ERURJ **2025**, 4, 3, *2749-2773*
(Review)

The interplay of gut microbiota in neurodegenerative disorders

Ahmed A. El-Husseiny [1, 2*], Nada S. Ali [1], Hadeer Saied Mahmoud [1]

[1] *Department of Biochemistry, Faculty of Pharmacy, Egyptian Russian University, Badr City 11829, Cairo, Egypt.*

[2] *Biochemistry and Molecular Biology Department, Faculty of Pharmacy (Boys), Al-Azhar University, Nasr City 11231, Cairo, Egypt.*

[*]Corresponding author: Assoc. Prof. Ahmed A. El-Husseiny**,** Email: ahmed-elhusseiny@eru.edu.eg

Received 09th January 2025 Revised 19th March 2025 Accepted 13th April 2025
DOI:10.21608/erurj.2025.351717.1218

ABSTRACT

Globally, populations are burdened with significant medical and public health costs due to degenerative illnesses of the neurological system. A couple of the most common neurodegenerative conditions include Parkinson's disease (PD) and Alzheimer's disease (AD). Since these illnesses are more common and severe as people age, more instances are anticipated as life expectancy continues to climb in many nations. Numerous studies throughout the years have revealed the genetic and metabolic processes that contribute to neurodegenerative disorders (NDDs). The microbial community in the human gut is diverse and dynamic, crucial to numerous physiological processes. It has been demonstrated that the gut microbiota **(**GM) is a part of the gut-brain axis (GBA) in many regulatory mechanisms and associated pathways, as well as in unique bacterial behaviors. Besides, it has been established that GM pose a danger for neurological problems that impact the neurological system, especially the CNS, or central nervous system, controlling the course of the disease and being responsive to treatment. The GBA promotes communication between the GM and the brain, indicating that it is essential for neurocrine, endocrine, and immune signaling pathways. This review clarifies the complex interaction between gut bacteria and human health, focusing on how it affects neurodegenerative diseases. Moreover, we have discussed the crucial role of the GM in the GBA from the brain to the gut and the gut to the brain, as well as the neurological pathways that interact with the GM.

Keywords: *Parkinson's disease, Alzheimer's disease, Gut microbiome, Neurodegenerative, probiotics.*

1. **Introduction**

Neurodegenerative diseases (NDDs) are a diverse range of neurological conditions that cause gradual degeneration of neurons in the peripheral or central nervous systems (CNS), negatively impacting the lives of millions of individuals worldwide [1]. The fundamental communication circuitry breaks down as a result of the disintegration among neural networks and neuronal death, since neurons cannot effectively regenerate themselves because they are terminally distinct. This leads to decreased memory, cognition, behavior, sensory, and/or motor function [1, 2]. Globally, populations are burdened with significant medical and public health costs due to degenerative illnesses of the neurological system. Amyotrophic lateral sclerosis (ALS), Parkinson's disease (PD), and Alzheimer's disease (AD) are some of the most common neurodegenerative diseases. Since these illnesses are more common and more severe as people age, more instances are anticipated in the near future as life expectancy continues to climb in many nations.

Neurodegenerative illnesses pose a major risk to human health and have a tendency to get worse over time. By 2040, neurodegenerative illnesses are predicted by the World Health Organization to surpass cancer as the second greatest cause of mortality worldwide. The progression of the disease cannot be stopped because the human neurological system is basically non-regenerative [3]. Previous Research has shown a link between inflammation and the pathogenesis of neurodegenerative diseases. The brain can sustain damage from the innate immune system when dangerous molecules are uncontrollable and trigger over time. The group of microorganisms that live in the gastrointestinal tract (GIT), including bacteria, protists, fungi, and archaea, is known as the gut microbiota (GM). The GM has around three million genes, 100 billion bacteria, and over 1000 species, making it 150 times greater in genetic diversity than the human body. Individual genetic modification affects physiological changes, human growth, dietary needs, and genetic variances; It has been discovered that age, gender, location, diet, and genetic variances all have an impact on these aspects [4]. Through their interactions inside the host-gut epithelium, They are called commensal bacteria that preserve intestinal balance and strengthen host defense [5].

Bidirectional communication (GBA) happens in the brain-gut axis as a channel that runs both ways between the host's nervous system and the stomach [6]. This information can be

transmitted by the immune system, hormones, and brain networks, which support the intestinal microbiota [7]. The GBA's reciprocal transmission preserves a reciprocal relationship that controls the innate and adaptive immune systems in conjunction with the host, and mechanistically controls brain dysfunction [8]. When circulating insulin-like growth factor-1 (IGF-1) or other growth hormones exist at the time of neurogenesis, the GM colonizes the brain and impairs cognitive performance during multiple biological functions such cell differentiation, myelination, apoptosis, axonal processing, and synaptogenesis [9].

