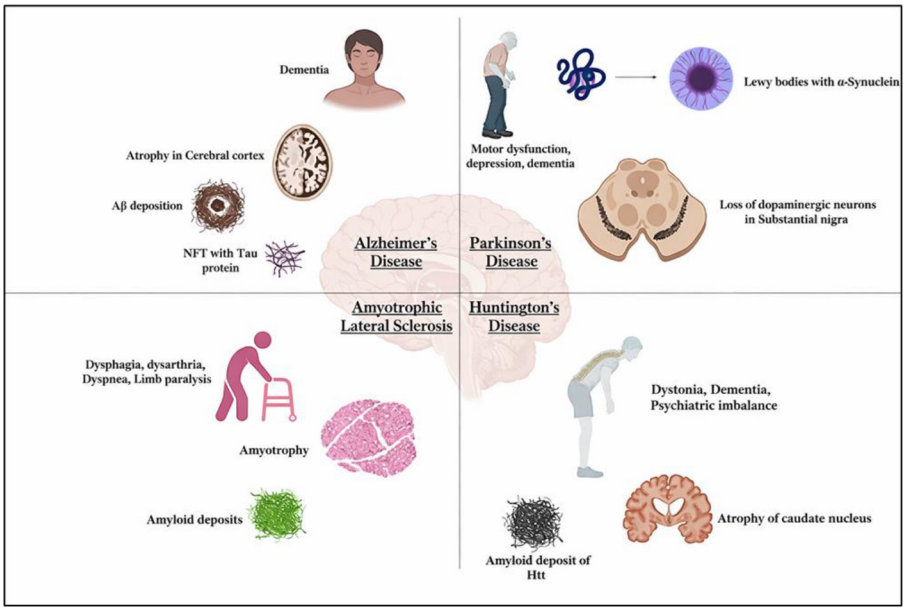


Figure 3. Clinical and pathological characteristics of principal neurodegenerative disorders. The diagram depicts characteristic clinical features and the most important neuropathological alterations of four major neurodegenerative disorders: Alzheimer's Disease (upper left): Marked by dementia, atrophy of the cerebral cortex, deposition of β-amyloid (Aβ) plaques, and tau protein neurofibrillary tangles. Parkinson's Disease (upper right): Marked by motor impairment, depression, dementia, Lewy bodies with α-synuclein, and loss of dopaminergic neurons within the substantia nigra. Amyotrophic Lateral Sclerosis (ALS) (lower left): Exhibits dysphagia, dysarthria, dyspnea, paralysis of limbs, amyotrophy of muscles, and amyloid deposition. Huntington's Disease (lower right): Characterised by dystonia, dementia, psychiatric illness, amyloid deposition of the Huntingtin (HTT) protein, and caudate nucleus atrophy.

to be multifactorial in nature; genetic vulnerability may synergistically act with environmental damage, lifestyle choices, and alterations related to ageing to modulate susceptibility and progression of the disease. This interaction also emphasises the need for integrated approaches to research as well as clinical management. Genetic testing and counselling are now valuable tools, especially for individuals with a family history of NDs. They can help identify risks, lead to early treatment, and guide reproductive choices. In addition, they offer psychological support and enable people to make educated health and lifestyle choices[15] (Figures 2 and 3).

2.2 Ageing and Neurodegenerative Diseases

Age plays a central part in the development and advancement of neurodegenerative diseases. Numerous neurological diseases are more characteristically associated with ageing, and the risk of developing these conditions rises when one becomes older. Neurodegenerative disorders such as Alzheimer's, Parkinson's, and ALS are highly associated with age. The prevalence of these conditions usually increases sharply in elderly age groups. Ageing is the accumulation of genetic mutations and environmental exposures over time[18]. These can lead to the formation of neurodegenerative diseases. The more years of life an individual has, the more chance these factors have of accumulating and causing disease onset[19]. Ageing involves cellular changes such as higher oxidative stress and a loss of ability to repair and maintain cells. Oxidative stress can also damage cellular structures, such as proteins, lipids, and DNA, and their damage is involved in the pathogenesis of neurodegenerative diseases. Most neurodegenerative diseases feature the pathological accumulation of aggregated misfolded proteins within the brain. Cellular ability to effectively clear these aggregated proteins lessens with age, resulting in their buildup and possibly toxicity[20]. Ageing is correlated with chronic low-grade inflammation, also called inflammaging. This sustained inflammatory condition can be responsible for the development of

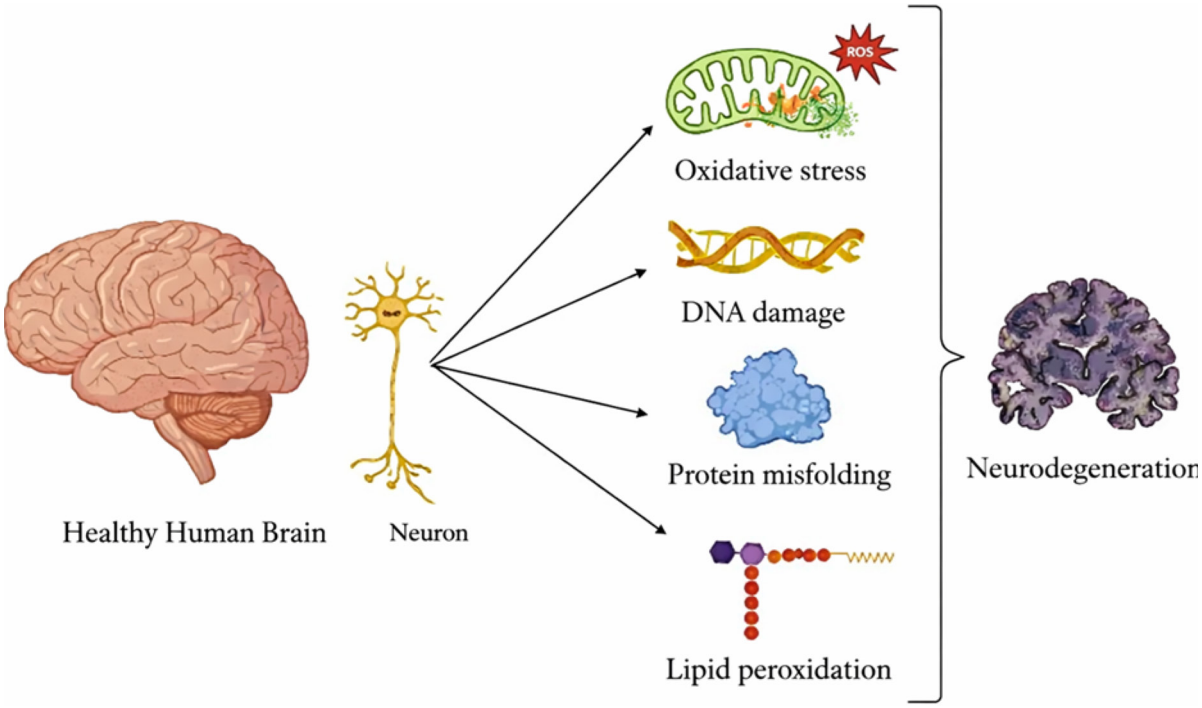


Figure 4. An illustration of how oxidative stress is linked to neurodegenerative disorders. Excessive ROS levels might cause harmful alterations to brain neurons. Since ROS can also oxidise DNA, RNA, and lipids, they can also be produced inside the mitochondria, for example, as a result of mitochondrial malfunction. This increases the amount of damage done to the mitochondria. Moreover, ROS contribute to protein aggregation, which in turn encourages oxidative stress. All of these well-known indicators of oxidative stress may contribute to a number of age-related neurodegenerative diseases.

neurodegenerative disorders by modulating several cellular and molecular mechanisms in the brain. Certain people might be genetically predisposed to neurodegenerative diseases, and ageing can enhance the expression of these genetic components. The interaction between genetic predisposition and the processes of ageing may affect the probability and severity of neurodegenerative diseases, with increased duration of life, brain areas responsible for higher-order functions showing reduced coordination, likely to be the result of progressive loss of neurons and myelinated fibres connecting different regions or changes in synaptic structure and function[21]. Each and every organism has an autonomous rate of gene expression change during the process of ageing, a phenomenon that governs the onset of age-related brain pathology and neurodegenerative disorders, including AD and PD. Chronic low-grade inflammation, referred to as "inflammaging", is encountered during ageing. This long-lasting state of inflammation is thought to affect the onset of ND's[22]. Inflammation may worsen neuronal injury and lead to the worsening of these diseases. Cellular senescence, in which cells no longer divide and perform their normal functions, is an ageing phenomenon. Senescent cells accumulate with age and release pro-inflammatory factors, and this microenvironment promotes neurodegeneration[23,24] (Figure 4).

Genetic variants predisposing an individual to neurodegenerative diseases exist in some people. The interaction of the genetic characteristics with ageing is complex, and age can alter gene expression and the disease-causing gene effect. Epigenetic changes, which involve alterations in gene expression patterns but without changing the underlying DNA sequence, are regulated by both genetic and environmental factors. Ageing has been associated with some epigenetic changes that may predispose the ageing brain to neurodegenerative disease[25]. Age has been identified as a key risk factor for neurodegenerative diseases by clinical observations. Understanding this association is crucial for health practitioners in diagnosing, treating, and managing these patients, especially with increased life expectancy. Although age is a prevailing consideration, neurodegenerative diseases also affect people younger than the general age of onset. Early-onset forms present special challenges, and researchers are investigating whether different mechanisms are involved in these cases. Precision medicine strategies involve development with age as a primary consideration for adjusting treatments. Appreciating age-related subtleties of ND is crucial to formulate therapeutic regimens that are functional and personalized[26].

