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Review

Brain modulation by the gut microbiota: From disease to therapy

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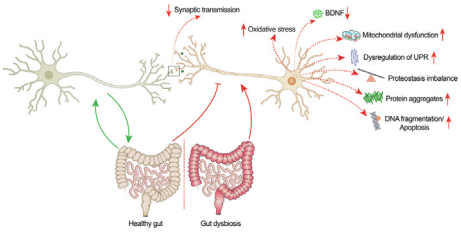
HIGHLIGHTS

- Gut microbiota (GM) and brain have a bidirectional relationship.
- A healthy GM composition promotes brain growth and protection by bidirectional gut-microbiota brain axis.
- GM alteration promotes age-related neurodegenerative disorders (NDDs).
- Selective GM population could be selective biomarkers for early diagnosis in NDDs.
- Clinical interventions based on GM modification and GM-derived metabolites in NDDs.

GRAPHICAL ABSTRACT



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ABSTRACT

Background: The gut microbiota (GM) and brain are strongly associated, which significantly affects neuronal development and disorders. GM-derived metabolites modulate neuronal function and influence many cascades in age-related neurodegenerative disorders (NDDs). Because of the dual role of GM in neuroprotection and neurodegeneration, understanding the balance between beneficial and harmful bacteria is crucial for applying this approach to clinical therapies.

Aim of the review: This review briefly discusses the role of the gut-brain relationship in promoting brain and cognitive function. Although a healthy gut environment is helpful for brain function, gut dysbiosis can disrupt the brain's environment and create a vicious cycle of degenerative cascades. The ways in which the GM population can affect brain function and the development of neurodegeneration are also discussed. In the treatment and management of NDDs, the beneficial effects of methods targeting GM populations and their derivatives, including probiotics, prebiotics, and fecal microbial transplantation (FMT) are also highlighted.

Key scientific concept of the review: In this review, we aimed to provide a deeper understanding of the mechanisms of the gut microbe-brain relationship and their twin roles in neurodegeneration progression and therapeutic applications. Here, we attempted to highlight the different pathways connecting the brain and gut, together with the role of GM in neuroprotection and neuronal development. Furthermore, potential roles of GM metabolites in the pathogenesis of brain disorders and in strategies for its treatment are also investigated. By analyzing existing *in vitro*, *in vivo* and clinical studies, this review attempts to identify new and promising therapeutic strategies for central nervous system (CNS)

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disorders. As the connection between the gut microbe-brain relationship and responses to NDD treatments is less studied, this review will provide new insights into the global mechanisms of GM modulation in disease progression, and identify potential future perspectives for developing new therapies to treat NDDs.

Contents

Introduction

Microorganisms in the human digestive system have a density of more than 1012 cells/g, and form a complex ecological community known as the gut microbiome [1–2]. Accumulating evidence from clinical and pre-clinical research suggests the involvement of the gut microbiome (GM) in host physiology and pathology, and many studies have pointed to its regulation of the central nervous system (CNS) [3]. Although the beneficial effects of GM on CNS development have been documented since the early 2000 [4], the association between compositional changes and neurodegeneration, has recently gained significant attention [5].

Communication between the gut and brain occurs via the gut–brain axis (GBA), a two-way signaling pathway connecting the gastrointestinal (GI) tract and CNS [6]; this consists of the immune system, vagus nerve, several neurotransmitters, hypothalamic–pituitary–adrenal axis (HPA), bacterial metabolites, and their byproducts [4,7–9]. Through the GBA, the brain controls gut movement, intestinal secretion, and sensory functions, and signals from the gut can also affect brain function [10]. Surprisingly, the roles of microorganisms in human health and the neuronal system begin during the neonatal stage, just after birth. However, many supporting factors such as food habits, environment, age, mode of birth, and stress affect the natural GM [11]. As a result, their beneficial action varies depending on age and hence influences many age-related diseases. The optimal functioning of GBA depends on the GM composition. Changes in GM composition are defined as dysbiosis, meaning an imbalance in microbial growth, which can occur when healthy microbiota and production of their metabolites is reduced, or when overgrowth of harmful microbiota occurs and production of their metabolites is increased [12–13]. This also includes the unavoidable spread of microbes, the beneficial effects of symbionts/commensals for pathogens, and changes in their metabolic activity [12]. Chronic stress, acute/chronic infections, antibiotic use, dietary changes, genetics, and increased age all contribute to altered microbiota [13]. However, the exact mechanism underlying the effects of gut dysbiosis remains unknown.

Notably, the progression of various CNS disorders is influenced by numerous factors, including environmental, diet, lifestyle, aging, genetics, and xenobiotic exposure, and all of these are also frequently encountered in cases of gut dysbiosis. Compelling evidence has shown that the GM interacts with these variables and functions as an intermediary between the host and the environment in various CNS disorders [5,14], from neurodegeneration to neuropsychiatric disorders, such as multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), Huntington's disease (HD), Parkinson's disease (PD), Alzheimer's disease (AD), frontotemporal lobar degeneration, autism, anxiety, and depression [15–16]. In contrast, a healthy gut has been reported to play a neuroprotective role in various neurodegenerative diseases (NDDs). Supplementation with probiotics and other therapeutics and maintaining a healthy gut improves memory function and helps prevent neurodegeneration [17].

As the precise mechanism whereby the GM modulates the brain remains elusive, in this review we attempted to combine existing knowledge of the pathways between the brain and GM in relation to the role of the GM in different neurodegenerative diseases. We also discuss the effects of modulating the GM and its metabolites in terms of neuronal development, and whether this can acts as a neurotropic or neuroprotective factor. The potential therapeutic applications of GM in the clinical field are also highlighted.

An overview of gut–microbiota–brain (GMB) interaction

The GMB interactions are complex and biochemically based. The microbiome utilizes a platform offered by the bidirectional GMB axis (GMBA) [18]; this is crucial for the natural functioning and homeostasis of both brain and gut [19]. Thus, modulation of this communication can cause many disorders related to behavioral [20] or neuronal functioning [21–22], as well as disrupt normal gut health [23–24].

GMBA includes two important signaling barriers, namely the intestinal barrier and blood–brain barrier (BBB) [25]; these control and integrate signaling pathways that operate bidirectionally. Because the signals that reach the gut from the brain vary considerably depending on the host condition, many factors such as GM composition, stress, and inflammation affect the permeability of both the gut barrier and BBB.

The intestinal barrier comprises a mucus layer and monolayer of epithelial cells interconnected by tight junctions. The microbiota inside these layers can act on the CNS and enteric nervous systems (ENS) through anatomic and metabolic pathways to communicate across the GMBA. The GM significantly influences the ENS, which in turn sends signals to the CNS [26], thus facilitating communication with the neuronal system. As a result, the GM can influence both CNS development and homeostasis through immunological, circulatory, and neurological pathways [27]. Evidence indicates that the GM modulates the CNS predominantly via neuroimmune and neuroendocrine processes, and often via the vagus nerve (VN) [28]. While intrinsic and extrinsic factors regulate the maturation and development of the CNS [29], GM can affect this process through numerous mechanisms, including the brain–neuroanatomical pathway, neuroendocrine–hypothalamic–pituitary–adrenal (HPA) axis [30], gut immune system [31], gut metabolism system, BBB, and intestinal mucosal barrier [32]. In brief, the neuroendocrine system responds to chemical and mechanical stimuli by releasing different metabolites, which can travel through the bloodstream to specific regions of the CNS or operate locally to stimulate the brain by stimulating afferent vagal terminals in the liver or GI tract. The HPA axis is a neuroendocrine pathway related to the stress response that regulates the release of several signaling molecules, including glucocorticoids, mineralocorticoids, and catecholamines. These signaling molecules determine GM composition; conversely, GM can activate the HPA axis by promoting increased intestinal barrier permeability or a GM-mediated pro-inflammatory state [33].

Microbes in the gut use specific signaling molecules to communicate with the ENS [34]. These include short-chain fatty acids (SCFAs), neuroactive molecules such as tryptophan metabolites [25],serotonin, GABA, catecholamines, free metabolites [35], microbe-induced cytokines, and secondary bile acids (2BAs) [36]. The most widely studied SCFAs are propionic acid, butyric acid, and acetic acid, which are present in the colon with approximate molar ratios of 20:20:60 [37], and are responsible for modulating various signaling pathways both inside and outside the GI tract. In the neurochemical pathway, propionate and butyrate modulate the levels of noradrenaline, adrenaline, dopamine biosynthesizing enzyme TH, and serotonin synthesizing enzyme TPH1 [38–40]. In the intestine, the epithelial cells and GM use SCFAs aslocal energy sources [41–43], which also stimulates the enteroendocrine cells to release various neuropeptides and hormones, such as peptide YY and glucagon-like peptide 1 (GLP-1) [44]. SCFAs play a crucial role in activating different G protein-coupled receptors (GPCR) in intestinal immune cells, adipocytes, and epithelial cells, thus affecting many signalling pathways [45], these receptors include GPR41-GPR43, GPR109, and Olfr78 [46]. Among all GPCRs, GPR43 is involved in intestinal inflammation, neutrophil migration, and release of different cytokines [47]. SCFAs are vital for CNS development and microglial function [48].

Other metabolites, such as GM-derived peptidoglycan, can stimulate innate immunity by activating Nod1 [49], and dipeptides or tripeptides maintain neurotransmitter levels through TLRs [50] and HSPs signaling through N-formyl methionyl–leucyl–phenylala nine [51–53]. Under stress or with a high-fat diet (HFD), bacterial lipopolysaccharide, which is produced in the outer membrane (gram-negative bacteria), can pass through the intestinal epithelial barrier and activate the HPA and immune response by modulating TLR4 [54]. In the hypothalamus, the expression of corticotropin-releasing factor (CRF), BDNF, NMDAR2 subtype, and 5-HT1a receptor is regulated by GM, which ultimately regulates HPA axis function. The signaling molecules produced by luminal microorganisms interact with the host cell receptors, and these circulating metabolites are theorized to provide support for a complex GMBA connection [55]. Bacterial metabolites also regulate signaling and neurotrophic factors, such as BDNF, NGF, and glial cell line-derived neurotrophic factor (GDNF). These molecules maintain neuronal and synaptic growth, survival, and differentiation and modulate memory and learning functions in various NDDs [56–58]. Receptors that control appetite and satiety have been found in the gut endocrine system, which is activated mainly by SCFAs [59], implying that they are also involved in host appetite management [60] and thus play a crucial role in host eating behavior.