Genetically engineered organisms' extended metabolic profiling has demonstrated how the regulation of brain growth affects maturation [10]. The CNS, or central nervous system, this is home to over 200 million neurons and controls the action of the whole digestive system. The central nervous system (CNS) comprises the nerve fibers and ganglia network in the myenteric and submucosal plexuses [11]. The system of enteric nerves (ENS), which primarily develops in the large and small intestines, is located in the wall of the GIT. It consists of the submucosal (Meisner) and myenteric (Auerbach) plexuses. The vagus nerve innervates these plexuses, and the interstitial cells of Cajal and pacemaker cells in the GIT wall control their activity, allowing the plexus to operate independently. The myenteric or peristaltic reflex is maintained by neurons in the myenteric, which are situated in the space between the outer longitudinal and inner circular muscles. They may be cholinergic neuron activators or inhibitors. There is a distinction between the Meissner's plexuses on the inside and outside. The submucosal glands are innervated by the internal part, which extends in the direction of the mucosae muscularis, in contrast, the outer plexus regulates blood flow, peristalsis, and digestive secretion in addition to innervating the circular muscle. Deeply situated between the digestive tract's circular and longitudinal layers, the myenteric plexus controls gastrointestinal motility (peristalsis) [12].

As of right now, there is ample evidence linking genetic modification to the rise in neurological diseases, neuro-inflammatory disorders, and neurobehavioral problems [13]. A number of neurological conditions, including brain damage, ALS, or amyotrophic lateral sclerosis, PD, autistic spectrum disorder (ASD), AD, epilepsy, stroke, and Huntington's disease (HD), are impacted by the GM in terms of their pathogenesis and management [14]. Several therapies have been researched for neurological issues caused by genetic modification, including fecal transplants, probiotics, postbiotics, prebiotics, symbiotics, and antibiotics [15]. From now on, this review will include the latest updated information on a number of neurological

conditions, as well as a comprehensive discussion of GM's role in the GBA, which is connected to neurological pathways. We have also explored the possible future effects of GM in neurological illnesses, which might necessitate planning more studies to address the pathogenic and therapeutic components of the condition.

2. The role of gut microbiota in healthy life

A crucial component of maintaining health and preventing disease is gut microbiota **(Fig. 1)**. As of right now, the microbiota of the gut is one of the most significant variables determining health, and changes to it are linked to the onset of chronic degenerative disorders [16]. Additionally, it controls a number of metabolic, immunological, physiological, and structural processes. It even influences behavior [17]. Within the first 1000 days of life, the GIT experiences fast growth and differentiation. Because gut function is closely related to our general health and well-being, ensuring the gut develops healthily is crucial. The digestion, absorption of nutrients, and excretion of waste products are the main functions of the stomach, which is the location of 100 trillion bacteria referred to as the "microbiota." However, it also significantly affects the relationship between the gut and the brain and the immune system's development and function [18].

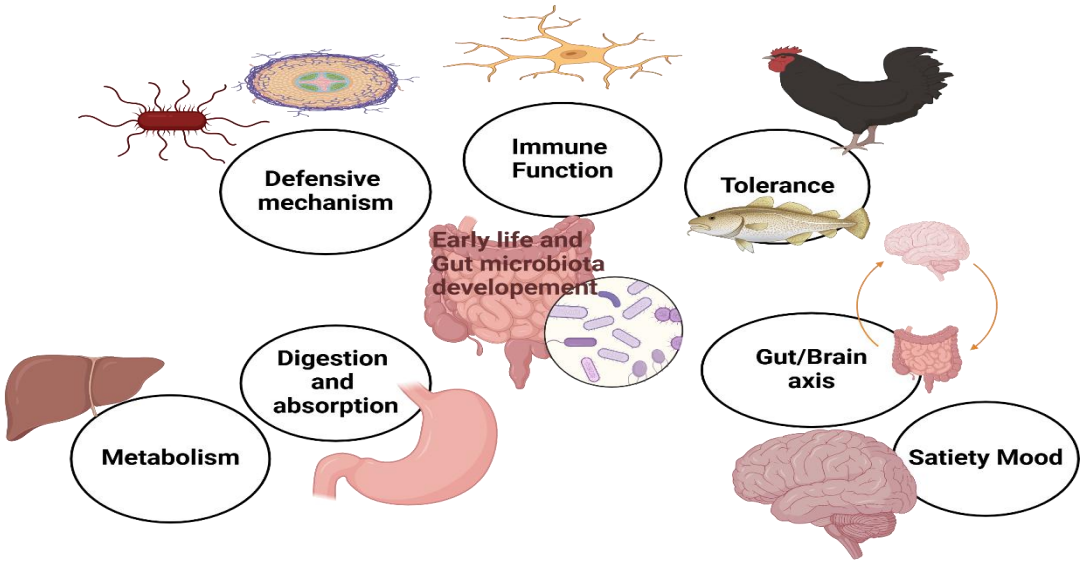

Figure (1): The functions of gut microbiota in a healthy life.