2. Current Therapeutic Approaches to Treat ND

ND management is frequently disease-specific. Several recognised management strategies already exist that either focus on the pathophysiology of the disease or attempt to manage the signs and symptoms. Therapeutic approaches for managing AD focus mainly on targeting different pathways for disease progression. Currently, there are three classes of drugs approved by the US-FDA for the management of AD. In June 2021, Aducanumab (Aduhelm) became the first disease-modifying medication authorised to treat individuals with AD. Cholinesterase inhibitors are being used as the first-line treatment for AD. Galantamine, rivastigmine, and donepezil are the three primary cholinesterase inhibitors utilised in therapeutic settings. Cholinesterase inhibitors continue to be the only treatment choice for AD patients, despite the development of several other medications[27].

Despite PD being the second most prevalent ND, there does not constitute an abundance of effective treatment that specifically changes the disease's pathogenesis. For patients' symptom alleviation, several choices instead treat the motor-related and non-motor-related symptoms independently. Restoring the depleted dopamine levels in the brain's substantia nigra is the main strategy for treating PD. Various strategies have been attempted to restore dopamine levels. A combination of levodopa and carbidopa is the most often used treatment. *Levodopa* is a dopamine immediate precursor that aids in the restoration of motor functioning when dopamine is depleted[4]. Levodopa and carbidopa are used to prevent levodopa from being broken down peripherally before it enters the brain. *Riluzole* and *edaravone* are the two authorised drugs for ALS patients. In 1995, the glutamate-receptor antagonist *Riluzole* was approved for use as an oral tablet at a dosage of 100 mg per

Table 1. Therapeutic strategies currently employed for the management of neurodegenerative diseases

Neurological Disorder	Drug Class	Mechanism	Drugs	References
Alzheimer disease	Amyloid-directed antibody	Acts by targeting and removing amyloid-beta plaques	*Aducanumab*	[29]
	Cholinesterase Inhibitors	Prevent the knockdown of acetylcholine	*Donepezil, rivastigmine, galantamine*	[30]
	Glutamate regulators	Antagonize N-methyl-D-aspartate (NMDA) receptor to improve signal-to-noise ratio of glutamatergic transmission	*Memantine*	[31]
Parkinson disease	Dopamine supplements	Replenish the decreased dopamine levels	*Levodopa*	
	Decarboxylase inhibitors	Prevent peripheral breakdown of levodopa	*Carbidopa*	
	Dopamine agonist	Produces dopamine-like effects	Apomorphine hydrochloride, pergolide, pramipexole dihydrochloride, ropinirole hydrochloride, rotigotine	
Amyotrophic Lateral Sclerosis	Glutamate-receptor antagonist	Inhibits glutamate receptors	*Riluzole*	
	Free-radical scavenger	Scavenges free radicals	*Edaravone*	[32]

day. According to clinical studies, *Riluzole* treatment increases ALS patients' survival by three to four months when compared to a placebo group. Recently approved in 2017 as an intravenous infusion at a dosage of 60 mg/day, *Edaravone* is a free-radical scavenger that helps reduce the advancement of the disease[28] (Table 1).

3. Gut-Brain Axis (GBA)

A complicated communication axis that ensures the proper maintenance of gastrointestinal homeostasis has been identified via insights into the GBA; also, neuroimmune endocrine mediators are involved in these GBA communication processes. Recent research suggests that gut bacteria are majorly important and they influence these interactions. Numerous processes in the brain and gut, and also the immune system function, Digestion, metabolism and behaviours are impacted by the GBA communication[33] (Figures 5, 6).

3.1 Neural Pathway

GBA has a connection between the CNS of the brain and the ENS of the gastrointestinal tract, also called the bidirectional communication pathway. Because of developments in neurology and medical engineering, this discipline is expanding quickly. In addition, microbiota can affect ENS activity by generating neurotransmitters, including GABA, serotonin, melatonin, histamine, and acetylcholine, that can function as local neurotransmitters. These pathways include the ENS and the vagus nerve, and they transmit the signal between the brain and gut. Gut microbiota plays a significant role, and they influence the GBA communication through various mechanisms like Neurotransmitter production and immune system modulation[34].

3.2 Hormonal Pathway

In reaction to nutrition, the gastrointestinal system releases peptide hormones that convey to the brain the energy balance that exists at that moment. These hormones control glucose homeostasis, energy expenditure, and hunger. They can act through the vagus nerve, the blood flow at the affected peripheral tissues, or significant brain regions such as the brainstem and hypothalamus that are linked with energy balance[35].

3.3 Immunological Pathway

There is a relationship between healthy CNS function and intestinal health. It is widely recognised that

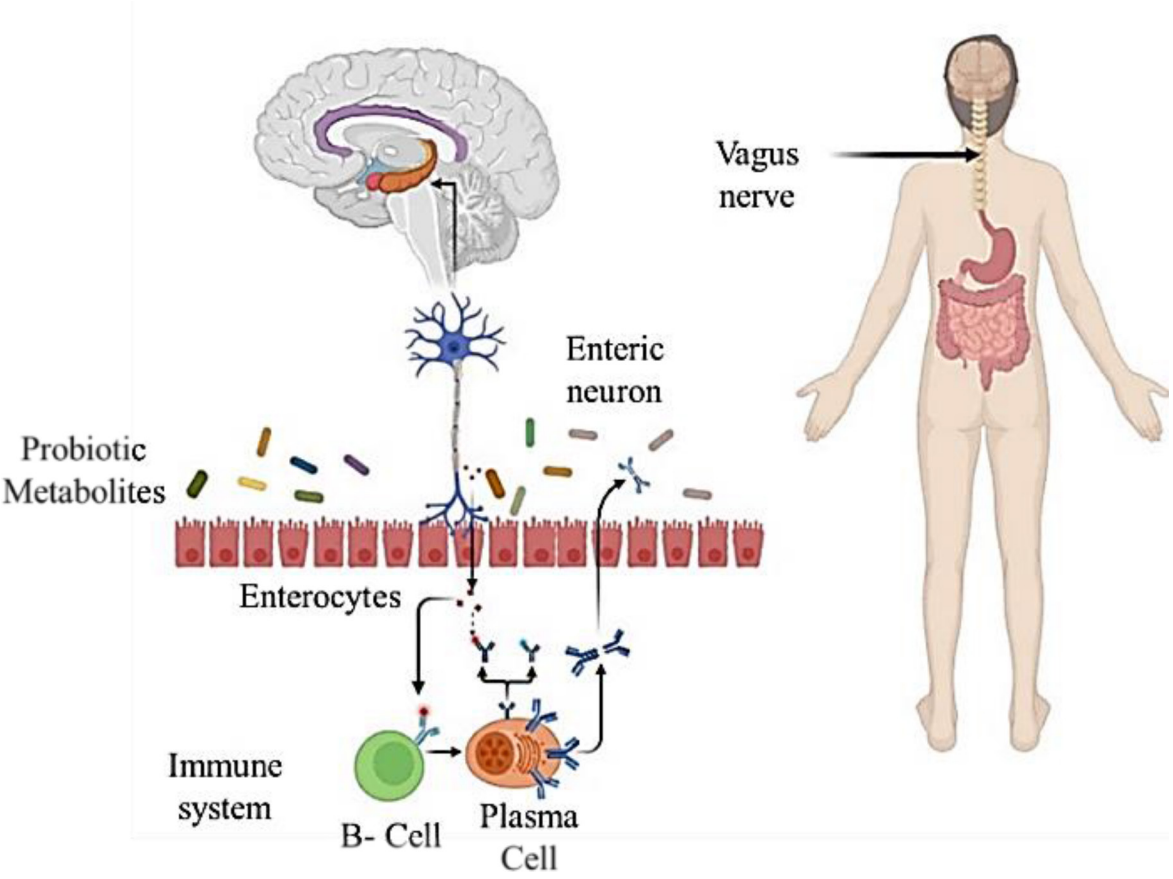


Figure 5. Schematic illustration of the gut-brain axis and its interaction with the immune system. The illustration shows how gut microbiota and their metabolites interact with intestinal epithelial cells (enterocytes) and activate enteric neurons. The signals are transmitted to the brain through the vagus nerve, impacting neurological functions. Microbial metabolites also modulate immune responses by interacting with B cells and plasma cells, playing a role in systemic immune regulation[38].

signals from the gastrointestinal tract can reach the brain directly or through autonomic neurons. These signals can come from hormones, neurotransmitters, and immune factors. The microbiota that inhabits the digestive tract coexists in symbiosis with its host, producing an ecosystem. The host's dietary habits are one of the primary external elements influencing the microbiome-host interaction, which is essential to maintain general well-being[36]. In contrast to Western and high-fat diets, diets high in fibre and low in fat and sugars have been demonstrated to improve intestinal health by encouraging the growth of healthy bacteria, enhancing mucus barrier function, and boosting immune tolerance while preventing pro-inflammatory responses and their downstream impacts[37].