Outside of the neuroendocrine mechanism, several anatomical mechanisms play a significant role in delivering signals across the BGM axis. These include the autonomic nervous system (ANS) and the VN, which transmit information from the luminal environment to the CNS. Communication can also occur across a bidirectional pathway including the ENS, enteroglial cells, ANS, and VN in the spinal cord [32]. The microbiota modifies ENS activity by producing local neurotransmitter molecules, such as GABA, serotonin, melatonin, histamine, and acetylcholine [61–62], and by converting catecholamines to their active forms in the gut lumen. As a result, ENS nerve fibers can detect microbiome signals via diffusion of bacterial substances and metabolites. Consequent to gut chemo-sensing, enteroendocrine cells (EECs) can interact with vagal afferents [63], affecting them in either direct or indirect ways. Indirect interaction occurs through the release of hormones from the gut, such as peptide YY, GLP-1, and cholecystokinin (CCK), which target the brain via vagal afferents [64]. Conversely, direct interaction is mediated through the release of 5-HT, which activates 5-HT3 receptors on the vagal afferent fibers [65]. Again, the VN can directly detect microbiota signals; similar to SCFAs generated by bacteria and depending on the component, they trigger vagal afferent fibers via varying mechanisms [66]. Thus, the VN plays a significant role in the GMBA.

Gut microbiota (GM) promotes brain health

On brain development

The strong and essential association between GM and brain development begins at birth and persists throughout life [67]. Because of the dynamic bidirectional relationship of the GMBA, many metabolites derived from the GM act as trophic factors for the development and nourishment of neurons, which eventually help protect against aging brain conditions and improve many

behavioral conditions. Therefore, the GM has also been called the "second brain" [3]. Dietary habits and microbiota composition are known to modulate neurogenesis [68]. As the proper function of GM depends on food intake and the metabolites synthesized from the microbiota largely depend on the food and microbial composition in the intestine, a healthy GM composition is essential for neurotropism [69]. Neurogenesis is vital for brain function, and reduced adult hippocampal neurogenesis is correlated with dementia, anxiety, and other psychiatric behaviors [70].

Kawase *et al.* showed differing hippocampal neurochemicals and amino acids between germ-free (GF) and specific pathogen-free (SPF) mice. GF mice had lower concentrations of essential amino acids such as L-Phe, L-Arg, L-Ala, L-Ile, L-Leu, L-Gln, L-Val, and GABA, compared to SPF mice [71]. Further reports have shown an increase in the genes and markers of reactive microglia and synaptic density in the hippocampus of GF mice [72]. This observation suggests that as early as the postnatal neurodevelopmental stage, the overexpression of synaptic genes and absence of reactive, functioning microglia in GF mice may cause inefficient pruning, possibly resulting in defective or non-functional synaptic connections [72]. The same study also concluded that *Bifidobacteria* establish functional neural circuits in the hippocampus.

GM also regulates neurogenesis, a mitochondria-dependent process that allows the adult mammalian brain to produce new neurons [73–74]. In adult neurogenesis, neuronal cells differentiate from neural stem cells (NSCs), which are highly sensitive to mitochondrial function [75]. Interestingly, bacterial SCFAs are recognized as essential modulators of mitochondrial function [76]. Hence, GM and neurogenesis may be linked via SCFAs, such as propionate and butyrate, which influence mitochondrial biogenesis and mass in NSCs and increase mtDNA copy number and Tfam expression [68]. Furthermore, studies have shown that SCFAs may stimulate mitochondrial biogenesis [68,77], indicating that they may be involved in neurogenesis. In addition to mitochondrial modulation, non-toxic levels of reactive oxygen species (ROS) can assist in the physiological signaling for neuronal differentiation of NSCs [74] and promote the transcription of pro-neural genes [78]. SCFAs enhance the accumulation of mitochondrial ROS and aid in the differentiation of NSCs [68].

BDNF modulates activity-dependent synaptic plasticity, neuronal survival, differentiation, and growth [79]. GF mice showed exaggerated stress and decreased expression of hippocampal and cortical BDNF. This condition was reversed by oral administration of *Bifidobacterium infantis* or fecal transplant of the SPF mice microbiome, successfully restoring the stress response [80]. Studies have shown that the hippocampus, amygdala, and cingulate cortex of GF mice exhibit less BDNF mRNA than those of SPF mice [81]. The cAMP-response element-binding protein (CREB) signaling pathway regulates genes related to neuronal differentiation, synaptic plasticity, learning, and memory. Zeng *et al.* revealed by microarray analysis that the absence of GM from birth was associated with reduced hippocampal CREB, but increased phosphorylated CREB. This phenomenon can be reversed by microbiota colonization during adolescence [82].

The role of the GM in neurotransmitter production is another significant aspect of neurotropism. Many microbiota help synthesize and regulate different neurotransmitters [83]. Catecholamines (CA) are neurotransmitters such as norepinephrine (NE) and dopamine (DA); these regulate body functions, including cognitive function, mood, and gut motility. In particular, DA is a crucial controller of cognitive functions such as decision-making, motivation, memory, attention, and reward [84]. Butyrogenic microbes prevent dopaminergic neuron loss and maintain optimal DA concentrations [85]. Sodium butyrate reduces dopaminergic neuron degeneration, improves locomotor impairment, and increases DA levels [86]. In addition, pathogenic *Escherichia coli* O157:H7 (EHEC) has an increased growth rate in the presence of DA and NE [87]. GABA is an inhibitory neurotransmitter involved in neuronal and behavioral functions. The microbiota influences circulating GABA levels, as GF animals have considerably low luminal and serum GABA [88]. One study showed that oral supplementation with *Bifidobacterium breve* NCIMB8807 pESHgadB, a strain engineered to produce GABA via overexpression of glutamate decarboxylase B, was beneficial to the host due to the synthesis of GABA [89]. This demonstrates that the GM plays a vital role in host metabolism by synthesizing different neurotropic substances that can improve host neurogenesis and behavioral patterns [90].

On promoting neuroprotection

Oxidative stress due to excess reactive oxygen species (ROS) is one of the most common causes of NDDs and CNS disorders. Considering the study of GMBA and GM metabolites, it is apparent that GM has a very close connection with the CNS and hence plays a role in different neurological disorders, which has been proven by a large number of studies as well as in pre-clinical models [91–95]. GM modulation has been shown to reduce brain oxidative stress through different metabolites, such as absorbable vitamins, polyphenols, neurotropic factors, antioxidants, and SCFAs, as these maintain exogenous and endogenous ROS [91,93]. Excessive ROS causes irreversible damage to cells, and neurons are particularly sensitive to low ROS levels [96]. However, ROS is essential in the neuronal system for long-term potentiation in the hippocampus [97], synaptic plasticity [98], and learning and memory function [98], suggesting that optimal ROS levels are crucial for proper neuronal functioning.

GM helps combat oxidative damage by secreting essential metabolites via multistep biosynthetic pathways, including vitamins, proteins, and antioxidants [99]. For example, GM converts bile acid to secondary bile acid, which exerts a neuroprotective effect in stroke and ALS [100] by decreasing oxidative stress [101] and improving demyelination [102].

Apart from interacting with host metabolites, the intestinal microbiome interacts with dietary molecules, such as fibers and polyphenols, and metabolizes them into more bioactive and bioavailable metabolites. Curcumin, a naturally occurring polyphenol compound found mainly in turmeric, is well-known for its neuroprotective action against different NDDs [103]. GM enzymes transform curcumin in the intestine [104–105]. It has been reported that curcumin exerts poor bioavailability, but the majority of its pharmacological effects can be attributed to its interaction with GM [96,105]. Curcumin modulates some GM species, whereas other GM species transform curcumin into various catabolites, namely 1-(4-hydroxy-3-methoxyphenyl)-2-propanol, dihydroferulic acid (DFA), and tetrahydrocurcumin (THC) [106]. THC is the most studied curcumin derivative for neuroprotection, and protects against oxidative stress, upregulates the Nrf2 pathway [107], inhibits mitochondrial damage, increases autophagy, and reduces apoptosis after traumatic brain injury [108]. THC is also reported to be effective in treating PD by blocking monoamine oxidase activity and enhancing dopamine (DA) levels, indicating that this metabolite may help prevent neurodegeneration [109–110].

Many studies have focused on the neuroprotective role of GM in different NDDs. A recent study found that GM protected against PD in a 6-hydroxydopamine-induced PD mouse model, and that osteocalcin increases the production of the microbial metabolite propionate, which protects against PD [111]. The *Lactobacillus buchneri* strain (KU200793), isolated from Korean fermented food, was reported to protect SH-SY5Y cells against 1-methyl-4-phenylpyridinium (MPP^+) via its antioxidant activity, indicating its neuroprotective properties [112]. Similarly, exopolysaccharides, which are a common metabolite of *Lactobacillus delbrueckii* ssp. *bulgaricus B3* and *Lactobacillus plantarum* GD2, were reported to

protect against $A\beta_{1-42}$-induced cell death in the same cell line [113]. Supplementation with heat-killed *Ruminococcus albus* strains also showed antioxidant activity by suppressing ROS in mouse models and neuroblastoma cell lines [114].