3. Mechanisms implicated in neurodegenerative disorders

Pathological protein aggregation, aberrant proteostasis, altered energy metabolism and ROS, cytoskeletal abnormalities, DNA and RNA errors, inflammation, hypoxia, and neuronal cell death are underlying mechanisms that characterize NDDs **(Fig. 2)**.

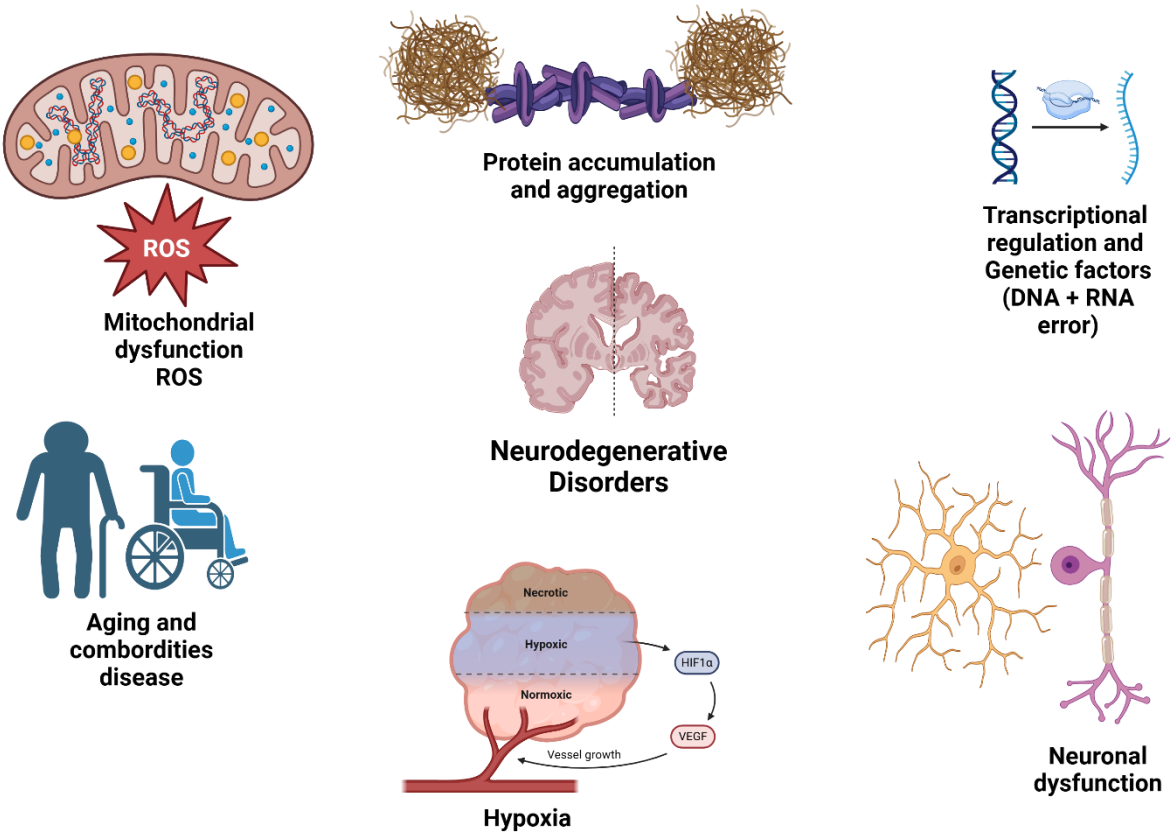

Figure (2): The key underlying mechanisms of neurodegenerative disorders.

3.1. Pathological protein aggregates

One important pathogenic feature of many NDDs is characteristic protein aggregation, which is frequently used for diagnosis and illness categorization [19]. Among the NDDs that fall under this category are proteinpathies, PD, AD, and primary tauopathies, which include progressive supranuclear palsy (PSP) [19]. These disease-causing mutations are linked to enhanced protein aggregation that is encoded via a characteristic shared by multiple NDDs. Many genes, including those encoding A-synuclein (PD and synucleinopathies), tau (AD and tauopathies), and the

amyloid precursor protein (APP) (AD), are implicated in this potentially dangerous gain-of-function mechanism, which have been linked to enhanced aggregation by hereditary mutations**.** Notably, certain hallmarks of non-verbal dementia disorders are also associated with the functions of the body and typical operation of genes linked to NDDs (such as tau, APP, and α-synuclein). Moreover, protein sequestration and aggregation in one area of the cell might result in its disappearance from another, consequently reducing its physiological capacity. The combined effects of toxic gain and function loss may cause concurrent anomalies in the NDDs hallmarks or multiple hits that encourage neurodegeneration [1]. Prion-like propagation**,** the primary mechanism underlying the rapid propagation of prion protein aggregation and misfolding, which causes neurodegeneration to spread throughout brain regions and cells, has been uncovered [20].