The microbiota is the collective term for the diverse range of commensal bacteria that inhabit the human body. The skin and various mucosal cavities (nasal, oral, pulmonary, and vaginal) are colonised by this host microbiota; however, the Gastrointestinal (GI) tract is where these organisms reach extraordinary densities because trillions of bacteria, fungi, and viruses coexist in symbiosis with the host for attainable mutual benefit. In the last 20 years, our gut microbiota has been extensively studied, even though it significantly influences our health and the development or advancement of diseases. Consequently, its vital functions in combating infections, regulating immunological, endocrine, and metabolic processes, as well as influencing drug metabolism and absorption, have started to be comprehended. This cranial nerve acts as a primary two-way communication pathway[39]. Signals travel from the gut to the brain, influencing mood, cognition, and behaviour, and vice versa, with the brain regulating gut functions

like motility and secretion. Neurotransmitters and neuromodulators play a significant role in gut-brain interaction. The mood-associated neurotransmitter serotonin also occurs in the gut, influencing motility and secretion. The gut is also a source of a number of neuropeptides and hormones, such as ghrelin and leptin, which send messages of hunger and satiety to the brain. The gut microbiota, a population of trillions of microbes residing in the intestines, plays a crucial role in the gut-brain axis. Microbiota can influence neurotransmitter synthesis and immune response, which modulate mood and behaviour. Dysbiosis, or imbalance of gut flora, has been implicated in conditions like depression, anxiety, and autism[40]. The gut plays a significant role in the body's defence mechanism. An impaired gut can activate inflammation and immune responses that affect the brain. Chronic gut inflammation has been connected with neurodegenerative and mood disorders. The gut-brain axis has also garnered significant attention when it comes to mental health. Recent evidence shows that changes in the gut microbiota and gut-brain communication can induce depression, anxiety, and even neurodevelopmental disorders. Diet significantly influences the gut-brain axis. Particular foods and eating patterns can alter gut microbiota composition and the production of molecules affecting brain function[41]. The Mediterranean diet, with high levels of fruit, vegetables, and whole grains, is linked to better mental health, but diets with high levels of processed food can do the opposite. Understanding the gut-brain axis has opened up new avenues for potential treatments. Techniques like probiotics, prebiotics, and dietary interventions are being explored to modulate gut microbiota and alleviate symptoms of mood disorders[43].

4. Probiotics Major Health Benefits

Probiotics are specific, live bacteria that can provide their host with a variety of health-enhancing advantages. These beneficial characteristics include inhibiting pathogenic infection, generating vitamins, boosting immunity, and preventing metabolic or inflammatory illnesses. Current probiotic research aims to characterise every individual›s common, healthy gut microbiota by determining the species composition and concentrations of various bacteria in every part of the intestine. The goal is to understand host-microbe interactions in the gut, microbe-microbe interactions in the microbiota, and the cumulative effects of these interactions on health. The aim is to define and characterise the microbiota as a source of novel bacteria for potential probiotic bacteriotherapy applications, as well as a tool for the nutritional management of certain gut-related disorders. In the future, this might include microbes that have been isolated, especially to give regional activities in illnesses such as irritable bowel syndrome[43].

Several *Lactobacillus* and *Bifidobacterium* species are used in the production of probiotics. Lactic acid is produced by the majority of probiotic microorganisms. It is known that lactic acid stops coliforms from developing in the digestive system. In terms of food microbiology and human nutrition, species of the genera *Lactobacillus* and *Bifidobacterium* are among the most significant taxa because of their roles in the production and preservation of food and feed as well as the probiotic qualities some strains of these species possess. These qualities are getting more and more attention from the market and consumers[44].

4.1 *Bifidobacteria*

Gram-positive polymorphic branched rods are known as *Bifidobacteria,* and they occur singly, in groups, or in chains. They are non-filamentous, non-motile, or non-spore-forming, have a fermentative type of metabolism, and are anaerobic chemoorganotrophs. A variety of carbohydrates generate acid but not gas. They are catalase-negative. They have been isolated from faces, the rumen of cattle, sewage, human vagina, dental cavities, and the honey bee gut; however, they can be found in both animals and humans. In the human gastrointestinal and genitourinary tracts, they are distributed in different ecological niches, with the specific ratio being mostly influenced by age and food. *Bifidobacteria* grow rapidly soon after birth and dominate the infants' native microbiota. They become less prevalent with age and finally represent third in terms of abundance (accounting for roughly 25% of the total adult gut flora) behind the genera *Eubacterium* and *Bacteroides*[45].

4.2 *Lactobacillus*

Lactobacilli are characterised as Gram-positive, non-spore-forming, and non-flagellated rods or coccobacilli in general. They are either anaerobic and mainly

fermentative or aerotolerant. In the homofermentative case, glucose is fermented primarily to lactic acid, or equimolar proportions of lactic acid, CO_2, and ethanol (and/or acetic acid). In the gastrointestinal and genital tracts, *Lactobacilli* are found in a wide range of ecological niches and play a significant role in the native microflora of humans and other higher animals. Numerous environmental parameters, including pH, oxygen availability, the concentration of particular substrates, the presence of secretions, and bacterial interactions, have an impact on their distribution. The strains used in technology are thought to be non-pathogenic and safe microorganisms because they are rarely associated with cases of gastrointestinal and extraintestinal infection[46].

Table 2 summarizes major probiotic microorganisms extensively researched and utilised in food, nutraceutical, and biomedical applications. *Lactobacillus* and *Bifidobacterium* genera prevail for their gut health and immunomodulatory properties, while *Streptococcus, Bacillus*, *Clostridium, Enterococcus*, and *Saccharomyces* genera are other examples of established or emerging strains with potential probiotic benefit.

5. Probiotic Metabolites and their Production

The metabolites generated by probiotic microorganisms during growth or metabolic activity in the gastrointestinal tract mediate most of the beneficial effects attributed to these microorganisms. Probiotics affect host physiology not only via colonisation but also through a plethora of low-molecular-weight metabolites that participate in intestinal homeostasis, immune modulation and systemic signalling. Probiotic metabolites derive from carbohydrate, protein, and lipid metabolism and represent both strain-specific characteristics and environmental signals in the gut[50].

Table 2. This table briefly summarises major probiotic microorganisms

Genus	Species	References
Lactobacillus	*L. acidophilus L. sporogenes L. plantarum L. rhamnosum L. delbrueck L. reuteri L. fermentum L. lactus L. cellobiosus L. brevis L. casei L. lactis L. animalis*	[46,47]
Bifidobacterium	*B. bifidum B. longum B. breve B. infantis B. lactis B. adolescentis*	[48]
Others	*Pediococcus Streptococcus thermophilus Escherichia coli Bacillus cereus Clostridium butyricum Enterococcus faecalis Enterococcus Faecium Saccharomyces cerevisiae*	[49]

Among the most widely recognised categories of probiotic bacterial metabolites is the class of Short-Chain Fatty Acids (SCFAs), which includes acetate, propionate, and butyrate, produced via the anaerobic fermentation of non-digestible carbohydrates. The role of SCFAs appears pivotal for maintaining epithelial integrity, given that they are recognised as essential substrates for the energy metabolism of intestinal cells, and also affect the gene expression of tight junction proteins. In addition, SCFAs have been demonstrated to affect the functions of immune cells and pathways of inflammation, establishing a potential mechanism between the metabolic function of the gut microbiota and other, specifically nervous, systems[51].

Organic acids like lactic and acetic acid are formed in carbohydrate fermentation. These accumulate and thus help in lowering the pH in the lumen, inhibiting the proliferation of pathogenic bacteria and promoting beneficial bacteria. These beneficial effects also help in increasing the bioavailability of nutrients, especially minerals. Certain probiotic strains have been known to produce bacteriocins. These bacteriocins are small antimicrobial peptides that are produced during certain phases of bacterial growth. These bacteriocins have inhibitory action on competitors or pathogens of probiotics and play an important role in maintaining stability in the bacterial community of the human body[52]. Another set of important metabolites participating in host–microbe interactions is exopolysaccharides produced by probiotics. These exopolysaccharides promote increased adhesion capacity of the bacterium to the epithelial lining and help in the biofilm-forming process, thus increasing mucosa-associated persistence. Another function associated with exopolysaccharides is the modulation of the immune response and/or antioxidant activity. There exist some probiotics that can produce neurometabolic compounds, and examples of these metabolites include γ-aminobutyric acid and precursors of monoamine transmitters. These

metabolites originate from amino acids, and there is continued recognition of the role of amino acid metabolites and neurometabolites, particularly in gut-brain axis communication. The metabolites can modulate nervous and immune functions that regulate stress and mood responses[53].

Probiotics help sustain the nutrition of the host through the production of vitamins, especially the B-vitamins and vitamin K. These vitamins are produced through localised bacterial biosynthesis that can serve to complement the dietary intake. The probiotic-catalysed biotransformation of polyphenolic compounds leads to the formation of antioxidants that help mitigate the problem of oxidative stress both locally and systemically. The production of probiotic metabolites is a host-conditioned phenomenon that is dependent on microbial and host biology. The role of these various metabolites is the basis for the multitude of reported beneficial effects observed using probiotics and their potential role in the treatment and maintenance of inflammatory and ND's[54].

Table 3 consolidates important probiotic species studied for neuroactive effects, noting their main metabolites (SCFAs, neurotransmitters, B-vitamins, exopolysaccharides) and hypothesised mechanisms to affect AD pathogenesis, such as modulation of neuroinflammation, oxidative stress, amyloid-β aggregation, BBB integrity, neurotransmitter balance, and immune responses.

6. Quorum-Sensing Peptides and Neurodegeneration

The interplay between Quorum Sensing (QS) peptides, probiotic microorganisms, and NDs has gained increasing attention in recent years due to its potential implications for brain health and disease modulation. This emerging field emphasises the importance of microbial communication in regulating both gastrointestinal and neurological functions through the GBA. Quorum sensing is a density-dependent signalling mechanism by which bacteria coordinate gene expression using small signalling molecules, such as Autoinducing Peptides (AIPs), commonly produced by Gram-positive bacteria[61].

In probiotic genera including *Lactobacillus* and *Bifidobacterium*, QS peptides play a pivotal role in orchestrating collective behaviours essential for host interaction and survival. These behaviours include biofilm formation, enhancement of stress tolerance, suppression of virulence traits, and competitive exclusion of pathogenic microorganisms. Through these regulatory systems, probiotics are better equipped to colonise the intestinal niche, sustain a balanced symbiotic relationship with the host, and respond adaptively to host-derived signals[62].