Furthermore, in H_2O_2-treated SH-SY5Y cells, this strain also increased glutathione (GSH) and superoxide dismutase (SOD) levels. A similar effect was observed in animal models treated with sodium arsenate [114]. *Parabacteroides distasonis* and *Megasphaera massiliensis* strains of GM showed good anti-oxidant activity in different brain cell lines; thus, they exhibited neuroprotective effects against oxidative stress. Furthermore, *Megasphaera massiliensis* were associated with reduced pro-inflammatory IL-6 secretion [115].

Other metabolites, such as sodium butyrate, have also been reported to exert a prominent histone deacetylase (HDACs) inhibitory effect, producing beneficial outcomes, such as improved locomotor symptoms and increased striatal dopamine in neurotoxicity-induced rats [116]. HDACs are a class of enzymes that modulate gene expression by eliminating acetyl groups from histones. The HDAC inhibitory activity of sodium butyrate reduces oxidative stress and has favorable effects on α-synuclein damage in PD models [117]. In addition, butyrate relaxes chromatin and inhibits heterochromatin formation, both of which play essential roles in epigenetic modulation. Inhibitors of HDACs have recently been employed as neuropharmacological drugs to reduce glioblastoma symptoms [118]. Furthermore, infusion of sodium butyrate suppresses neuronal apoptosis in mice [119]. These findings suggest that the inherent HDAC inhibitory activity of butyrate may have therapeutic applications in the treatment of neurological diseases.

Many studies have focused on applying GM modulation to various NDDs and, more importantly, how they can be used as neuroprotectors [111], which will be discussed in subsequent sections of this review. However, a critical consideration is that for the GM to exert a neuroprotective effect, the natural healthy composition of GM must be maintained by following a healthy lifestyle and regulating microbiome-related factors [120–121]. GM may aid in the breakdown of nutrients by host cells, and many of these substances have been implicated in neurological activity. The unique involvement of GM in influencing neuroimmune activities outside the GI tract may have a significant effect on the neurodegenerative process (Fig. 1).

Gut microbiota (GM) in the pathogenesis of neurodegenerative disorders (NDDs)

Alzheimer's disease (AD)

Concerns about AD, a leading cause of dementia, are increasing because it is a rising source of healthcare costs, morbidity, and death rates [122–124]. Neuroinflammation is a common phenomenon in AD, causing a progressive decline in cognitive and memory function [123]. The histopathological hallmarks of AD are the presence of intracellular neurofibrillary tangles (NFT) due to the microtubule-associated protein tau [125], and extracellular neurotic plaques resulting from the aggregation of amyloid-beta (Aβ) peptide in the neocortical area of the brain, medial temporal lobe, and most other part of the brain crucial to memory function [126–128]. The etiology of AD includes aging, oxidative stress [129], and environmental [130] and genetic factors [131]. Despite numerous proposed therapeutic solutions, some of which have elicited benefits, many studies and clinical trials have failed to identify an effective treatment or cure for AD [132–134].

The GM plays an essential role as a critical target for therapeutic interventions for AD [135–136]. Alteration of the GM population directly affects cognitive function, which is actively involved in AD pathogenesis and progression [137–139]. Accumulating evidence has shown that aging highly influences gut dysbiosis, and favors the growth of many pro-inflammatory bacteria such as *Bacteroides fragilis*, *Eubacterium hallii*, *Eubacterium rectale*, *Faecali bacterium prausnitzii*, and *Bacillus fragilis*, which in turn promote the development of NDDs [140]. Pro-inflammatory bacteria accumulate in the GI tract, resulting in increased GI tract permeability, decreased BBB integrity, and increased neuroinflammation [6]. BBB alteration due to dysbiosis allows the passage of Aβ peptide, pro-inflammatory factors, and immune cells from the periphery into the brain, altering brain homeostasis and composition of the cerebral milieu [141]. Cattaneo *et al.* found that infection with pro-inflammatory bacteria such as *Salmonella enterica* was typical in patients with amyloidosis, and the same results were observed in transgenic mice expressing human APP mutants. Moreover, this study also showed *Candida albicans* infection in transgenic *Caenorhabditis elegans,* expressing human $A\beta_{1-42}$ peptides [137]. Bacteria such as FapC (*Pseudomonas fluorescens*), TasA (*Bacillus subtilis*), curli (*E. coli*), phenol soluble modulins (*Staphylococcus aureus*), and CsgA (*S. Typhimurium*), are known to secrete amyloids, which are considered seeding factors for Aβ aggregation [17]. Besides bacteria-derived amyloids, other components, such as bacterial lipopolysaccharides (LPS), also influence AD progression. For example, inoculation of LPS derived from bacteria in the fourth ventricle of the brain of experimental animals was found to generate symptoms mimicking AD [17,142]. In contrast, altered production of SCFAs, including butyrate, valerate, propionate, and acetate, may promote cognitive decline through Aβ plaque deposition, microglial dysregulation, and metabolic dysfunction [143–144]. These SCFAs interfere with protein–protein interactions, which are necessary for converting Aβ peptides to neurotoxic Aβ aggregates [145].

Amyotrophic lateral sclerosis (ALS)

ALS, also called "motor neuron disease," is a disease that slowly damages the upper and lower motor neurons of the brain and spinal cord [146]. ALS is a multisystem NDD, with disease heterogeneity at the genetic and neuropathological levels [146–147]. Its clinical features include adult-onset focal muscle weakness and wasting, primarily in the limb muscles [148–149]. In some cases, the disease has a bulbar onset, and dysarthria, dysphagia, dysphonia, masseter weakness, and frontotemporal dementia with mild behavioral and cognitive changes may occur [150]. ALS is progressive, with a median survival of approximately 2–3 years after the onset of symptoms, although there is substantial variation in individual outcomes [149,151]. However, current neuroprotective therapies are considered inadequate. The cytoplasmic aggregation of TDP-43 protein, which is expressed by *TARDBP* and found in more than 95 % of ALS cases, is the main characteristic of the disease [152]. Several studies have found evidence that ALS is caused by genetic mutations (similar to those in C9ORF72 and SOD1) [153–156]. However, both monogenic and sporadic ALS result from multiple processes [157]. Although several studies suggest that ALS is associated with environmental risk factors, there is no evidence to suggest that individual risk factors to overall risk; nevertheless, these may influence the GM [158].

A recent study from 2022 investigated the bidirectional relationship between ALS and 98 genera of human GM. A higher relative abundance of OTU4607 *Sutterella* and *Lactobacillales* ORDER was associated with higher risk of ALS [159]. Studies using the $SOD1^{G93A}$ mouse model reported that low levels of *Butyrivibrio fibrisolvens*, which produces butyrate, are associated with ALS, and supplementation with butyrate improved intestinal barrier function and delayed death in comparison to untreated controls [160–161]. Using shotgun metagenomics, another study demon-