3.2.DNA and RNA defects

Many different types of NDDs have been linked to the buildup of DNA damage and RNA metabolism abnormalities [21]. Cells' genomes and transcriptomes are vulnerable to external or intracellular agents and spontaneous deterioration. The central nervous system's main genotoxins are considered reactive oxygen species (ROS) resulting from mitochondrial oxidative phosphorylation. Adverse molecular processes that might lead to cell malfunction and death, such as DNA replication fork collapse, RNA transcription block, chromosome rearrangements, and mutagenesis, can be triggered by persistent changes in DNA [22].

3.3.Inflammation

One of the pathogenic characteristics of NDDs, which include AD, PD, ALS, HD, and stroke, is neuroinflammation, which includes microgliosis and astrogliosis. In addition to the fact that postmortem brain samples from NDD patients always include inflammation, the classic neuroinflammatory disease and its related NDDs provide conclusive evidence of the role of neuroinflammation in neurodegeneration. All NDDs, including non-proteinopathies and proteinopathies, consistently exhibit microgliosis. Aberrations in the sensing, cleaning, and defensive roles that microglia typically perform in the brain can result in neurodegeneration [23]. Interestingly, short-chain fatty acids mitigate neuroinflammation and neurodegeneration. The microbial fermentative activity of gut microbiota is vital for the production of SCFAs, including butyrate, acetate, and propionate, from non-digestible dietary fibers. SCFAs are saturated fatty

acids composed of one to six carbon atoms. The predominant SCFAs found in the human body are acetate (C2), propionate (C3), and butyrate (C4), which comprise ~95% of the total SCFA pool. Numerous studies have illustrated the link between SCFAs and human physiological processes, including immunity, intestinal homeostasis, and control of glucose homeostasis and energy balance. SCFAs exert their physiological activities by acting as endogenous ligands for G-protein-coupled receptors (GPCRs), and modulating gene expression by inhibiting histone deacetylases (HDACs). GPCRs are the most prominent family of cell surface receptor proteins that regulate diverse physiological and pathological processes, and as such, are one of the most intensively studied targets for drug development. Moreover, GPCRs play a pivotal role in enabling the nervous system to accurately respond to external stimuli and internal states, SCFAs are endogenous ligands for a subset of GPCRs, including GPR43 and GPR41, which were subsequently renamed as free fatty acid receptor 2 (FFAR2) and FFAR3, respectively. Another important GPCR activated by SCFA is GPR109A, also known as hydroxycarboxylic acid receptor 2 (HCAR2), which is activated by butyrate and β-D-hydroxy butyrate. It has been reported that the FFAR2-deficient SPF mice developed microglial defects resembling GF mice. On the other hand, HDACs are part of the epigenetic regulatory mechanisms that control gene expression. Histone deacetylation by HDACs is associated with transcriptional repression by inducing a closed chromatin structure. Dysregulated epigenetic regulations and the consequent impact on gene expression and cellular processes are important contributors to aging and age-related human pathologies, including neurodegenerative diseases. In addition, an in vitro study has demonstrated that acetate exerts anti-inflammatory effects in Aβ-induced BV-2 microglial cells by upregulating the levels of GPR41 and inhibiting the ERK/JNK/NF-κB signaling pathway. Acetate and butyrate have been shown to inhibit the inflammatory response of LPS-stimulated primary microglia by inhibiting HDAC activity and NF-κB activation. Furthermore, the inhibition of microglial HDAC1 expression by propionate and butyrate has been shown to alleviate microglial activation and reduce the levels of pro-inflammatory factors in GF mice. Conversely, the anti-inflammatory effects of butyrate on LPS-induced BV-2 cells were blocked by HDAC3 agonist ITSA-1 and MCT1 inhibitor AZD3965 [24].

3.4.Neuronal cell death

Neural degeneration in NDDs may be particularly likely to occur in neurons due to a number of intrinsic characteristics. Among them are: (1) Their nature of post-mitotic, this causes age-

related damage to proteins, lipids, DNA, and organelles to gradually accumulated and the incapacity of brain cells to proliferate and replenish themselves; (2) Its severe energy requirements, mostly because of the necessity of maintaining synaptic function and the resulting creation of ROS by oxidative phosphorylation in mitochondria; (3) their vast axons and dendrites, which demand structural organization and long-distance transport.

Furthermore, their glial cell-based defense, energy, and maintenance needs. Because of this, neurons seem more prone to cell death, a trait made worse by reduced resilience mechanisms associated with aging. Individually and together, the NDDs hallmarks likely contribute to neuronal cell death, resulting in unique pathological and clinical symptoms. Various features of NDD work together to eventually override innate neuronal resistance to shock from the outside and inside [25].

3.5.Altered energy homeostasis and ROS

Since neurons are among the body's most active and energy-demanding cells, it has been demonstrated that energy metabolism abnormalities contribute to various NDDs [26]. The main element involved in the metabolism of brain energy, Oxidative phosphorylation, which is powered by the metabolism of lactate or glucose, produces ATP in mitochondria via the electron transport chain. Glucose and lactate are energetic substrates that can reach neurons directly from the bloodstream or indirectly through astrocytes [27].