Action within the gut ecosystem, QS peptides favour microbial homeostasis by promoting the growth

Table 3. Major probiotic strains, their bioactive metabolites, and proposed roles in Alzheimer's Disease (AD)

Probiotic Strain	Metabolites Produced	Effect on AD	References
Lactobacillus rhamnosus	Gamma-Aminobutyric Acid (GABA)	GABA may exert neuroprotective effects by reducing neuroinflammation and oxidative stress, thereby supporting neuronal survival in neurodegenerative disorders.	55
Bifidobacterium bifidum	Short-chain fatty acids (SCFAs)	SCFAs, particularly butyrate, help regulate inflammatory responses and protect neurons, contributing to improved cognitive function.	56
Lactobacillus plantarum	Lactic acid, Acetic Acid	May help to regulate the gut-brain axis and modulate inflammation, impacting AD progression.	57
Lactobacillus acidophilus	Acetic acid, Propionic acid	SCFAs modulate the gut–brain axis by influencing immune signalling and neuroinflammatory pathways involved in disease progression.	58
Bifidobacterium longum	Short-chain fatty acids (Acetate, Propionate)	Changes in gut microbiota composition affect SCFA production, which can alter inflammatory cascades linked to neurodegeneration.	59
Lactobacillus reuteri	Propionic acid, Lactic acid	Propionate may attenuate systemic inflammation and protect against neuroinflammatory pathways associated with neurodegenerative disorders.	60

of beneficial biofilms, which fortify the intestinal barrier and stabilise the microbial community. They also provoke the production of antimicrobial peptides, thus impeding the overgrowth of opportunistic and pathogenic bacteria. Furthermore, QS-mediated signalling modulates the host immune response by repressing dendritic cell activity and cytokine secretion profiles, with the consequent mitigation of intestinal inflammation. Collectively, these mechanisms contribute to maintaining gut integrity and preventing dysbiosis, a condition now increasingly associated with the aetiology and pathogenesis of many ND's[63].

The gut-brain axis is a two-way communication system between the Central Nervous System (CNS) and the Enteric Nervous System (ENS), regulated by microbial metabolites and immune mediators. QS peptides, by controlling microbial behaviour, modulate the structure and function of the gut microbiota, affecting neurophysiology by Zhu *et al.*[64].

- Regulating neurotransmitter synthesis: Some QS-modulated probiotics increase the biosynthesis of Gamma-Aminobutyric Acid (GABA), serotonin, and dopamine neurotransmitters essential for cognitive and emotional processes.
- Modulating Short-Chain Fatty Acids (SCFAs): SCFAs, including butyrate, propionate, and acetate, generated by microbial fermentation, exert neuroprotective, anti-inflammatory, and BBB-stabilising properties.
- Decreasing systemic and neuroinflammation: QS-directed probiotics are able to downregulate pro-inflammatory cytokine expression (*e.g.*, IL-6, TNF-α) and suppress the activation of Toll-Like Receptor 4 (TLR4) by Lipopolysaccharides (LPS), thus reducing inflammation that leads to neurodegeneration[65].

NDs like AD, PD, and ALS are being increasingly connected with chronic gut inflammation, oxidative stress, and microbial dysbiosis. Alteration of the gut microbiota can weaken the intestinal barrier, causing enhanced permeability ("leaky gut"), which allows for translocation of microbial metabolites such as LPS into the circulatory system. Such molecules may cross the BBB, inducing neuroinflammation and neuronal injury.

- QS peptides, through the regulation of microbial activity, can: Prevent pathogenic colonisation: Via competitive inhibition and antimicrobial peptide secretion.
- Maintain BBB integrity: By suppression of endotoxemia and systemic inflammation.
- Induce neurotrophic support: By increasing the microbial secretion of BDNF (brain-derived neurotrophic factor) and decreasing ROS.
- Regulate gut motility and absorption: Affecting nutrient availability and the gut's intrinsic neuromodulator production[66].

QS-modulated probiotics are an innovative and promising way to intervene in ND. To be able to fully exploit this, more information about the specific QS circuits found in probiotic organisms, the target genes, and the specific downstream effects of QS signal modulation is required. Challenges are:

- Signal specificity and cross-talk: That QS peptides only affect desired pathways without unanticipated side effects.
- Stability and bioavailability: Maintaining functional QS activity within the host gastrointestinal environment.
- Host-microbe interactions: Compensation for inter-individual variation in microbiota composition and immune response.
- To overcome these issues, interdisciplinary approaches involving synthetic biology, omics-based profiling, and personalised medicine may become necessary. The synergy between QS-based probiotic treatment and standard pharmacological therapies could yield synergistic benefits, including slowing or even reversing the neurodegenerative processes[67].

7. Probiotic Action in Gut-brain Communication: Metabolite Production, Cytokine Modulation, and Vagal Signalling

Probiotics influence gut–brain communication through multiple, closely linked mechanisms involving microbial metabolite production, immune regulation, and neural signalling. One of the principal modes of action is the synthesis of bioactive metabolites, including SCFAs, bile acid derivatives, polyamines, and microbially derived neurotransmitter-like compounds formed during the fermentation of dietary components.

These metabolites contribute to the maintenance of intestinal barrier integrity, regulation of oxidative stress, and modulation of neuroinflammatory pathways by interacting with host receptors and intracellular signalling systems. SCFAs produced by members of the *Lactobacillus* and *Bifidobacterium* genera are particularly important for strengthening epithelial tight junctions and limiting inflammatory responses, thereby reducing systemic immune activation that may impact central nervous system function[68].

In addition to metabolic activity, probiotics play an important role in modulating host immune responses through the regulation of cytokine production. Several probiotic strains have been reported to suppress the expression of pro-inflammatory cytokines while promoting anti-inflammatory mediators, contributing to immune balance and intestinal homeostasis. Structural components of probiotic cell walls, including peptidoglycans and lipoteichoic acids, interact with host immune receptors and further influence cytokine signalling. Certain strains also produce polyamines, such as putrescine and spermidine, which are involved in cellular proliferation, epithelial repair, and preservation of gut barrier function, indirectly supporting gut–brain axis stability[69].

Neural pathways, particularly vagus nerve signalling, represent another important route through which probiotics affect gut–brain communication. Microbial metabolites and immune-derived signals can activate vagal afferent fibres either directly or

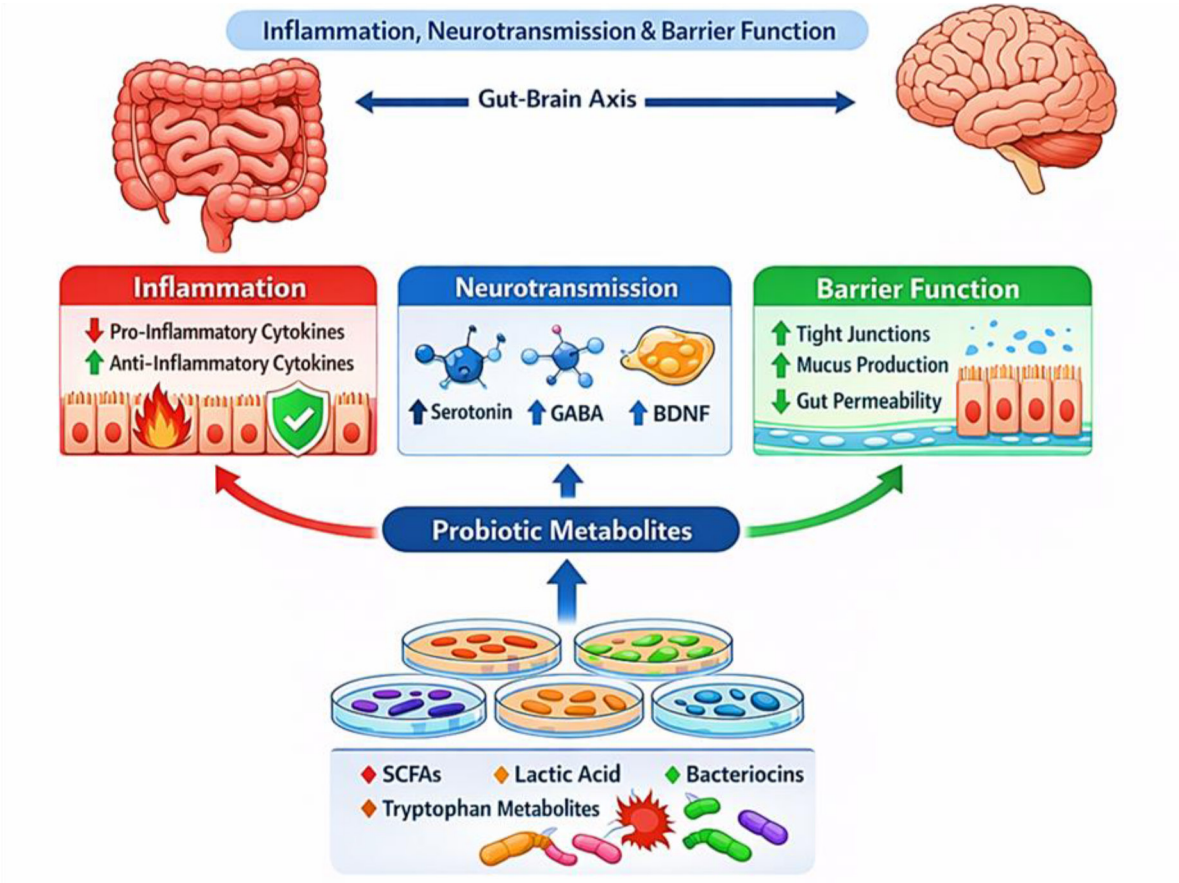


Figure 6. Schematic of the representation of the gut-brain axis through probiotic metabolites. The major classes of metabolites produced by probiotics, including SCFAs, lactic acid, bacteriocins, and tryptophan metabolites, control bidirectional gut-brain interactions via mechanisms involving the reduction of intestinal inflammation, neurotransmission, and enhancement of barrier function. They suppress pro-inflammatory cytokines and enhance anti-inflammatory responses, enhance neurotransmitter production - serotonin, GABA, and neurotrophic factors-BDNF, and enhance gut barrier function via the promotion of tight junctions and mucus production; all these factors put together contribute to maintaining gut and brain homeostasis.

via enteroendocrine and immune cells, leading to changes in neurotransmitter release and central neural activity. This vagus nerve–mediated signalling integrates microbial, immune, and metabolic cues from the gut and conveys them to the brain, influencing neuroinflammation and neurotransmission. Together, metabolite production, cytokine modulation, and vagal signalling form an interconnected framework through which probiotics contribute to gut homeostasis and brain health. While the beneficial effects of probiotics are well established in gastrointestinal disorders, further clinical evidence is required to clarify their role in neurological and neurodegenerative conditions[70].