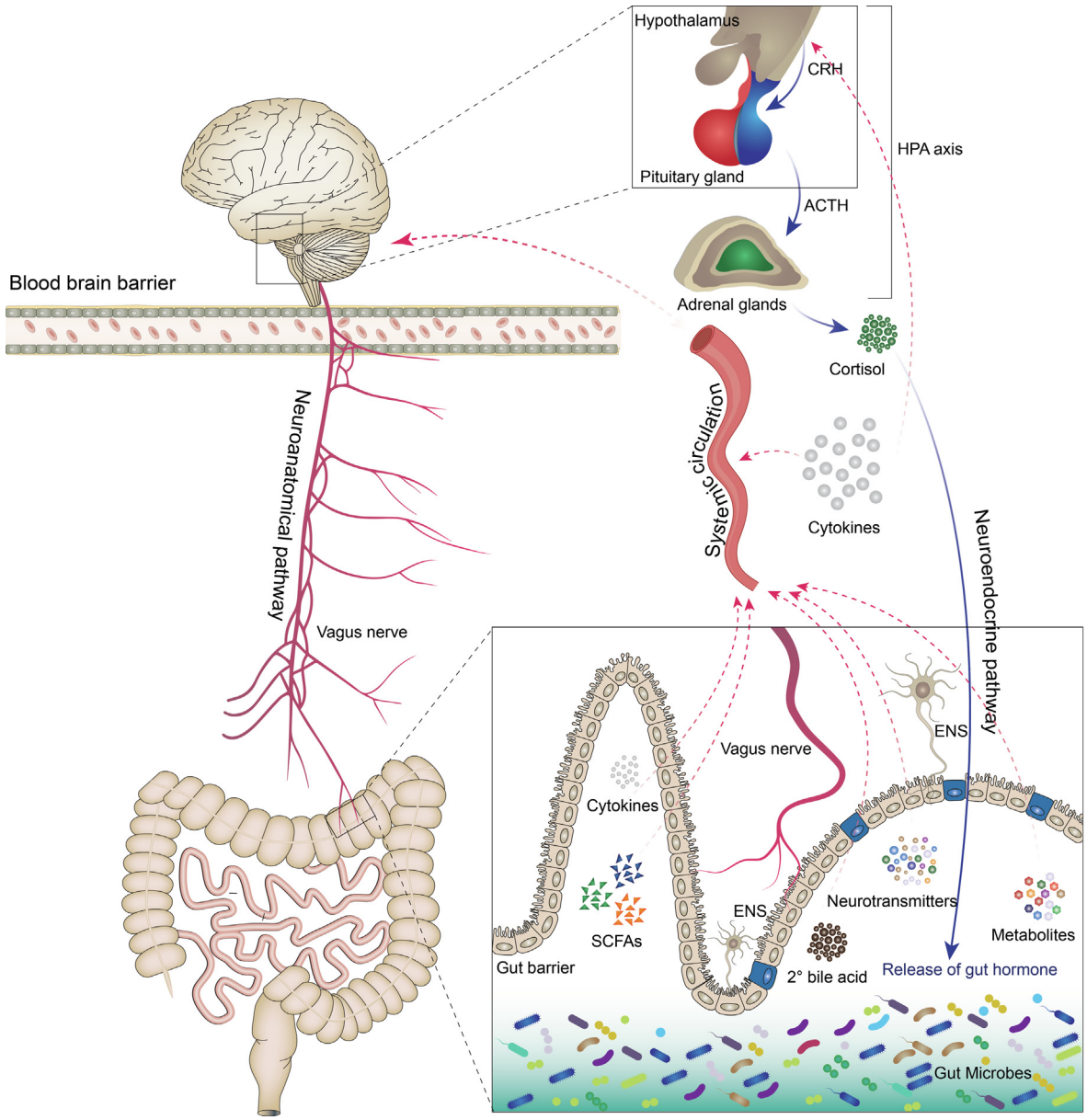

Fig. 1. A graphical representation of pathways involved in the bidirectional relationship between the brain and gut microorganisms. The communication routes between the brain and gut are regulated by multiple direct and indirect pathways. Evidence of the pathways presented in this illustration has been derived from several different animal studies. The gut-brain signaling pathways involve neuroanatomical, neuroendocrine, and immune pathways. The neuroanatomical pathway consists of the vagus nerve (afferent and efferent neurons) and the enteric nervous system. The hypothalamus–pituitary–adrenal (HPA) axis is part of the neuroendocrinal pathway. Several different inflammatory cytokines are involved in the immune pathway. In addition, several gut microbiota-derived metabolites, molecules, and neurotransmitters are involved in these pathways. The hypothalamus and pituitary glands modulate cortisol release from the adrenal gland, which regulates inflammatory cytokines and gut hormones. GM directly or indirectly modulate the release of various signaling molecules, short chain fatty acids (SCFAs such as acetate, butyrate, propionate), amino acids (tyramine, tryptophan), and neurotransmitters (γ-aminobutyric acid, dopamine, norepinephrine, serotonin) and convert bile acids into secondary bile acids. Other neuroactive bacterial metabolites that pass from the gut lumen through the gut barrier into the systemic circulation eventually enter the brain through the blood–brain barrier (BBB) to modulate brain function and cognitive behavior. The GM population and these metabolites also assist in maintaining the integrity of the gut barrier and BBB.

strated that alterations in microbial metabolites and microbiome composition occur in ALS [7]. Additionally, gut dysbiosis and GM changes were identified in the ALS SOD1^{G93A} mouse model, particularly in the pre-symptomatic stage (prior to immune cell activation/expansion, muscle atrophy, and motor impairment). Immunological responses and gut dysbiosis were also shown to be associated with ALS prognosis [162]. Blacher *et al.* showed that manipulating GM of SOD1^{G93A} through gut microbial supplements with *Parabacteroides distasonis* and *Ruminococcus torques* may increase the severity of ALS SOD1^{G93A}, whereas *Akkermansia muciniphila* species improved disease outcomes [7]. The authors demonstrated that bulk RNA sequencing of nicotinamide- or *Akkermansia muciniphila*-treated spinal cord tissue of SOD1^{G93A} mice altered oxidative stress and mitochondrial function [7].

As the most common genetic cause of ALS is the GGGGCC-repeat expansion of C9ORF72 [160], a recent study found that a proinflammatory phenotype was induced by the loss of C9ORF72 in a C9ORF72-null mouse model, which was eventually ameliorated when GM was reduced [163]. In addition, gut dysbiosis is associated with increased *E. coli* and *Enterobacteria* in ALS mice [160]. This observation proves that GM modulation is associated with ALS disease progression, mortality, and morbidity. Another study in the SOD1^{G93A} transgenic (SOD1-Tg) ALS mouse model provided evidence that *Akkermansia muciniphila* may influence ALS

disease progression by mediating changes in the NAM metabolic pathway, highlighting a probable causative association between GM and ALS progression [164].

Parkinson's disease (PD)

Various complications including tremors, muscle rigidity, bradykinesia, akinesia, postural instability, gait unsteadiness, hyposmia, mood disorders, dementia, depression, and GI tract abnormalities may result from PD, a neurodegenerative disorder that also affects the neuronal cytoskeleton. Other symptoms include [165–167]. The pathological consequences of PD include cytoplasmic inclusions of α-synuclein, known as Lewy bodies, which cause neuronal death and neurodegeneration, especially in nigrostriatal dopaminergic neurons [167–169]. However, apart from the substantia nigra, other extranigral pathologies also coexist [169–171]; specifically, studies suggest that the pathology of PD might progress primarily via the gut [170–176]. Almost 80 % of PD patients are reported to have GI symptoms preceding motor symptoms [175]. PD is associated with dysbiosis, as an abundance of *Enterobacteriaceae* is related to postural instability and gait disorders (PIGD) in PD. In addition, substantially lower levels of *Faecalibacterium, Prevotellaceae*, and *Lachnospiraceae* are seen in the stools of PD patients compared to controls [16,176], demonstrating that therapy targeting GM alteration could be a more effective method for preventing PD progression.

GM alteration may influence PD because the mesenteric organs (GI tract, spleen, and pancreas) account for almost half of the body's dopamine (DA) production [84,170,178–179]. GM is related to DA bioavailability [179], specifically *Bacillus* spp., which are gut microbes that produce DA [180]. V. A. Petrov, I. V. Saltykova, and colleagues reported reduced taxonomic diversity and considerable variation in the contents of 9 genera and 15 species of GM in PD patients [181]. The increased abundance of *Lactobacillaceae* and decreased abundance of *Prevotellaceae* may be associated with lower levels of gut hormones such as ghrelin [182], which may modulate nigrostriatal dopamine activity and restrict PD progression [183].

The primary component of Lewy bodies is α-synuclein; its aggregation in the lower brain stem is suggested to be initiated by intestinal pathways such as vagal innervations [184–186]. A mouse model of PD has shown that GM signals enhance α-synuclein-mediated motor impairment and brain degeneration [186]. In a transgenic (overexpressing) mouse model of PD, the GF condition resulted in lower levels of α-synuclein inclusion and activation of microglia, as well as reduced motor deficits. After administering SCFAs, which are the primary metabolites produced by the GM, all the main features of PD were restored [186]. This indicates that mediators modulated by GM are essential for PD prevention.

Multiple sclerosis (MS)

Multiple sclerosis (MS) is a chronic inflammatory demyelinating condition primarily affecting young and middle-aged individuals. Demyelination in MS is due to compromised selectivity of the BBB, which causes a wide range of inflammatory immune cells to enter the CNS. CD4 + T helper 1 (Th1) and T helper 17 (Th17) lymphocytes are crucial in initiating MS by generating several inflammatory cytokines [187]. Following neurodegeneration, progressive neuroinflammation leads to neuronal death in the peripheral nervous system (PNS) and CNS [185–187]. MS affects up to two million people globally and over 100,000 people in the UK [188–190]. Historically, MS has been regarded as a two-stage disease, with early inflammation leading to rebound and retarded neurodegeneration, resulting in non-relapse, that is, secondary and primary gradual MS [190–192]. Although MS is characterized by inflammation, demyelination, and axonal degeneration at the neuropathological level [192], its etiology is not clearly known. Environment and genetics appear to play key roles in disease progression. In addition, GM is a crucial factor for MS [193], as gut dysbiosis can impact the integrity of the BBB [194], modify the immune system of the host, and can affect the CNS due to GMBA [195]. One clinical study reported that patients with MS have a distinct type of GM population (lower abundance of *Bacteroidetes* and *Clostridium* compared to healthy individuals), indicating that gut dysbiosis occurs in MS [193]. This relationship with gut dysbiosis indicates that improving dysbiosis may impact MS progression.

Huntington disease (HD)

Inheritance of a trinucleotide (CAG) repeat expansion in the huntingtin (*HTT*) gene results in HD, a degenerative disorder that affects cognition, movement, and mental health [196]. Notably, CAG repeat frequency is are associated with HD onset and severity [197–199], resulting in a glutamine residue stretch at the *N*-terminus of HTT [199]. HTT is highly expressed in the brain and peripheral tissues such as the gut, heart, and skeletal muscles [200–202]. The striatum is the primary site of neuropathological changes, although the cerebellum, thalamus, and cerebellar cortex have also shown significant modifications [202–204]. As seen in several types of spinocerebellar ataxia, intracellular accumulation of HTT aggregates is the main hallmark of HD [204]. Generally, HD is characterized by psychiatric disturbances, dementia, movement disorders [186], progressive weight loss, altered metabolic homeostasis, skeletal muscle atrophy, and GI dysfunction [187–189]. GI disturbances, including nutrient deficiencies, gastritis, diarrhea, and weight loss [189–192], are clinical features of HD. The exact composition of GM in patients with HD has not yet been studied. However, many recent studies have reported a possible influence of gut dysbiosis [186–190], implying that the microbiota population and microbe-derived metabolites are modified in HD.

Stress-related disorders

Stressful lifestyles and events play key role in mental illness and the psychological state; however, non-specific progression or etiology leads to many hurdles when choosing a treatment strategy. Recent findings have suggested that GM and host brain functions influence host stress and emotional responses [205]. Moreover, several gut-regulated signalling pathways have been linked to the etiology of mood and anxiety disorders [206]. In addition, GM composition influences stress-related behaviors, anxiety, and depression [20]. For example, irritable bowel syndrome (IBS) and mood disorders have been shown to coincide, and both are related to intestinal dysbiosis [207]. Specific GM profiles have been linked to posttraumatic stress and depression, which are also connected to IBS [208].

Increased bacterial wall adherence and dysbiosis can be induced by chronic stress, whereas neuroendocrine systems can be altered by interactions between the microbiota and host [209]. The HPA axis is crucial for the stress response system, as it alters the GM by releasing glucocorticoids, cortisol, and corticosterone from the adrenal cortex.