The pathogenic mechanism underlying several NDDs entails a reduction in mitochondrial activity, either directly or indirectly, most likely as due to insufficient ATP availability and as a result of impairment in high-energy-demanding neuronal processes, especially at synapses: proteostasis, calcium homeostasis, ion balance, cytoskeletal dynamics, and ATP-consuming membrane pumps [28]. Furthermore, ROS can target nucleic acids, lipids, and/or proteins causing macromolecular damage due to oxidative stress brought on by an increased free electron release when reacting with nitrogen or oxygen. This is a consequence of mitochondrial failure [29].

3.6.Cytoskeletal abnormalities

The three primary polymeric structures that make up the neuronal cytoskeleton are tubulin-based microtubules, actin-based microfilaments, and intermediate filaments (also known as neurofilaments), which are characterized by their diameter and protein composition [30]. These

structures interact with one another and support energy balance and synaptic function by allowing neurons to grow, maintain, and alter their architectural design in addition to organizing and moving payloads inside cells as well as mitochondria throughout their prolonged lengths.

To maintain their dynamic structure, high energy requirements, they serve as microtubule anchor sites for mitochondria and actin drivers to induce plastic alterations, The cytoskeleton of pre- and postsynaptic structures is distinct and dynamic. The NDDs are linked to changes in the neuronal cytoskeleton that impair the transmission of information and cargo between the synaptic terminals and the cell body, containing vital core components and mitochondria for meeting energy needs. This often leads to a process known as dying-forward or dying-back [31].

3.7Aberrant proteostasis

Accumulating ubiquitinated proteins (tau, TDP-43, α-synuclein, and HTT) in aggregates in many NDDs implies aberrant proteostasis. Two key biological processes for preserving protein homeostasis are the autophagy-lysosome pathway (ALP) and the ubiquitin-proteasome system (UPS). The UPS mostly breaks down labeled proteins, whereas the ALP eliminates protein clumps and malfunctioning organelles. This includes mitophagy, which breaks down damaged mitochondria by engulfing cellular material in an autophagosome, a double-membrane structure [1].

3.8.Neuronal and synaptic network dysfunction

Disruption of certain neural networks has been demonstrated in many NDDs. Synaptic dysfunction and toxicity seem to be a recent development before the loss of neurons. Neuronal network function requires precise synaptic function and controlled synapse stability and deletion. Post-synaptic signaling, cytoskeletal changes, neurotransmitter and calcium fluctuations, presynaptic vesicle dynamics, and other elements affect synaptic function [32].

4. The gut-brain axis and the function of gut microbiota

To evaluate GM's influence on etiology and treatment outcome, there is an increasing tendency toward understanding its involvement in the neurodevelopment process in the GBA. There are two anatomical mechanisms via which the stomach and brain can communicate [33]. First, the vagus nerve (VN) in the autonomic nerve system (ANS) and spinal cord connects the brain and the intestines. Second, bi-communication in the GIT-ENS is made possible by a two-way

connection between the brain and the stomach. The nervous systems of the sympathetic (SNS), parasympathetic (PNS), and ENS are the ANS components. The medulla gives rise to the vagus nerve, the tenth cranial nerve, which exits the skull through the jugular foramen. It sends data via the GIT, heart, and lung, and has afferent and broad visceral efferent components. That connects the brain and associated glands. Consequently, it links GIT and the brain. It controls the defensive mechanism (immune system), peristalsis, breathing, cardiac rhythms, and mood. Based on current investigation, yoga's activation of the vagus nerves may be beneficial for PTSD, IBD, and resistant depression, which results in parasympathetic dominance and elevated vagal tone. Additionally, the production of cytokines is decreased by decreasing the vagal tone. Vagus nerve stimulation affects the monoaminergic brain system, which is significant in mood and anxiety disorders. GM possesses anti-anxiety and anti-stress qualities by affecting the vagus nerve's activity and releasing neurotransmitters like GABA, serotonin, and short-chain fatty acids [33].

4.1. Brain to Stomach

It has been demonstrated that GM's involvement in the absence of colonization by microbes is connected to modifications in synthesis of neurotransmitters [34]. All problems were corrected when these creatures established themselves in a manner specific to a specific bacterial species while being impacted by higher cortisol and ACTH levels. The animals that were free of germs (GF) showed a higher level of stress response and comparatively less anxiety. Brain-derived neurotrophic factor (BDNF) expression changes have also been connected to memory loss [35]. It has been demonstrated that some substances are helpful in controlling the growth of new neurons, the regeneration of muscles, differentiation, and cognitive functions. [36]. The GM reported on the effects of probiotic or antibiotic therapy and gut bacterial colonization on GBA. Since GBA has been proven to use neurotransmitter receptors to transmit data, bacteria must possess these receptors. The host normally provides enteric neurotransmitter binding sites, which GM's function is changed [37]. The vagus nerve, which the GBA inhabits, allows the GIT and the brain to communicate functionally [38].