Certain probiotics also help produce neurotransmitters like GABA and serotonin, which modulate mood and stress response. Production of neurotransmitter precursors, control of bile salt metabolism, production of polyamines, and immunomodulation by cell wall moieties also contribute to the intricate regulation of the gut-brain axis. Probiotics also influence the synthesis of serotonin, a neurotransmitter involved in the regulation of mood. This may potentially have implications for mood and emotional state[71]. Probiotics can help in the production of neurotransmitter precursors. For instance, some strains have the ability to increase tryptophan availability, an amino acid precursor to serotonin. Through regulation of precursor levels, probiotics can affect gut neurotransmitter production indirectly and the gut-brain axis by extension. Probiotics have the ability to modulate bile salt metabolism, which is involved in fat digestion and absorption. Bile acids also function as signalling molecules that influence physiological processes, for instance, inflammation[72].

8. Short-chain Fatty Acids as Emerging Neuroprotective Metabolites in Neurodegenerative Disorders

Primary products of the anaerobic fermentation of dietary fibers by commensal gut microbiota are short-chain fatty Acetate, propionate and butyrate, which are primary microbial metabolites. They are highly water soluble, which means that SCFAs are easily absorbed across the intestinal lumen into the systemic circulation, and therefore prevent them from having actions other than in the gastrointestinal tract, such as in the central nervous system. Among these metabolites, the most common in the circulation is acetate, but the other ones are butyrate and propionate, which are becoming more and more acknowledged due to their high level of biological activity[73].

The evidence is increasing supporting that SCFAs serve as a key mediator in the communication of the gut-brain axis, particularly in the neurodegenerative disorders of AD and PD. Butyrate, specifically, has also gained a lot of attention because of its ability to act as a histone deacetylase inhibitor, which can, in turn, regulate the activity of the epigenetic mechanism of gene expression. In this process, butyrate inhibits neuroinflammatory signalling by inhibiting the production of pro-inflammatory cytokines and modulating the activation of microglia, which are the key to the developmental process of neurodegeneration.

In addition to epigenetic regulation, SCFAs also play a role in immune homeostasis, mitochondrial regulation, and oxidative stress regulation in the brain. It is also known to improve intestinal epithelial integrity of barriers, thus reducing the translocation of endotoxins and reducing systemic inflammation that may worsen neuroinflammatory cascades. These versatile activities make SCFAs metabolically active compounds that have a direct linkage to neuroprotection[74].

The dietary composition is decisive in determining the SCFA production, with high faecal fermentable fibres favouring the growth and activity of the SCFA-producing bacteria such as *Faecalibacterium prausnitzii*, *Roseburia spp*., and selected *Lactobacillus* and *Bifidobacterium* strains. In this regard, there has been an increase in research interest in the targeted isolation and characterisation of probiotic strains that have a high SCFA-generating ability. The discovery of these strains is an encouraging approach to develop microbiota-based interventions that would increase endogenous SCFA supply[75].

SCFA-producing probiotics isolated can be studied under experimental and clinical circumstances to obtain a controlled assessment of their metabolic potential, stability and functionality. These strains could be bioactive candidates of next-generation probiotic preparations used to control gut microbial

metabolism, strengthen gut-brain communication, and reduce neurodegenerative pathology. The combination of SCFA-sensitive probiotic isolation and dietary manipulation represents a logical basis for the development of microbiota-derived therapy of neurodegenerative diseases[76].

8.1 Anti-inflammatory Effects

SCFAs, especially butyrate, have anti-inflammatory properties. Chronic inflammation is associated with all major neurodegenerative conditions, and the ability of SCFAs to modulate immune responses may be protective for the nervous system. The anti-inflammatory effects of SCFAs, namely butyrate, propionate, and acetate, are an important aspect of their potential function in many physiological processes, including neuroprotection (Figure 7). SCFAs can modulate the immune cell function, such as in macrophages and dendritic cells, through the inhibition of pro-inflammatory signalling. Butyrate, for example, has been shown to block the activation of Nuclear Factor-kappa B (NF-κB), a transcription factor with an important role in pro-inflammatory gene expression. Blocking NF-κB by SCFAs diminishes the production of inflammatory cytokines. SCFAs increase Tregs' differentiation and function, a subset of immune cells that dampens excessive immune responses and inflammation. Tregs produce anti-inflammatory cytokines, such as Interleukin-10 (IL-10), which inhibit inflammation[77]. Butyrate, in particular, has been found to inhibit HDAC activity. Inhibition of HDAC causes elevated histone acetylation, which is capable of causing an open chromatin conformation. This epigenetic change facilitates the transcription of genes that are responsible for anti-inflammatory functions and immunoregulation. SCFAs have a direct effect on the expression and secretion of pro-inflammatory mediators. For example, butyrate has been shown to diminish the secretion of pro-inflammatory cytokines, such as Tumour Necrosis Factor-alpha (TNF-α) and Interleukin-6 (IL-6), thus contributing to a generalised anti-inflammatory condition. Neutrophils are central figures in inflammation. SCFAs may control neutrophil function, possibly dampening their pro-inflammatory activity and curbing tissue damage due to excessive inflammation. SCFAs help to preserve the intestinal barrier[78]. A functioning gut barrier prevents the translocation of pathogenic bacteria and bacterial metabolites, which have the ability to induce systemic inflammation. By stabilising the gut barrier, SCFAs indirectly play a role in anti-inflammatory actions. Microglial cells within the central nervous system may become activated and make a contribution to neuroinflammation. SCFAs are able to modulate microglial activation, lower the production of pro-inflammatory cytokines and induce an anti-inflammatory microglial phenotype. The anti-inflammatory activities of SCFAs are diverse and include modulation of immune cell function, suppression of pro-inflammatory signalling, and

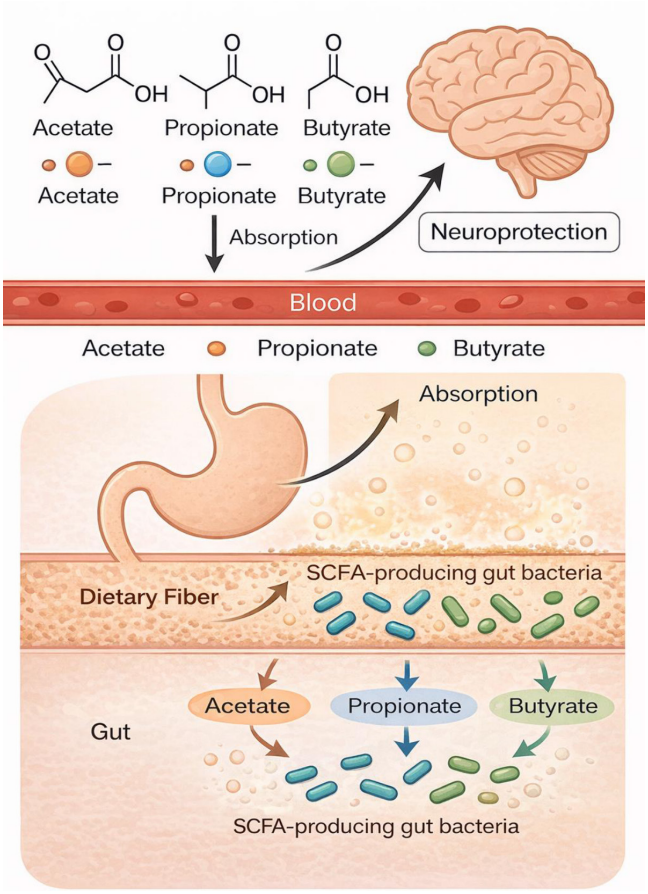


Figure 7. Diagram illustrating the production and systemic effects of SCFAs: acetate, propionate, and butyrate. The gut food fibre is fermented by SCFA-producing microbes to form the metabolites. SCFAs enter the bloodstream when they are produced, from which they are distributed to other organs, including the brain. Their presence is associated with a neuroprotective effect, which can be used to reduce inflammation and preserve brain function.

promotion of regulatory mechanisms. These traits position SCFAs as potentially significant molecules in the alleviation of inflammatory processes involved in different health disorders, such as neurodegenerative disorders[79].