The therapeutic applications of gut microbiota (GM) modulation in neurodegenerative disorders (NDDs)

Alzheimer's disease (AD)

Gu *et al.* examined the cognitive abilities of 8-month-old Tg-APP/PS1 transgenic (Tg) mice, and found that Tg mice had lower levels of SCFA-producing bacteria (such as *Blautia* and *Parasut-*

terella) and higher levels of gut dysbiosis than wild-type mice, whereas wild-type mice had more *Bacteroidetes*/*Firmicutes* than did APP/PS1 mice [210]. On the other hand, another study investigating $A\beta_{1-40}$ and $A\beta_{1-42}$ peptides suggested a dose-dependent effect of SCFA on protein aggregation. This indicated that a higher dose of valeric acid significantly reduced protein oligomerization. In addition, $A\beta_{1-40}$ oligomerization was similarly hindered by butyric acid and propionic acid, but to a lesser extent than by valeric acid [145]. Multiple studies have revealed that SCFAs produced by microorganisms can restore impaired microglial function in GF animals [48,211], where microglia aid in clearing protein aggregates, such as senile plaques [212]. Thus, maintaining a balance between the population of specific microbiota and their metabolites can protect against AD progression. Additionally, the link between these microbial populations and their metabolites and AD progression suggests that they may be biomarkers of AD. Several *in-vivo* studies have reported changes in microbial populations prior to the initiation of AD development. For example, *Rikenellaceae*, *Bacteroidaceae, Bifidobacteriaceae, Wolbachia, Erysipelotrichaceae, Verrucomicrobiaceae, Prevotellaceae, and Proteobacteriaceae* were detected well before any plaque deposition was detected in the brain [213].

As discussed earlier, neurotransmitters (acetylcholine, dopamine, and serotonin) generated by GM play a significant role in synaptogenesis, synaptic transmission, signaling, and neurotransmission. Low levels of GABA, NMDA, and BDNF, all of which are involved in cognitive behavior, have been observed in GF animals [214]. In addition, deficits in spatial and working memory in these animals indicate that microbes may play a role in regulating these aspects of cognitive function. Thus, reduced BDNF expression could also be a reliable marker of AD and gut dysbiosis [215]. Considering these factors, maintaining optimal GM composition homeostasis is a potential strategy for managing AD. Future studies should focus on targeting GM modulation as a preventive strategy for AD management.

Amyotrophic lateral sclerosis (ALS)

One previous study demonstrated reduced *Firmicutes*/*Bacteroidetes* ratios in patients with ALS [216]. Nicholson *et al.* found a lower relative abundance of anti-inflammatory SCFA-producing bacteria (especially *Eubacterium rectale* and *Roseburia intestinalis,* which predominantly produce butyrate) in the GI systems of patients with ALS than in healthy controls [217]. Another study showed that a higher *Firmicutes*/*Bacteroidetes* ratio and greater species diversity in GM are associated with an increased risk of death [218]. ALS samples were shown to have lower *Firmicutes*/*Bacteroidetes* ratios and higher species diversity than healthy controls in one of the most recent investigations [219]. In addition, GM-produced SCFAs and butyrate have been suggested as possible treatments to prevent ALS development [220–222]. As this evidence shows a bidirectional relationship between ALS and the GM, microbiome-targeted metabolite interventions could be future avenues for preventing ALS and its progression.

Parkinson's disease (PD)

Using gene sequencing of 16S ribosomal RNA, a recent study identified that levels of the SCFA-producing intestinal bacterial genera *Roseburia*, Lachnospiraceae, and *Faecalibacterium* are decreased in PD patients compared to healthy controls, but also showed an increase in mucin layer-degrading *Akkermansia* [222]. In a rotenone-induced Drosophila PD model, St. Laurent *et al.* demonstrated that administration of sodium butyrate significantly ameliorated locomotor impairment and early mortality [86]. In addition, the reduction of SCFA-producing GM is related to the progression of PD, as decreased SCFA is seen in patients' fecal samples [223–226], whereas increased propionate levels could render neuroprotection [226]. A recent study reported that oral administration of berberine in a mouse model significantly affects gut microbial components, increasing DA production, which also improves PD [227]. Koutzoumis *et al.* showed that GM modification by oral administration of nonabsorbable antibiotics in a rodent model of PD resulted in a significant reduction in 6-OHDA-induced dopaminergic neuron loss and improved motor deficits [228]. These studies indicate that modifying the GM substantially reverses PD development by attenuating dopaminergic neuron loss and increasing dopamine production.

SCFAs can cross the BBB and influence neuroinflammation by regulating serotonin (5-hydroxytryptamine, 5-HT) and dopamine production [229]. Using a mouse model of 6-OHDA-induced PD, a recent study demonstrated that increased gut microbial propionate production could trigger free fatty acid receptors (FFAR) in enteric neurons, providing neuroprotective effects [111]. In another recent study, MPTP-induced PD mice were treated using the fecal microbial transplantation technique; gut dysbiosis was subsequently restored to normal conditions, and a significant improvement in motor functions was also observed [230]. Substantial evidence exists to support the influence of GM on the success of PD management. New strategies should be implemented to target GM modulation and prevent the onset and progression of PD.

Huntington disease (HD)

As mentioned in earlier sections, the GMBA and altered GM profiles are reported to be involved in many other neuronal diseases, and can be targeted as a therapeutic approach. Many clinical studies have reported gut dysbiosis influences on HD progression. In a recent study, 33 HD patients and 33 healthy subjects underwent a clinical assessment. Fecal and blood samples were collected and DNA was extracted. The results indicated that certain GM components (*Actinobacteria*) are more abundant in HD patients than in healthy subjects [231]. Kong *et al.* showed a 16 s RNA sequencing genomic profile of the GM from a fecal sample of transgenic HD mice, which confirmed the presence of gut dysbiosis in the HD mouse model [232]. GM profiling by 16 s rRNA sequencing of R6/1 HD mice revealed a sex-specific effect on GM composition. In addition, this study showed that exercise effects the concentration of SCFA in male mouse models. Research has revealed that gut dysbiosis modulates the development and progression of HD symptoms [232]. R6/2 mice with HD had increased intestinal permeability and substantial alterations in the intestinal microbiota; specifically, *Bacteroidetes* ($Gram^-$) were more prevalent than *Firmicutes* ($Gram^+$) [233]. Other studies have shown that the absence of GM in GF mice adversely influences HD phenotypes by reducing callosal myelination and white matter plasticity in the prefrontal cortex, due to reduced gene expression of myelin-related proteins and reduced levels of mature oligodendrocytes [234]. All these studies reflect a common bridge between neuronal disorders and gut dysbiosis, and the role of the optimum concentration of beneficial microbiota on HD progression.

Multiple sclerosis (MS)

In a 2017 study, it was reported that probiotic administration comprising *Bifidobacterium bifidum, Lactobacillus casei, Lactobacillus acidophilus, and Lactobacillus fermentum* downregulated inflammatory gene expression, exerting a positive impact on several disease conditions [235]. GF-colonized animals with segmented filamentous bacteria (SFB)-induced Th 17 cells in the gut tend to experience MS induction [236]. Interestingly, microbial transplantation from patients with MS into GF mice led to initiation of severe symptoms of experimental autoimmune encephalomyelitis [237],

which is pathologically similar to MS. This suggests that GM modulation should be considered as a potential therapeutic strategy for MS. Another study reported that continuous administration of kanamycin, colistin, and vancomycin to mice sensitized against a myelin oligodendrocyte glycoprotein led to suppression of EAE progression, but this effect was absent in Vα14 natural killer T (iNKT) cell-deficient mice [238]. These findings indicate that the GM population significantly affects the development of autoimmune diseases such as MS, and future research should consider gut microbial modulation as a therapeutic strategy for MS.

Stress-related disorders

Administration of *Lactobacillus* spp. during the early stress period of stress-related disorders can stabilize basal corticosterone levels [239]. Current research suggests that interaction with this axis using different therapeutic approaches, such as probiotics, prebiotics, symbiotics, and probiotics, can lessen the effects of stress on GM. A healthy diet is vital for maintaining low-stress during gut dysbiosis. Mild stress can encourage unhealthy eating, leading to intestinal dysbiosis. The *Bacteroidetes* phylum was shown to be underrepresented in the microbiota of individuals with depression, and the *Lachnospiraceae* family was found to be associated with depression. Although the *Bacteroidetes* phylum was less common, specific operational taxonomic units linked with depression were identified as members of the *Bacteroidetes* phylum [240].

In the open field test, GF rats displayed stress- and anxiety-like behaviors. CRF mRNA expression in the hypothalamus was higher in GF rats than in SPF rats, but GR mRNA expression in the hippocampus was lower. In the frontal brain, hippocampus, and striatum, the dopaminergic turnover rate was lower in GF rats than that in SPF rats. Stress and anxiety-like behaviors are controlled by the dopaminergic turnover rate in the upper structures of the brain [241]. In 2004, Sudo *et al.* found that GF mice had a more pronounced HPA axis response to stress, and lower cortical and hippocampal BDNF expression than that of SPF mice. A single dose of *Bifidobacterium infantis* alleviated the symptoms of HPA stress in GF mice. Stress regulation by GM has also been studied in animals subjected to mother separation (MSp), a popular model for studying early life stress and BGA dysfunction. This research indicated that an adjusted diet could help regulate intestinal permeability and restore the growth rates of microbes that MSp had decreased. Similarly, *Lactobacillus* spp. treatment corrected gut physiology, inhibited bacterial adhesion to the mucosa, and reversed MSp-induced elevated corticosterone levels [242]. The complex relationship between GM and stress conditions indicates that probiotic or prebiotic therapeutic approaches can improve stress and depressive mental states.

Therapeutic implication of gut microbiota (GM)

The association between GM modulation and progression of different diseases has been evidenced by an enormous amount of recent research (Table 1). In this review, we highlighted the roles of GM and its metabolites under different NDD conditions. As GM is closely related to these diseases, a therapeutic approach that introduces beneficial microbiota could have immense potential. Prebiotics, probiotics, and fecal transplantation are the main therapeutic methods of introducing microbiota.