4.2. Gut to Brain

Social stressors have been shown to alter the GM population's profiles and lower the primary phyla's corresponding abundances that are involved with the microbiota [39]. Numerous characteristics are produced by the microbiome in the GBA, such as mucus secretion, motility,

acidity, bicarbonate, intestinal secretions management, and mucosal immune reaction. These pressures impact these factors. Failure of the GBA disrupts the regular mucosal environment, which modifies the GM [40]. Modifications in intestinal permeability may impact the microbiota's composition and abilities [41]. During surgery, norepinephrine was released, which changed Pseudomonas aeruginosa GM expression and caused gut sepsis. Moreover, the research by Truccollo et al. has demonstrated that certain enteric pathogen strains, like Campylobacter jejuni and Escherichia coli, are more hazardous when norepinephrine is present because it encourages their proliferation.

5. Neurology pathway in the gut-brain axis

A part of the neurological pathway is the vagus nerve, ENS, and GIT's neurotransmitter activity, which causes the release of many hormones from the sensory nerves, such as histamine, melatonin, and serotonin. The GIT also releases catecholamines, acetylcholine, and GABA [42]. Endocrine and immunological systems are the two main routes implicated in this pathway.

5.1. The endocrinal pathway

Enteric endocrine cells (EECs) discharge peptides with physiological activity in the endocrine route to modify the GM's nutrient availability. This indicates a connection between Peptide release from EECs and nutrient sensing, and that the physiologically dynamic peptide alters the GBA [43]. In the gut lumen, EECs create about twenty hormones and/or peptides that serve as indicators for microorganisms, poisons found in food, nutrition, and non-nutrient pollutants. They also control the absorption of nutrients, the intestinal immune response, and the protection of the epithelial barrier [44]. EECs affect food intolerances, the process of breaking down and absorbing nutrients, and defense systems against poisons [45]. The EECs' secretory components are discharged into the circulation and target neurons through paracrine processes [46]. Pre- and post-synaptic proteins, as well as the survival, growth, and function of neurons, are supported by neurotrophin receptors. Synaptic protein synthesis increases the likelihood of synapses forming between neurons using the ENS and EECs to feed the intestinal lumen. One active peptide is galanin which influences blood pressure regulation, appetite, mood, nociception, cell cycle regulation, sleep/wake cycles, and neurotrophic and parental functions [47]. In order to centrally activate the HPA axis, it also influences the synthesis of adrenocorticotropic hormone and

corticotrophin-releasing factor. Galanin causes the adrenal cortex to secrete more glucocorticoids while releasing cortisol from the adrenal cortex and the adrenal medulla's norepinephrine [48].

5.2. Immune pathway

The immunological pathway, which involves immunity through intestinal cytokine regulation, is another significant mechanism. The GBA allows cytokines to enter the bloodstream and travel to the brain. The immune system is recognized as a key coordinator of the brain and microbiota through the GBA. When bacteria with related molecular patterns (MAMPs) trigger the immune system, it can result in neuroinflammation or neurological diseases. This can happen in both the gut and the brain. Upon binding these MAMPs to toll-like receptors (TLRs), TNF-α, IL1β, IL6, and IL17 are among the cytokines activated immune cells produce that promote inflammation. These cytokines transcend the cerebral blood barrier and induce neurological problems [49]. The GM regulates the inflammatory metabolism during dysbiosis in the GIT, primarily through their immune system's release of many inflammatory cytokines, such as IFN-y, IL-10 and IL-4 [50]. ENS dysregulation, which causes aberrant microbial populations, enhanced Permeability of the intestinal epithelium, activation of the permeability and sensory pathways in the gut, and mucosal innate immune responses, is one well-established feature of IBS, or irritable bowel syndrome. The immune system's effects may impact GIT and GBA functions on intestinal secretion and motility and cause cellular entero-endocrine function anomalies and visceral hypersensitivity [51]. When the inflammatory caspase-1 is activated, Certain MAMPs release pro-inflammatory cytokines, such as IL1β and IL18, which cause neurological disorders [52]. Research has demonstrated a correlation between anti-TNF-α and a 78% decrease in Parkinson's disease [53]. Citrobacter rodentium infection in Pink1−/− mice is connected to an increase in the brain pathology of Parkinson's disease and motor disability. It also improves auto-reactive CD8 T cells and mitochondrial antigen presentation [54]. Furthermore, other findings imply that a reduction in tight junction marker expression and an elevation in TLR4 expression of CD3 in the colonic mucosa mediate the connection between microbes and Parkinson's disease regulation. Helicobacter pylori intestinal infections positively correlate with AD and induce pro-inflammatory innate and adaptive immunological responses [55]. Research indicates that there may be a larger or lower frequency of Th17 cells in MS patients due to their positive correlation with Streptococcus and negative correlation with Prevotella in the small intestine. Thus,

controlling immune cell homeostasis has been shown to be a different method of transferring microorganisms in the GBA, from the brain to the stomach [41].