8.2 Antioxidant Properties

Current research has also emphasised the antioxidant effects of SCFAs derived from probiotic bacteria. SCFAs, especially butyrate, have been reported to exhibit anti-inflammatory and anti-proliferative action and thus may be useful in preventing and treating cancer. Probiotics like Bifidobacterium bifidum and *Lactobacillus* produce high levels of SCFAs and express antioxidant activity. These SCFAs are able to regulate cellular oxidative status, guard against oxidative damage, and boost antioxidant enzyme activities in the cells lining the intestine. Additionally, SCFAs secreted from probiotics display anti-cancer activities by retarding the growth of pathogens, inhibiting cancer cell proliferation, and promoting the production of anti-inflammatory cytokines[80]. The association of probiotics with other bioactive compounds, such as quercetin, can synergistically promote antioxidant activity. These results indicate that SCFAs derived from probiotics possess enormous potential in ensuring cellular redox homeostasis and countering oxidative stress-associated disorders[81]. SCFAs have the potential to augment the body's antioxidant defence mechanisms, thus decreasing oxidative stress within cells. Butyrate, for instance, has been shown to enhance the synthesis of antioxidant enzymes such as catalase and Superoxide Dismutase (SOD), which are responsible for eliminating ROS and reducing oxidative stress. Through enhanced mitochondrial activity, SCFAs, such as butyrate, specifically reduce ROS production. Decreased oxidative damage due to excessive free radicals is the outcome of enhanced mitochondrial efficiency. They also aid in reducing oxidative stress indirectly by altering immune responses and lowering inflammation. Because ROS are often generated as a byproduct of inflammation, reducing inflammation can assist in lowering oxidative damage. They can enhance redox homeostasis, lower oxidative damage to proteins, lipids, and DNA, and help cells keep oxidants and antioxidants at a healthy equilibrium[82].

9. Conclusion

The potential of probiotics in addressing neurodegenerative diseases through the gut-brain axis is an emerging area of research. Studies suggest that gut microbiota dysbiosis plays a role in conditions such as Alzheimer's and Parkinson's diseases, highlighting the possibility of using probiotics to restore microbial balance and influence brain health. Probiotics exert beneficial effects by reducing neuroinflammation, modulating oxidative stress, and regulating neurotransmitter production. They can also contribute to the maintenance of the blood-brain barrier and influence amyloid plaque and α-synuclein aggregation, which are key pathological processes in neurodegeneration. However, despite promising results from preclinical and small-scale clinical studies, significant challenges remain. The variability in individual gut microbiota, limited large-scale human trials, and incomplete understanding of mechanistic pathways make it difficult to establish standardised probiotic treatments. Additionally, safety, efficacy and regulatory considerations must be addressed before probiotics can be widely integrated into neurodegenerative disease management. Future research may lead to personalised probiotic therapies; microbiota-based strategies are likely to play an increasing role in supporting brain health and mitigating neurodegenerative disorders.

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11. References

1. Maftei NM, Raileanu CR, Balta AA, Ambrose L, Boev M, Marin DB, *et al.* The potential impact of probiotics on human health: An update on their health-promoting properties. Microorganisms. 2024; 12(2):234. https://doi.org/10.3390/microorganisms12020234 PMid:38399637 PMCid:PMC10891645
2. Balakrishnan R, Kang S-I, Lee J-Y, Rho Y-K, Kim B-K, Choi D-K. Gut microbiota-immune system interactions in health and neurodegenerative diseases: Insights into molecular

mechanisms and therapeutic applications. Aging Dis. 2024; 16(6):3421-3452. https://doi.org/10.14336/AD.2024.1362 PMid:39656490 PMCid:PMC12539548

3. Ansari F, Neshat M, Pourjafar H, Jafari SM, Samakkhah SA, Mirzakhani E. The role of probiotics and prebiotics in modulating of the gut-brain axis. Front Nutr. 2023; 10. https://doi.org/10.3389/fnut.2023.1173660 PMid:37565035 PMCid:PMC10410452
4. Lamptey RNL, Chaulagain B, Trivedi R, Gothwal A, Layek B, Singh J. A Review of the common neurodegenerative disorders: current therapeutic approaches and the potential role of nanotherapeutics. Int J Mol Sci. 2022; 23(3):1851. https://doi.org/10.3390/ijms23031851 PMid:35163773 PMCid:PMC8837071
5. Lamptey RNL, Chaulagain B, Trivedi R, Gothwal A, Layek B, Singh J. A Review of the common neurodegenerative disorders: Current therapeutic approaches and the potential role of nanotherapeutics. Int J Mol Sci. 2022; 23(3):1851. https://doi.org/10.3390/ijms23031851 PMid:35163773 PMCid:PMC8837071
6. Hou Y, Dan X, Babbar M, Wei Y, Hasselbalch SG, Croteau DL, *et al*. Ageing as a risk factor for neurodegenerative disease. Nat Rev Neurol. 2019; 15(10):565-581. https://doi.org/10.1038/s41582-019-0244-7 PMid:31501588
7. Monti P, Biganzoli E, Bollati V. Impact of air pollution and occupational inhalation exposures on neurodegenerative disorders: An epigenetic perspective. iScience. 2025; 28(7):112825. https://doi.org/10.1016/j.isci.2025.112825 PMid:40599315 PMCid:PMC12209981
8. Klemmensen MM, Borrowman SH, Pearce C, Pyles B, Chandra B. Mitochondrial dysfunction in neurodegenerative disorders. Neurotherapeutics. 2024; 21(1):e00292. https://doi.org/10.1016/j.neurot.2023.10.002 PMid:38241161 PMCid:PMC10903104
9. Fan T, Peng J, Liang H, Chen W, Wang J, Xu R. Potential common pathogenesis of several neurodegenerative diseases. Neural Regen Res. 2026; 21(3):972-988. https://doi.org/10.4103/NRR.NRR-D-24-01054 PMid:40522761 PMCid:PMC12296512
10. Șerban M, Toader C, Covache-Busuioc RA. The redox revolution in brain medicine: Targeting oxidative stress with AI, multi-omics and mitochondrial therapies for the precision eradication of neurodegeneration. Int J Mol Sci. 2025; 26(15):7498. https://doi.org/10.3390/ijms26157498 PMid:40806624 PMCid:PMC12347410
11. Pettas S, Karagianni K, Kanata E, Chatziefstathiou A, Christoudia N, Xanthopoulos K, *et al*. Profiling microglia through single-cell RNA sequencing over the course of development, aging, and disease. Cells. 2022; 11(15):2383. https://doi.org/10.3390/cells11152383 PMid:35954228 PMCid:PMC9368511
12. Chen C, Qin H, Tan J, Hu Z, Zeng L. The role of ubiquitin-proteasome pathway and autophagy-lysosome pathway in cerebral ischemia. Oxid Med Cell Longev. 2020; 2020:1-12. https://doi.org/10.1155/2020/5457049 PMid:32411332 PMCid:PMC7204103
13. Yassin LK, Skrabulyte-Barbulescu J, Alshamsi SH, Saeed S, Alkuwaiti SH, Almazrouei S, *et al*. The microbiota-gut-brain axis in mental and neurodegenerative disorders: Opportunities for prevention and intervention. Front Aging Neurosci. 2025; 17. https://doi.org/10.3389/fnagi.2025.1667448 PMid:41104042 PMCid:PMC12521449
14. Lanoiselée HM, Nicolas G, Wallon D, Rovelet-Lecrux A, Lacour M, Rousseau S, *et al*. APP, PSEN1, and PSEN2 mutations in early-ons*et al*zheimer disease: A genetic screening study of familial and sporadic cases. PLoS Med. 2017; 14(3):e1002270. https://doi.org/10.1371/journal.pmed.1002270 PMid:28350801 PMCid:PMC5370101
15. Kulcsárová K, Piel JHA, Schaeffer E. Environmental toxins in neurodegeneration - A narrative review. Neurol Res Pract. 2025; 7(1):93. https://doi.org/10.1186/s42466-025-00452-6 PMid:41250117 PMCid:PMC12625418
16. Jahabardeen A, Nirenjen S, Narayanan J, Chitra V. A review on the role of SNCA gene in neurodegenerative diseases. Cureus. 2024; 16(9):e69450. https://doi.org/10.7759/cureus.69450 PMid:39411638 PMCid:PMC11476641
17. Wilson DM, Cookson MR, Van Den Bosch L, Zetterberg H, Holtzman DM, Dewachter I. Hallmarks of neurodegenerative diseases. Cell. 2023; 186(4):693-714. https://doi.org/10.1016/j.cell.2022.12.032 PMid:36803602
18. Dugger BN, Dickson DW. Pathology of neurodegenerative diseases. Cold Spring Harb Perspect Biol. 2017; 9(7):a028035. https://doi.org/10.1101/cshperspect.a028035 PMid:28062563 PMCid:PMC5495060
19. Kesidou E, Theotokis P, Damianidou O, Boziki M, Konstantinidou N, Taloumtzis C, *et al*. CNS ageing in health and neurodegenerative disorders. J Clin Med. 2023; 12(6):2255. https://doi.org/10.3390/jcm12062255 PMid:36983254 PMCid:PMC10054919
20. Maldonado E, Morales-Pison S, Urbina F, Solari A. Aging hallmarks and the role of oxidative stress. Antioxidants. 2023; 12(3):651. https://doi.org/10.3390/antiox12030651 PMid:36978899 PMCid:PMC10044767
21. Jurcau MC, Jurcau A, Cristian A, Hogea VO, Diaconu RG, Nunkoo VS. Inflammaging and brain aging. Int J Mol Sci. 2024; 25(19):10535. https://doi.org/10.3390/ijms251910535 PMid:39408862 PMCid:PMC11476611
22. Korovesis D, Rubio-Tomás T, Tavernarakis N. Oxidative stress in age-related neurodegenerative diseases: An overview of recent tools and findings. Antioxidants. 2023; 12(1):131. https://doi.org/10.3390/antiox12010131 PMid:36670993 PMCid:PMC9854433
23. Swenson BL, Meyer CF, Bussian TJ, Baker DJ. Senescence in aging and disorders of the central nervous system. Transl Med Aging. 2019; 3:17-25. https://doi.org/10.1016/j.tma.2019.01.002