Application of probiotics

Probiotics are microorganisms that provide health benefits when used at suitable concentrations. Probiotics support mucosal barrier integrity, have antimicrobial effects, and aid host immunomodulation [243]. Oral administration of probiotic preparations, containing either single or multiple microorganism strains, has proven to be a successful therapeutic strategy. Due to several recent studies, the mechanism whereby probiotics function in gut and brain signaling is well understood. Many reports focusing on animal studies support the therapeutic potential of *Lactobacilli* and *Bifidobacteria* [244]. One animal study reported that *Bifidobacterium breve* strain A1 (B. breve A1) could prevent cognitive dysfunction induced by Aβ, by increasing plasma acetate levels in AD model mice [244]. Another study reported that *Lactobacillus plantarum* MTCC1325 could potentially ameliorate cognitive deficits and restores ACh and histopathological features in an AD mouse model [245]. Other report showed that administering probiotics containing the SLAB51 strain to transgenic AD mice improved common phenotypic conditions, including decreased weight of the brain and cortical areas, thus decreasing brain shrinkage and damage. Moreover, treatment with SLAB51 reduced the size and number of amyloid plaques [246]. *Lactobacillus helveticus* IDCC3801, found in fermented milk, has been demonstrated to improve APP metabolism in cell-based tests, favoring memory in scopolamine-treated mice, and also reducing Aβ serum levels in rats, according to another study [247]. In a clinical trial performed in 2016, patients with AD were given 200 ml/day of probiotic milk containing *Bifidobacterium bifidum*, *Lactobacillus acidophilus*, *Lactobacillus fermentum*, and *Lactobacillus casei*, and that this had beneficial effects on triglyceride levels, hs-CRP, MDA, markers of insulin metabolism, and Mini-Mental State Examination (MMSE) scores [13].

Another clinical trial showed that a group of AD patients who received selenium (200 μg/day) plus probiotics consisting of *Bifidobacterium longum, Bifidobacterium bifidum*, and *Lactobacillus acidophilus* had significantly lower insulin levels, reduced serum triglycerides, and substantially improved cognitive function [248]. *Lactobacillus bulgaricus*, *Streptococcus thermophiles*, *Bifidobacterium animalis* subsp. lactis, and *Lactococcus lactis* subsp. lactis are all found in fermented milk products (FMPP) [249]. This group of *lactobacilli* and *bifidobacteria* is very useful in producing antioxidants, vitamins, and bioactive compounds; limiting excessive levels of free radicals; and reducing numerous disorders associated with oxidative stress [250–254]. The daily consumption of fermented milk beverages containing *Lactobacillus casei* Shirota may considerably reduce constipation and improve bowel movement in patients with PD [254]. Even in healthy women, long-term exposure to FMPP may alter the reactivity of a wide range of brain networks [249].

Fecal microbiota transplant (FMT)

Restoring GM is one of the most effective treatment strategies for gut dysbiosis and its resulting symptoms. FMT is a therapeutic method used to reverse gut dysbiosis and restore a healthy gut microbial population. This method generally includes fecal solution transplantation from a healthy donor into the intestinal tract of patients [255]. This approach benefits IBS and neuropsychiatric, neurodegenerative, autoimmune, cardiovascular, and cancer diseases. Many studies have evaluated the efficiency of FMT in various NDDs, such as AD, PD, ALS, and other cognitive dysfunctions. In a 2018 study, it was reported that FMT from healthy mice to antibiotic-induced GF mice improved cognitive functions including memory and learning, as determined by the Morris water maze test [256]. Furthermore, a *meta*-analysis reported the beneficial effect of FMT in AD, PD, stroke, epilepsy, autism, neuropathic pain, and multiple sclerosis [255]. A study conducted in 2020 demonstrated the effect of FMT on patients with PD. In this study, FMT

Table 1
Effects of gut microbiota modulation (GM) on different NDDs.

Name of disease	Experimental subject	Microbiota modulation or analysis	Applicational reagent	Mechanism (main findings)	Ref.
Alzheimer's disease (AD)	$APP_{Swe}/PS1_{\Delta e9}$ mice	Absence of gut microbiota	Antibiotic/ABX	ABX treatment decreased Aβ plaques, increased soluble Aβ, and changed microbiota population.	[287]
	Triple-transgenic AD mice	Lactic acid bacteria and *bifidobacterial* (SLAB51)	SLAB51 formulation	SLAB51 treated mice had restored ubiquitin proteasome system and autophagy.	[246]
	APPS1 mice	Absence of gut microbiota		GF mice had reduced levels of Aβ amyloid.	[288]
	Triple-transgenic AD mice	Lactic acid bacteria and *bifidobacterial* (SLAB51)	Probiotic formulation (SLAB51)	SLAB51 administration reduced oxidative stress in Tg AD mice brain.	[281]
	60 AD patients	Administration of *Lactobacillus acidophilus*, *Lactobacillus casei*, *Bifidobacterium bifidum*, *Lactobacillus fermentum*	Probiotic formulation	Probiotic supplements improved cognitive function.	[289]
	Male mice C57BL/6N	Absence of gut microbiota	Antibiotics (ampicillin, bacitracin, meropenem, neomycin, and vancomycin)	Antibiotic treatment caused gut dysbiosis and cognitive dysfunction.	[290]
	C57BL/6J mice	Assessing enteric bacteria composition	10 Gy gamma ray	Abdominal irradiation caused cognitive deficits, reduced BDNF, and altered some species of microbiota.	[291]
	$APP_{Swe}/PS1_{\Delta e9}$ transgenic mice		Antibiotics (gentamicin, vancomycin, metronidazole, neomycin, ampicillin, kanamycin, colistin, and cefaperazone)	Postnatal antibiotic treatment of Tg mice reduced amyloid plaque deposition in brains.	[292]
	ADLP mice	Faecal microbiota transplant from wild-type (WT) mice to Tg mice		Microbiota transfer improved cognitive function and tau pathology, improved memory,	[293]
	P301L tau mouse model	Analysis of fecal microbiota composition		Composition of the gut microbiota changed with aging.	[294]
	$APP_{Swe}/PS1_{\Delta e9}$ transgenic mice		Probiotic *Clostridium butyricum* (CB)	*Clostridium butyricum* can decrease cognitive defects and microglial neuroinflammation in Tg mice, reduce COX2 and CD11b levels, and modulate brain gut microbiota axis.	[295]
	APP PS1-21 mice	Analysis of fecal microbiota composition	Antibiotics (kanamycin, gentamicin, colistin, metronidazole, and vancomycin)	ABX treatment improved Aβ pathology, altered microglia morphology, nad caused sex-specific change in microbiome, Aβ pathology, and inflammatory mediators.	[258]
	D-galactose- and $A\beta_{1-42}$-induced deficient rats		Fructo-oligosaccharides from *Morinda officinalis*	Fructo-oligosaccharides (FOS) reduced oxidative stress, inflammation, synthesis of neurotransmitters, caused increased *Bifidobacterium*, immunological enhancement, decreased neuronal apoptosis, swelling brain tissue, and amyloid deposition.	[296]
Parkinson's disease (PD)	26 RBD patients and 137 controls (meta study)			↑mucin-layer-degrading genus, ↓SCFA producing genus, ↑BMI, mucus layer progression of α-synucleinopathy.	[297]
	Male C57BL/6 J mice		Osteocalcin, 6-OHDA antibiotics (ampicillin, neomycin, metronidazole, and vancomycin) propionate, FFAR3 agonist AR420626, cisplatin	Osteocalsin can prevent motor impairments and dopaminergic neuronal loss by modulating the gut microbiota. Increased propionate provides neuroprotection.	[298]
	ICR mice, Sprague–Dawley (SD) rats, and C57BL mice	*Enterococcus faecalis* *Enterococcus faecium*	Dihydroberberine (dhBBR)	↑brain dopamine levels ↑blood/fecal L-dopa, ↑dopa/dopamine BH2, improved brain function.	[299]
	Male Sprague-Dawley rats (Dopamine depletion model)		6-hydroxydopamine (6-OHDA) and non absorbable antibiotics	Antibiotics ameliorated the neurotoxicity of 6-OHDA and motor function in a PD model. Antibiotics decreased pro-inflammatory markers.	[228]
	Humans (24 PD patients, 69 controls)		Vegetable and quinoa fiber supplements	Improved motor symptoms and increased SCFA production.	[300]
	GF and SPF Thy1-αSyn mouse	Fecal microbiome transplant from PD patients	Ampicillin, neomycin, gentamycin, erythromycin, and SCFAs	PD patients' microbiota caused altered SCFA production. PD patients' microbiota caused αSyn overexpression.	[186]
	Humans (64 PD patients, 64 controls)	Fecal microbiota analysis		Decreased abundance of *Prevotella* in PD patients.	[301]

Table 1 (*continued*)