6. The interplay of gut microbiota in neurodegenerative disorders

6.1. Role of GM in Parkinson's disease

In Parkinson's disease, Dopaminergic nerve cells in the substantia nigra, which is a part of the brain's central nervous system, are coated with α-synuclein (α-syn). A characteristic of Parkinson's disease is that When α-syn is present, which is transmitted via the vagus nerve from the gut to the brain. Neurodegeneration and the modification of several cellular pathways are the outcomes of alterations associated with age in the pathogenesis or the disease's advancement [56, 57]. Parkinson's disease (PD) is rare in those under 50, and as people age, their chance of developing the illness rises five to ten times. Men are primarily affected, and for every 100,000 people, there are 5–35 new instances per year [58]. PD patients experience intestinal dysbiosis due to GIT abnormalities, which have been connected to α-syn deposits in the ENS [59].

The GM's role has been shown to increase the possibility that the host microbiota may interact physiologically through cytokine networking PD [60]. Also connected to ENS deterioration in PD patients is idiopathic constipation [61]. Also, it has been demonstrated that when compared to the proportions of Enterobacteriaceae, there was a significant drop in Prevotellaceae species in the PD patients' stool samples. As mediators of neuroinflammatory processes, SCFAs, or short-chain fatty acids, have been found in an in vivo study using the PD model [62].

Antibiotic supplementation aids PD sufferers and their behavioral signs. Using the Parkinson's disease paradigm, Tyrosine decarboxylases produced by intestinal microbes have been demonstrated to decrease levodopa plasma levels in rats [63]. These results suggest that GM alterations are important for both the genesis and management of Parkinson's disease. The figure (3) illustrates how GM functions in the GBA in the context of microbial balance and imbalance in the pathophysiology of Parkinson's disease. A healthy brain (left side) is the result of microbial balance. In order to maintain the health of the brain and biological system, it involves altering elements like the growth of beneficial bacteria, balanced SCFAs, eubiosis, increased neurotropic factors, the synthesis of antioxidant enzymes, anti-inflammatory cytokines, omega-3 fatty acids, polyphenols, and dietary fibers, as well as lifestyle modifications like exercise, yoga, and meditation in the host's intestine. PD is pathogenic due to a microbial imbalance (right side).

Constipation, immunological dysregulation and inflammation, intestinal dysbiosis, reduced short-chain fatty acids (SCFA), the western diet, alcohol, etc. are some of the causes, these elements encourage the buildup of α-synuclein, ROS, and pro-inflammatory cytokines (IL1β, IL6, IL17, and TNF-α) in parkinson's disease. These substances are carried from the gut to the brain through the vagus nerve, as shown in **(Fig. 3)**.