24. Dash UC, Bhol NK, Swain SK, Samal RR, Nayak PK, Raina V, *et al*. Oxidative stress and inflammation in the pathogenesis of neurological disorders: Mechanisms and implications. Acta Pharm Sin B. 2025; 15(1):15-34. https://doi.org/10.1016/j.apsb.2024.10.004 PMid:40041912 PMCid:PMC11873663
25. Fan J, Liu Q, Liu X, Gong M, Leong II, Tsang Y, *et al*. The effect of epigenetic aging on neurodegenerative diseases: A Mendelian randomization study. Front Endocrinol (Lausanne). 2024; 15. https://doi.org/10.3389/fendo.2024.1372518 PMid:38800486 PMCid:PMC11116635
26. Hou Y, Dan X, Babbar M, Wei Y, Hasselbalch SG, Croteau DL, *et al*. Ageing as a risk factor for neurodegenerative disease. Nat Rev Neurol. 2019; 15(10):565-581. https://doi.org/10.1038/s41582-019-0244-7 PMid:31501588
27. Palanisamy CP, Pei J, Alugoju P, Anthikapalli NVA, Jayaraman S, Veeraraghavan VP, *et al*. New strategies of neurodegenerative disease treatment with Extracellular Vesicles (EVs) derived from Mesenchymal Stem Cells (MSCs). Theranostics. 2023; 13(12):4138-4165. https://doi.org/10.7150/thno.83066 PMid:37554286 PMCid:PMC10405853
28. Cho H, Shukla S. Role of edaravone as a treatment option for patients with amyotrophic lateral sclerosis. Pharmaceuticals. 2020; 14(1):29. https://doi.org/10.3390/ph14010029 PMid:33396271 PMCid:PMC7823603
29. Zhang Y, Chen H, Li R, Sterling K, Song W. Amyloid β-based therapy for Alzheimer's Disease: Challenges, successes and future. Signal Transduct Target Ther. 2023; 8(1):248. https://doi.org/10.1038/s41392-023-01484-7 PMid:37386015 PMCid:PMC10310781
30. Wilkinson DG, Francis PT, Schwam E, Payne-Parrish J. Cholinesterase inhibitors used in the treatment of Alzheimer's Disease. Drugs Aging. 2004; 21(7):453-478. https://doi.org/10.2165/00002512-200421070-00004 PMid:15132713
31. Olivares D, Deshpande VK, Shi Y, Lahiri DK, Greig NH, Rogers JT, *et al*. N-Methyl D-Aspartate (NMDA) receptor antagonists and memantine treatment for Alzheimer's Disease, vascular dementia and Parkinson's Disease. Curr Alzheimer Res. 2012; 9(6):746-758. https://doi.org/10.2174/156720512801322564 PMid:21875407 PMCid:PMC5002349
32. Lee BJ, Egi Y, van Leyen K, Lo EH, Arai K. Edaravone, a free radical scavenger, protects components of the neurovascular unit against oxidative stress *in vitro*. Brain Res. 2010; 1307:22-27. https://doi.org/10.1016/j.brainres.2009.10.026 PMid:19840779 PMCid:PMC2797401
33. Lu S, Zhao Q, Guan Y, Sun Z, Li W, Guo S, *et al*. The communication mechanism of the gut-brain axis and its effect on central nervous system diseases: A systematic review. Biomed Pharmacoth. 2024; 178:117207. https://doi.org/10.1016/j.biopha.2024.117207 PMid:39067168
34. Kandpal M, Indari O, Baral B, Jakhmola S, Tiwari D, Bhandari V, *et al*. Dysbiosis of gut microbiota from the perspective of the gut-brain axis: Role in the provocation of neurological disorders. Metabolites. 2022; 12(11):1064. https://doi.org/10.3390/metabo12111064 PMid:36355147 PMCid:PMC9692419
35. Bauer PV, Hamr SC, Duca FA. Regulation of energy balance by a Gut-Brain Axis and involvement of the gut microbiota. Cellular Mole Life Sci. 2016; 73(4):737-755. https://doi.org/10.1007/s00018-015-2083-z PMid:26542800 PMCid:PMC11108299
36. Suganya K, Koo BS. Gut-Brain Axis: Role of gut microbiota on neurological disorders and how probiotics/prebiotics beneficially modulate microbial and immune pathways to improve brain functions. Int J Mol Sci. 2020; 21(20):7551. https://doi.org/10.3390/ijms21207551 PMid:33066156 PMCid:PMC7589356
37. de Vos WM, Tilg H, Van Hul M, Cani PD. Gut microbiome and health: mechanistic insights. Gut. 2022; 71(5):1020-1032. https://doi.org/10.1136/gutjnl-2021-326789 PMid:35105664 PMCid:PMC8995832
38. Taj T, Kaushik M, Islam A, Das J, Kumar B, Hussain MS, *et al*. Microbiota-brain interaction: The role of gut-derived proteins in addressing various neurological disorders including Parkinson's (PD) and Alzheimer's diseases (AD). Biomed Pharmacoth. 2025; 193:118861. https://doi.org/10.1016/j.biopha.2025.118861 PMid:41365116
39. Tlaskalová-Hogenová H, Štěpánková R, Kozáková H, Hudcovic T, Vannucci L, Tučková L, *et al*. The role of gut microbiota (commensal bacteria) and the mucosal barrier in the pathogenesis of inflammatory and autoimmune diseases and cancer: Contribution of germ-free and gnotobiotic animal models of human diseases. Cell Mol Immunol. 2011; 8(2):110-210. https://doi.org/10.1038/cmi.2010.67 PMid:21278760 PMCid:PMC4003137
40. Mittal R, Debs LH, Patel AP, Nguyen D, Patel K, O'Connor G, *et al*. Neurotransmitters: The critical modulators regulating Gut-Brain Axis. J Cell Physiol. 2017; 232(9):2359-2372. https://doi.org/10.1002/jcp.25518 PMid:27512962 PMCid:PMC5772764
41. Park KJ, Gao Y. Gut-Brain Axis and neurodegeneration: Mechanisms and therapeutic potentials. Front Neurosci. 2024; 18. https://doi.org/10.3389/fnins.2024.1481390 PMid:39513042 PMCid:PMC11541110
42. Berding K, Vlckova K, Marx W, Schellekens H, Stanton C, Clarke G, *et al*. Diet and the microbiota-Gut-Brain Axis: Sowing the seeds of good mental health. Adv Nut. 2021; 12(4):1239-1285. https://doi.org/10.1093/advances/nmaa181 PMid:33693453 PMCid:PMC8321864
43. Kechagia M, Basoulis D, Konstantopoulou S, Dimitriadi D, Gyftopoulou K, Skarmoutsou N, *et al*. Health benefits of probiotics: A review. ISRN Nutr. 2013; 2013:1-7. https://doi.org/10.5402/2013/481651 PMid:24959545 PMCid:PMC4045285

44. Saez-Lara MJ, Gomez-Llorente C, Plaza-Diaz J, Gil A. The role of probiotic lactic acid bacteria and bifidobacteria in the prevention and treatment of inflammatory bowel disease and other related diseases: A systematic review of randomized human clinical trials. Biomed Res Int. 2015; 2015:1-15. https://doi.org/10.1155/2015/505878 PMid:25793197 PMCid:PMC4352483
45. Alessandri G, van Sinderen D, Ventura M. The genus Bifidobacterium: From genomics to functionality of an important component of the mammalian gut microbiota. Comput Struct Biotechnol J. 2021; 19:1472-1487. https://doi.org/10.1016/j.csbj.2021.03.006 PMid:33777340 PMCid:PMC7979991
46. Shah AB, Baiseitova A, Zahoor M, Ahmad I, Ikram M, Bakhsh A, *et al*. Probiotic significance of Lactobacillus strains: A comprehensive review on health impacts, research gaps, and future prospects. Gut Microbes. 2024; 16(1). https://doi.org/10.1080/19490976.2024.2431643 PMid:39582101 PMCid:PMC11591481
47. Mendonça AA, Pinto-Neto W de P, da Paixão GA, Santos Dd, De Morais MA, De Souza RB. Journey of the probiotic bacteria: Survival of the fittest. Microorganisms. 2022; 11(1):95. https://doi.org/10.3390/microorganisms11010095 PMid:36677387 PMCid:PMC9861974
48. O'Callaghan A, van Sinderen D. Bifidobacteria and their role as members of the human gut microbiota. Front Microbiol. 2016: 15:7. https://doi.org/10.3389/fmicb.2016.00925
49. Markowiak P, Slizewska K. The role of probiotics, prebiotics and synbiotics in animal nutrition. Gut Pathog. 2018; 10(1):21. https://doi.org/10.1186/s13099-018-0250-0 PMid:29930711 PMCid:PMC5989473
50. Ma T, Shen X, Shi X, Sakandar HA, Quan K, Li Y, *et al*. Targeting gut microbiota and metabolism as the major probiotic mechanism - An evidence-based review. Trends Food Sci Technol. 2023; 138:178-198. https://doi.org/10.1016/j.tifs.2023.06.013
51. Markowiak-Kopeć P, Śliżewska K. The effect of probiotics on the production of short-chain fatty acids by human intestinal microbiome. Nutrients. 2020; 12(4):1107. https://doi.org/10.3390/nu12041107 PMid:32316181 PMCid:PMC7230973
52. Atasoy M, Álvarez Ordóñez A, Cenian A, Djukić-Vuković A, Lund PA, Ozogul F, *et al*. Exploitation of microbial activities at low pH to enhance planetary health. FEMS Microbiol Rev. 2024; 48(1). https://doi.org/10.1093/femsre/fuad062 PMid:37985709 PMCid:PMC10963064
53. Konieczna C, Słodziński M, Schmidt MT. Exopolysaccharides produced by *Lactobacillus rhamnosus* KL 53A and *Lactobacillus casei* Fyos affect their adhesion to enterocytes. Pol J Microbiol. 2018;67(3):273-281. https://doi.org/10.21307/pjm-2018-032 PMid:30451443 PMCid:PMC7256689
54. Latif A, Shehzad A, Niazi S, Zahid A, Ashraf W, Iqbal MW, *et al*. Probiotics: Mechanism of action, health benefits and their application in food industries. Front Microbiol. 2023; 14. https://doi.org/10.3389/fmicb.2023.1216674 PMid:37664108 PMCid:PMC10470842
55. Işık M, Köse F, Özbayer C, Budak Ö, Kaya RK, Erdoğan DG, *et al*. Promising antidepressant potential: The role of *Lactobacillus rhamnosus* GG in mental health and stress response. Probiotics Antimicrob Proteins. 2025; 17(6):5235-5265. https://doi.org/10.1007/s12602-025-10470-0 PMid:39962033 PMCid:PMC12634810
56. Gavzy SJ, Kensiski A, Lee ZL, Mongodin EF, Ma B, Bromberg JS. Bifidobacterium mechanisms of immune modulation and tolerance. Gut Microbes. 2023; 15(2). https://doi.org/10.1080/19490976.2023.2291164 PMid:38055306 PMCid:PMC10730214
57. Quansah M, David MA, Martins R, El-Omar E, Aliberti SM, Capunzo M, *et al*. The beneficial effects of lactobacillus strains on gut microbiome in Alzheimer's Disease: A systematic review. Healthcare. 2025; 13(1):74. https://doi.org/10.3390/healthcare13010074 PMid:39791681 PMCid:PMC11720007
58. O'Riordan KJ, Moloney GM, Keane L, Clarke G, Cryan JF. The gut microbiota-immune-brain axis: Therapeutic implications. Cell Rep Med. 2025; 6(3):101982. https://doi.org/10.1016/j.xcrm.2025.101982 PMid:40054458 PMCid:PMC11970326
59. Silva YP, Bernardi A, Frozza RL. The role of short-chain fatty acids from gut microbiota in Gut-Brain communication. Front Endocrinol (Lausanne). 2020; 11. https://doi.org/10.3389/fendo.2020.00025 PMid:32082260 PMCid:PMC7005631
60. Cheng J, Hu H, Ju Y, Liu J, Wang M, Liu B, *et al*. Gut microbiota-derived short-chain fatty acids and depression: Deep insight into biological mechanisms and potential applications. Gen Psychiatr. 2024; 37(1):e101374. https://doi.org/10.1136/gpsych-2023-101374 PMid:38390241 PMCid:PMC10882305
61. Zhu F, Yin S, Wang Y, Zhong Y, Ji Q, Wu J. Effects of probiotics on neurodegenerative disease-related symptoms and systemic inflammation: A systematic review. Int J Gen Med. 2024; 17:5941-5958. https://doi.org/10.2147/IJGM.S499406 PMid:39678681 PMCid:PMC11645901
62. Salman MK, Abuqwider J, Mauriello G. Anti-quorum sensing activity of probiotics: The mechanism and role in food and gut health. Microorganisms. 2023; 11(3):793. https://doi.org/10.3390/microorganisms11030793 PMid:36985366 PMCid:PMC10056907
63. Ostaff MJ, Stange EF, Wehkamp J. Antimicrobial peptides and gut microbiota in homeostasis and pathology. EMBO Mol Med. 2013; 5(10):1465-1483. https://doi.org/10.1002/emmm.201201773 PMid:24039130 PMCid:PMC3799574
64. Zhu X, Han Y, Du J, Liu R, Jin K, Yi W. Microbiota-gut-brain axis and the central nervous system. Oncotarget. 2017; 8(32):53829-53838. https://doi.org/10.18632/oncotarget.17754 PMid:28881854 PMCid:PMC5581153