Name of disease	Experimental subject	Microbiota modulation or analysis	Applicational reagent	Mechanism (main findings)	Ref.
	M83 heterozygous transgenic (A53T) mice		Peripheral α-syn fibril injections	Adoptive cellular therapy improved gut microbiota dysbiosis in PD patients.	[302]
	Humans (14 PD patients) Thy1-SNCA mice		Lipopolysaccharide	LPS in Thy1-αSyn mice causes early motor manifestations. LPS injection caused microglial inflammation, oxidative stress, cellular apoptosis, and decreased dopamine.	[303]
Amyotrophic lateral sclerosis (ALS)	G93A mice	Analysis of intestinal microbiota	Not available	Damaged tight junction structure, ↓antimicrobial peptides and defensin 5 alpha. Abnormal intestinal microbiome.	[160]
	SOD1 transgenic (SOD1-Tg) mice	*Ruminococcus torques* and *Parabacteroides distasonis*	Antibiotics	Accumulation of nicotinamide in the CNS. Increased motor symptoms.	[7]
	$SOD1^{G93A}$ mice	Analysis of fecal microbiota	2 % sodium butyrate and antibiotics (metronidazole and clindamycin)	Butyrate treatment reduced $SOD1^{G93A}$ aggregation, and enhanced muscle function in intestine.	[304]
	G93A transgenic mice		2 % Butyrate	Butyrate restored intestinal homeostasis and decreased G93A SOD1 aggregation.	[161]
	$SOD1^{G93A}$ mice		Antibiotics (ampicillin, metronidazole, gentamycin, vancomycin, and neomycin)	Antibiotics depleted beneficial bacteria and caused deterioration of the disease condition.	[305]
	$SOD1^{G93A}$ mice	Fecal microbiota metabolomics analysis	2 % Sodium butyrate	Butyrate treatment effects fecal metabolism, increases healthy metabolites, and decreases IL7 and LPS in ALS mice.	[306]
	20 humans, including 10 patients	Microbiota analysis from rectal swab		ALS patients lacked butyrate metabolizing enzyme.	[307]
Huntington's disease (HD)	R6/1 mice HD model	Fecal microbiota analysis		HD mice showed gut dysbiosis and weight reduction. Increased microbial diversity in male HD mice,	[308]
	BACHD mice	Fecal microbiota analysis		↓ levels of myelin -related proteins and numbers of mature oligodendrocytes in the prefrontal cortex. Low levels of microbiota *Prevotella* (phylum *Bacteroidetes*)	[309]
	Humans (33 HD patients, 33 control)	Fecal microbiota analysis		Increased α- and β-diversity in HD patients. Increased cytokines in HD patients.	[231]
	R6/2 mice HD model	Assessment of enteric bacteria composition		HD mice had increased intestinal permeability and gut dysbiosis.	[233]
Multiple sclerosis (MS)	SJL/J anti-MOG TCR transgenic RR mice (EAE-induced)	Monocolonization of GF with specific pathogen-free microbiota	MOG injection for EAE induction. Antibiotics (metronidazole, neomycin, and vancomycin)	Commensal gut flora without pathogenic microbes can triggering immune processes, causing relapse or remittance of autoimmune diseases.	[310]
	Female SJL/J mice (EAE-induced)	Infection with *Bacteroides fragilis*	Antibiotics + PSA (ampicillin, vancomycin, neomycin sulfate, and metronidazole)	Infection with *B. fragilis,* which produces polysaccharide A, restored susceptibility to EAE.	[311]
	Human and mouse microbiome (EAE)	Colonization with *Akkermansia muciniphila* and *Acinetobacter calcoaceticus*	Antibiotic treatment	Both species induced proinflammatory responses in human peripheral blood mononuclear cells and in monocolonized mice.	[237]
	Female C57BL/6J, Ifnar1, IL-27ra, GFAP-Cre, and AhRfl/fl mice		MOG35–55 peptide for EAE induction, antibiotics (ampicillin and vancomycin), Trp-indoles, and TnAse	Microbial metabolite tryptophan activated AhR signaling, decreasing CNS inflammation.	[312]
	C57BL/6 mice	*Candida kefyr* administration		↑Treg and dendritic cells. ↓Th17 *Candida kefyr* reduced EAE symptoms.	[315]
	C57BL6/J mice, $Rag^{-/-}$, and MOG-Tg mice (EAE-induced)	Colonized germ-free animals with segmented filamentous bacteria (SFBs)	EAE MOG_{35-55} peptide induction, *mycobacterium tuberculosis* H37Ra, and pertussis toxin	SFB-induced animals showed increased Th17 cell responses. SFB colonization induced EAE.	[314]
	Female B6 mice (EAE-induced)		MOG to induce EAE and antibiotics (kanamycin, colistin, and vancomycin (KCV))	KCV suppressed EAE by changing iNKT cell function KCV treatment decreased inflammatory cytokines.	[238]
	SJL and C57BL/6 mice (EAE)		Ampicillin, vancomycin, neomycin sulfate, and metronidazole	Antibiotic treatment can modulate peripheral immune tolerance, increasing the frequency of FoxP3 + Treg cells, which can protect against EAE.	[315]

improved both motor and non-motor symptoms in patients with PD [257].

Another 2019 study found that FMT has an effect on AD mice. In this study, FMT from APPS1-21 male mice to antibiotic-treated APPPS1-21 mice reduced Aβ severity and restored microglial morphology. However, this effect was specific to male mice [258]. One case report also found rapid improvement in an 82-year-old patient following FMT taken from a healthy individual. A 300 ml FMT from the donor improved memory function and stopped AD progression [259]. Altogether, these studies suggest that FMT has excellent potential to improve cognitive function and neurodegeneration. Although many clinical studies have proven the effective of this method for promoting cognitive improvement, more attention is needed for FMT to be established as a standard therapeutic approach.

Prebiotic therapy

Gut bacteria, such as saccharolytic microbes, preferentially digest prebiotics and dietary carbohydrates, which benefits gut health and impart favorable health benefits [260]. Many murine studies have demonstrated the influence of prebiotics on psychophysiological aspects. Prebiotic chitosan oligosaccharides (COS) have been shown to improve memory function by decreasing oxidative stress and neuroinflammatory reactions in an $A\beta_{1-42}$-induced rat model of AD [261].

Another study found that rats fed prebiotics consisting of galacto-oligosaccharides (GOS) and fructo-oligosaccharides (FOS) for five weeks had better memory function, altered synaptic plasticity receptors, increased expression of hippocampal NR1 and NR2A subunits, increased BDNF expression, and increased glutamate neurotransmission amino acids [56]. BDNF and NMDAR expression in the hippocampus was similarly elevated in newborn rats administered B-GOS, and oligo-oligosaccharide prebiotic supplement [262]. GOS reduced astrocyte and microglial activation and motor neuron loss in an ALS SOD1G93A mouse model [263]. Studies conducted in both mouse and rat models have reported increased BDNF expression in cortical structures and increased long-term potentiation following administration of a human milk oligosaccharide, and 2′-fucosyllactose [264–266]. In conclusion, the emerging role of prebiotics in modulating neural networks and improving neurodegeneration should be explored further by conducting further research. Moreover, the use of prebiotics as a therapeutic measure in neurodegenerative diseases should be given more attention. The applications of different GM-based therapeutics are highlighted in Fig. 2.

Future prospective and conclusion

In this review, we have highlighted the significance of the GMBA in brain development and disorders (Fig. 3). GM plays a dual role in NDDs, activating many pathogenic factors and functioning

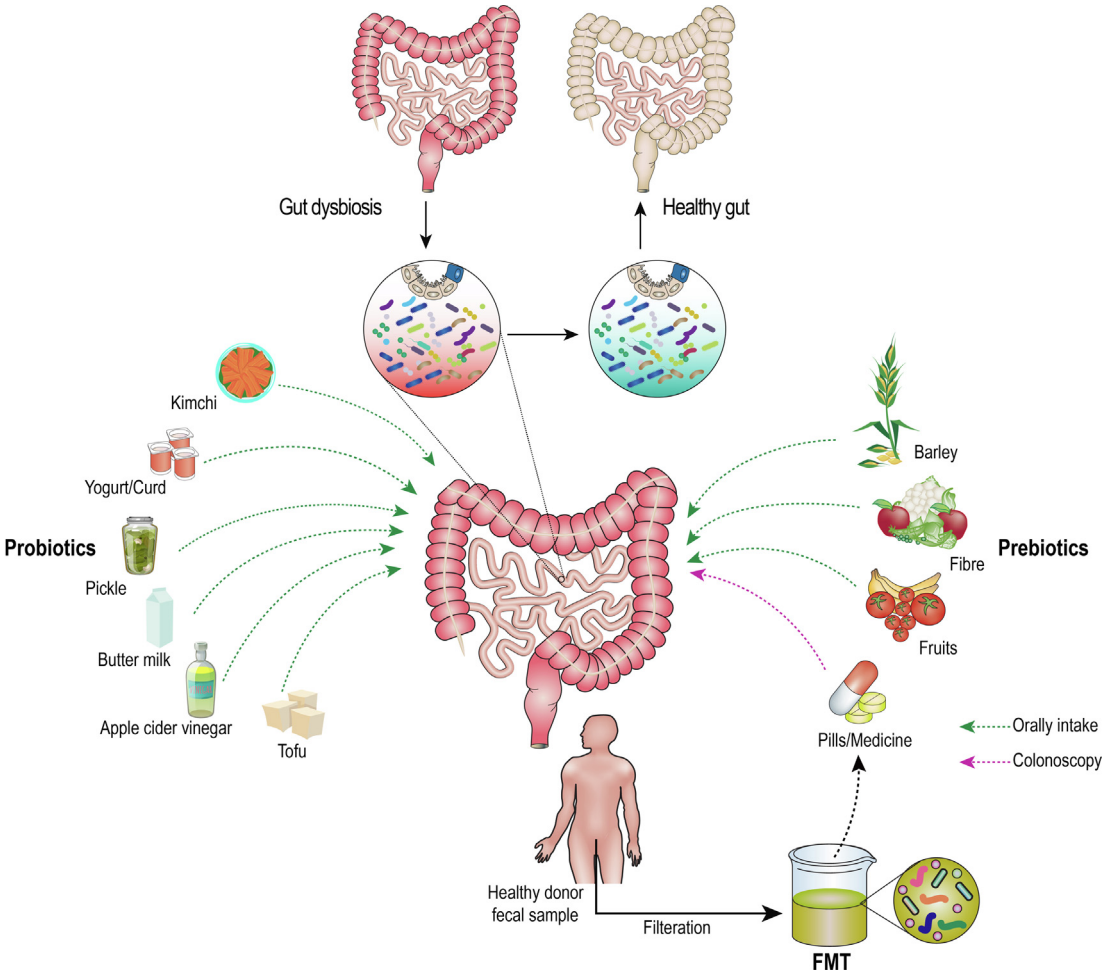

Fig. 2. Possible gut microbiota-targeted therapies for altering gut dysbiosis-mediated neurodegeneration, including probiotics (kimchi, yogurt/curd, pickle, buttermilk, apple cider vinegar, and tofu), prebiotics (barley, fiber, and fruits), and fecal microbiota transplantation (FMT).

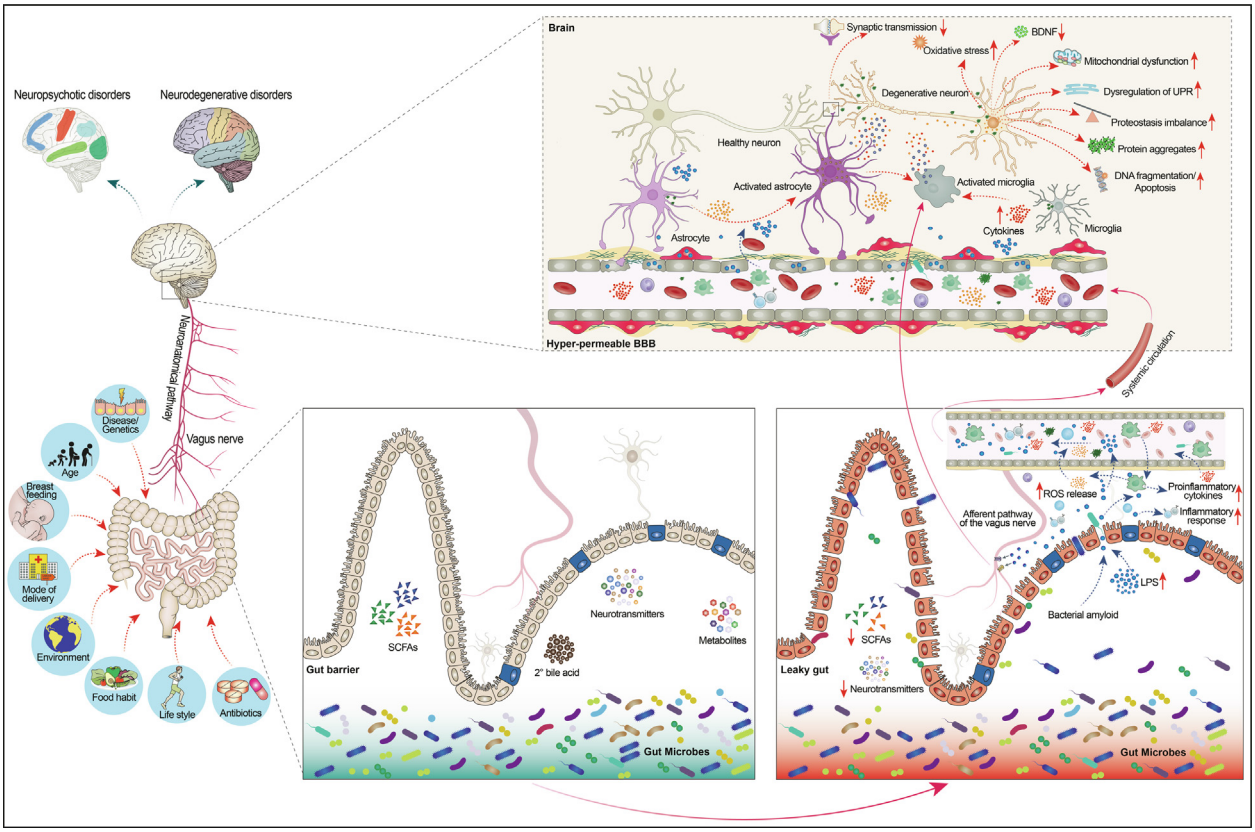

Fig. 3. Visual representation of the gut-brain axis in neurodegenerative diseases. Brain and gut communication are affected by gut dysbiosis in different neurodegenerative disease conditions. Many external and internal factors regulate intestinal health, including environment, food habits, genetics, body weight, mental state, exercise, birth history, smoking, age, medications, etc. Therefore, gut dysbiosis causing disruption of the tight junction of the gut barrier may occur, leading to a pathological state called leaky gut. It allows gut microbes (GM) to be released into systematic circulation. As the population of beneficial microbes decreases, pro-inflammatory microbes increase, which causes the release of some toxic metabolites, such as lipopolysaccharides (LPS) and bacterial amyloid. A leaky gut releases these toxic metabolites into the systemic circulation, increasing inflammatory cytokines and systematic inflammation. These metabolites can subsequently cross the blood–brain barrier to enter the brain, causing neuroinflammation. Increased inflammatory cytokines in the blood cause mitochondrial dysfunction and increased oxidative stress. A lower abundance of beneficial microbes reduces the production of healthy neurotransmitters and metabolites, such as SCFAs. Together, these factors cause excessive inflammatory cytokine release, activating astrocytes and microglia, impairing autophagy and the unfolded protein response (UPR), increasing DNA fragmentation, and reducing BDNF levels. This leads to neurons degeneration and decreased synaptic transmission, which causes cognitive dysfunction and neurodegenerative and neuropsychiatric diseases.

as a therapeutic agent via neuroprotective and neurodevelopmental mechanisms. As discussed in the earlier sections of the text, gut dysbiosis is related to NDDs; thus, microbial population assessment can be a crucial factor for early diagnosis and risk analysis of NDD, especially in age-related diseases. As suggested by many studies, modulation of GM by modifying food habits, administration of prebiotic therapy and probiotics, and performing FMT could be introduced to improve brain health and promote neuronal growth (Table 1).

Promoting the protein clearance system by maintaining a healthy proteostasis network has been identified as an excellent therapeutic strategy for ameliorating many age-related NDDs, as this system is often overwhelmed in severe pathological conditions [266–271]. GM-derived metabolites can help restore disrupted proteolytic systems; however, few studies have explored the mechanisms whereby this occurs.

Some evidence suggests a bidirectional relationship between autophagy and GM [271–273]. An abnormal microbial population may cause impaired autophagy in macrophages; dendritic cells; ENS, ANS, CNS nerve cells; Paneth and goblet cells; EECs; T and B cells; and natural killer cells, by disrupting mitochondrial dynamics [273]. Reportedly, *E. coli* can control autophagy via the NF-κB signaling pathway, which downregulates ATG-specific genes and impairs autophagy [274]. Intestinal dysbiosis increases LPS synthesis, which can also modulate autophagy. In the rat hippocampus, LPS activates the NLRP3 inflammasome and downregulates the expression of the autophagic marker LC3 [275]. In addition, LPS triggers the expression of IL-1 β and TNF α, which ultimately causes NF-κB activation and reduces autophagic flux in ATG7-deficient mice [276]. Another study reported that LPS induces microglial cell inflammation by inhibiting autophagic flux via activation of the PI3K/Akt/mTOR pathway, ultimately suppressing autophagosome formation [277]. However, the exact role of LPS in autophagy is not entirely understood, as LPS can also induce autophagy via activation of TLR4 in the gut epithelium [278]. Bacterial SCFAs have a significant impact on autophagy modulation by regulating HDACs. Butyrate and acetate inhibit HDACs, promote histone hyperacetylation, and increase autophagic flux [279]. In addition, many bacterial species can catabolize arginine into putrescine, spermidine, and spermine, consequently initiating autophagy [280]. Bonfili *et al.* designed a probiotic formulation (SLAB51) comprising bifidobacteria and lactic acid bacteria that was used to treat the early stage of AD using a triple-transgenic mouse (3xTg-AD). This treatment successfully restored the defective proteolytic systems, that is, autophagy and the ubiquitin–proteasome system, indicating a restoration of a balanced proteostasis system [246]. A later mechanistic study of SLAB51 showed activation of SIRT1-related pathways during autophagy activation and balancing oxidative stress, which is the main cause of proteostasis failure [281]. By focusing on this mechanism of GM, a new therapeutic approach can be designed to promote neuronal autophagy and clearance of protein aggregates.

Protein aggregation clearly has various pleiotropic effects, implying that a multi-target strategy may be necessary in order to modulate the proteostasis network. Multitarget methods for treating NDDs are becoming more common because of the complexity of neurodegeneration and its multifactor nature [282–284]. Thus, proteostasis may be restored in NDDs by employing GM modulation and GM-derived metabolites to target proteostasis; drug developers deem these "privileged structures," since they typically interact with many protein targets in various signaling systems, as described earlier. Further studies are needed to understand how GM modulation and GM-derived metabolites might modulate the proteostasis network machinery, particularly, the unfolded protein response, chaperone, and autophagy systems, using suitable cellular and transgenic models.

GM modulation by secondary metabolites from dietary nutrients is an attractive strategy for treating and preventing various NDDs. However, more studies are needed to explore which concentrations of specific metabolites or foods could induce beneficial or deleterious effects, and their direct or indirect mechanisms of CNS modulation. In this context, the new term "postbiotics" has recently been introduced; this refers to metabolic byproducts derived from non-viable beneficial microbes [284–286]). These can mimic the functions of probiotics without requiring specific manufacturing or storage conditions [286]. However, because postbiotic therapies are still new, their safety and possible hazards have not been well investigated; therefore, more studies are required. Furthermore, screening of GM-derived metabolites should be undertaken in pre-clinical and clinical studies, as we expect these approaches to provide potential pharmacological leads for treating age-related NDDs.

Thus, future research on GM modulation could integrate multi-omics-based studies, encompassing genomics to metabolomics, to better understand the GM population, its influence on transcriptome and proteome levels, and metabolomics for drug design and development. Furthermore, *in vitro* and *in silico* bioinformatics tools should be designed to help identify potent GM metabolites that can cross the BBB and modulate the CNS. Potential new molecules derived from GM metabolites may create opportunities for new drug design and new therapeutic approaches to the treatment of NDDs.

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Compliance with Ethics Requirements

Not Applicable.

CRediT authorship contribution statement

Sarmistha Mitra: Conceptualization, Methodology, Writing – original draft. **Raju Dash:** Writing – original draft, Software, Visualization. **Amena Al Nishan:** Writing – original draft. **Sarmin Ummey Habiba:** Writing – original draft. **Il Soo Moon:** Supervision.

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.

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