65. Zhu X, Han Y, Du J, Liu R, Jin K, Yi W. Microbiota-gut-brain axis and the central nervous system. Oncotarget. 2017; 8(32):53829-53838. https://doi.org/10.18632/oncotarget.17754 PMid:28881854 PMCid:PMC5581153
66. Nie T, You L, Tang F, Duan Y, Nepovimova E, Kuca K, *et al*. Microbiota-gut-brain axis in age-related neurodegenerative diseases. Curr Neuropharmacol. 2025; 23(5):524-546. https://doi.org/10.2174/1570159X23666241101093436 PMid:39501955 PMCid:PMC12163470
67. Davares AKL, Arsene MMJ, Viktorovna PI, Vyacheslavovna YN, Vladimirovna ZA, Aleksandrovna VE, *et al*. Quorum-sensing inhibitors from probiotics as a strategy to combat bacterial cell-to-cell communication involved in food spoilage and food safety. Fermentation. 2022; 8(12):711. https://doi.org/10.3390/fermentation8120711
68. Lu S, Zhao Q, Guan Y, Sun Z, Li W, Guo S, *et al*. The communication mechanism of the gut-brain axis and its effect on central nervous system diseases: A systematic review. Biomed Pharmacoth. 2024; 178:117207. https://doi.org/10.1016/j.biopha.2024.117207 PMid:39067168
69. Mazziotta C, Tognon M, Martini F, Torreggiani E, Rotondo JC. Probiotics mechanism of action on immune cells and beneficial effects on human health. Cells. 2023; 12(1):184. https://doi.org/10.3390/cells12010184 PMid:36611977 PMCid:PMC9818925
70. Savulescu-Fiedler I, Benea SN, Căruntu C, Nancoff AS, Homentcovschi C, Bucurica S. Rewiring the brain through the gut: Insights into microbiota-nervous system interactions. Curr Issues Mol Biol. 2025; 47(7):489. https://doi.org/10.3390/cimb47070489 PMid:40728958 PMCid:PMC12293201
71. Wadan AHS, El-Aziz MKA, Ellakwa DES. The microbiota-gut-brain-axis theory: Role of Gut Microbiota Modulators (GMMs) in gastrointestinal, neurological, and mental health disorders. Naunyn Schmiedebergs Arch Pharmacol. 2025; 398(10):13397-13426. https://doi.org/10.1007/s00210-025-04155-2 PMid:40323507 PMCid:PMC12511254
72. Ansari F, Neshat M, Pourjafar H, Jafari SM, Samakkhah SA, Mirzakhani E. The role of probiotics and prebiotics in modulating of the gut-brain axis. Front Nutr. 2023; 10. https://doi.org/10.3389/fnut.2023.1173660 PMid:37565035 PMCid:PMC10410452
73. Nireeksha, Maniangat Luke A, Kumari N S, Hegde MN, Hegde NN. Metabolic interplay of SCFA's in the gut and oral microbiome: A link to health and disease. Front Oral Heal. 2025; 6. https://doi.org/10.3389/froh.2025.1646382 PMid:40927228 PMCid:PMC12414996
74. Wachamo S, Gaultier A. The emerging role of microbiota derived SCFAs in neurodegenerative disorders. Brain Behav Immun Health. 2025; 46:101012. https://doi.org/10.1016/j.bbih.2025.101012 PMid:40502529 PMCid:PMC12152874
75. Venegas DP, De la Fuente MK, Landskron G, González MJ, Quera R, Dijkstra G, *et al*. Short Chain Fatty Acids (SCFAs)-Mediated gut epithelial and immune regulation and its relevance for inflammatory bowel diseases. Front Immunol. 2019; 10. https://doi.org/10.3389/fimmu.2019.01486 PMid:31316522 PMCid:PMC6611342
76. Abouelela ME, Helmy YA. Next-generation probiotics as novel therapeutics for improving human health: Current trends and future perspectives. Microorganisms. 2024; 12(3):430. https://doi.org/10.3390/microorganisms12030430 PMid:38543481 PMCid:PMC10972033
77. Yu W, Sun S, Yan Y, Zhou H, Liu Z, Fu Q. The role of short-chain fatty acid in metabolic syndrome and its complications: Focusing on immunity and inflammation. Front Immunol. 2025; 16. https://doi.org/10.3389/fimmu.2025.1519925 PMid:39991152 PMCid:PMC11842938
78. Davie JR. Inhibition of histone deacetylase activity by butyrate. J Nutr. 2003; 133(7):2485S-2493S. https://doi.org/10.1093/jn/133.7.2485S PMid:12840228
79. Colonna M, Butovsky O. Microglia function in the central nervous system during health and neurodegeneration. Annu Rev Immunol. 2017; 35(1):441-468. https://doi.org/10.1146/annurev-immunol-051116-052358 PMid:28226226 PMCid:PMC8167938
80. Pant K, Venugopal SK, Pisarello MJL, Gradilone SA. The role of gut microbiome-derived short-chain fatty acid butyrate in hepatobiliary diseases. Am J Pathol. 2023; 193(10):1455-1467. https://doi.org/10.1016/j.ajpath.2023.06.007 PMid:37422149 PMCid:PMC10548274
81. Pant K, Venugopal SK, Lorenzo Pisarello MJ, Gradilone SA. The role of gut microbiome-derived short-chain fatty acid butyrate in hepatobiliary diseases. Am J Pathol. 2023; 193(10):1455-1467. https://doi.org/10.1016/j.ajpath.2023.06.007 PMid:37422149 PMCid:PMC10548274
82. Hoffmann A, Kleniewska P, Pawliczak R. Antioxidative activity of probiotics. Arch Med Sci. 2021; 17(3):792-804. https://doi.org/10.5114/aoms.2019.89894 PMid:34025850 PMCid:PMC8130477

Author Contribution

Conceptualisation, C.M.N. and A.P.; methodology, C.M.N. and A.P.; software, C.M.N.; validation, C.M.N., A.P., and C.S.; formal analysis, C.M.N. and A.P.; investigation, C.M.N., A.P., B.S.K.S., and S.C.M.R.; resources, C.S. and R.P.M.L.; data curation, C.M.N., A.P., B.S.K.S., and S.C.M.R.; writing–original draft preparation, C.M.N. .; writing review and editing, C.S., R.P.M.L., and S.P.K.; visualisation, C.M.N., A.P., and B.S.K.S.; supervision, C.S., B.S.K.S. and A.P. All authors have read and agreed to the published version of the manuscript.