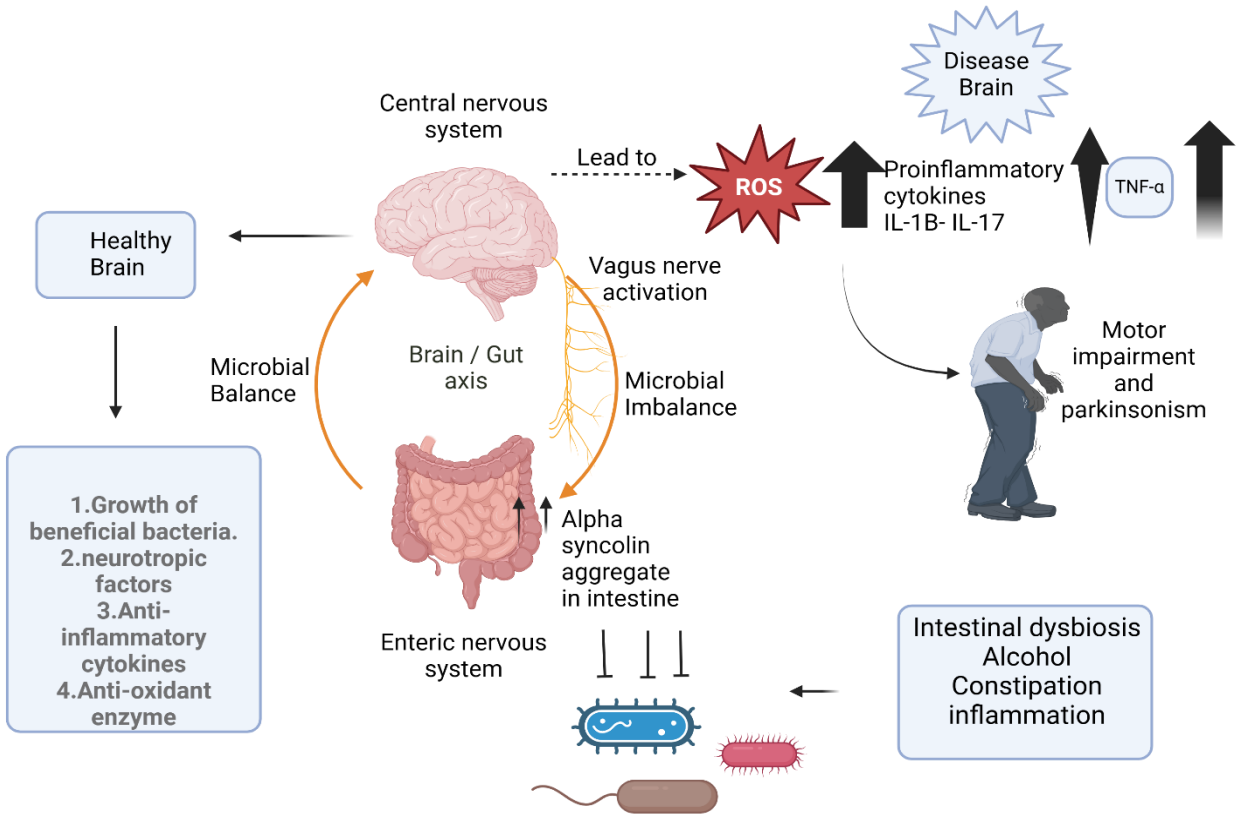

Figure (3): The gut microbiota actions in the GBA in the context of microbial balance and imbalance in the etiology of Parkinson's disease

6.2. Role of GM in Alzheimer disease

The most prevalent neurological illness in the world, AD causes 60–70% of dementia cases [64], and as baby boomers approach retirement age, the frequency of it as well as associated societal and economic difficulties, are growing dramatically. Clinically, AD is characterized by increasing memory and cognitive impairment, which leads to a progressive reduction in mental, behavioral, and functional activities as well as a notable decrease in the patients' life quality daily [65]. Out of all the compounds evaluated for treating AD over the past few decades, the only one the FDA authorized in 2021 was Aducanumab [66].

The absence of a clear understanding of the precise mechanisms underlying the development and progression of AD is one of the primary causes of therapeutic difficulties [67]. Intraneuronal neurofibrillary tangles (NFTs) and extracellular β-amyloid (Aβ) plaques are two pathological features of the AD brain that are required for a definitive AD diagnosis [68]. The accumulation of Aβ as a result of excess production and/or insufficient clearance is thought to be one of the key processes in the development of AD [69].

Historically, Aβ has been associated with the amyloidogenic processing pathway, which comprises the sequential cleavage of the amyloid precursor protein (APP) by β-secretase (BACE1) and related enzymes [70]. In the brains of AD patients, mitochondrial failure results in aberrant mitophagy and oxidative damage, compromising mitochondrial quality control [71]. It has been shown that genetically modified species profile is altered and amounts of Increased levels of cytokines that promote inflammation in non-centrifuged, not stimulated blood, spirochaetes, and Chlamydia pneumonia [72].

In individuals with brain amyloidosis and cognitive impairment, Shigella and Escherichia coli are examples of pro- and anti-inflammatory microorganisms that can upset the microbiota, aggravating neurodegeneration and inducing systemic inflammation [73]. Increased production of the GM inflammasome proteins occurs, and these proteins are essential because they act as a bridge before inflammatory and cytotoxic mediators are later activated. A crucial treatment for neurological issues linked to the AD hereditary predisposition may be genetic modification of the genome, because neuro-inflammation may be exacerbated by the gastrointestinal inflammasome NLRP3 protein [74].

A study by Peterson et al. revealed that, in contrast to mice of the wild type, the age-dependent fecal short-chain fatty acid (SCFA) content as well as microbiological makeup in AD mouse models indicated a notable rise in Proteobacteria and Verrucomicrobia and a notable decline in Butyricoccus and Ruminococcus. Together with the reductions in SCFA levels, these alterations in the composition and diversity of microorganisms suggest that at least 30 metabolic pathways have been disrupted.

Interestingly, It has been shown that eating probiotics and implementing dietary modifications, such as ketogenic diets, can slow the progression of AD [75]. These results imply that genetically modified organisms influence the mechanisms behind AD and its management. Figure 4 shows how GM contributes to AD pathogenesis through GBA under both microbial

imbalance and balance situations. A state of microbial balance in the intestine results in a healthy brain (left side). The development of good bacteria, balanced SCFAs, eubiosis, elevated neurotropic factors, synthesis of antioxidant enzymes, anti-inflammatory cytokines, omega-3 fatty acids, polyphenols, dietary fibers, and lifestyle modifications like yoga and meditation are all factors that impact brain health, when there is a microbial imbalance, a pathogen (right side) causes Alzheimer's disease. It could result from intestinal dysbiosis, immunological dysregulation and inflammation, dietary fiber constipation, short-chain fatty acids (SCFA) reduction, and other issues. GM inflammasome proteins cause tau protein hyperphosphorylation and the development of amyloid-load plaque in the brain. Inflammasome activation also results in systemic inflammation, neurodegeneration, cognitive decline, and brain amyloidosis, all of which contribute to the pathophysiology of AD, as shown in **(Fig. 4)**.

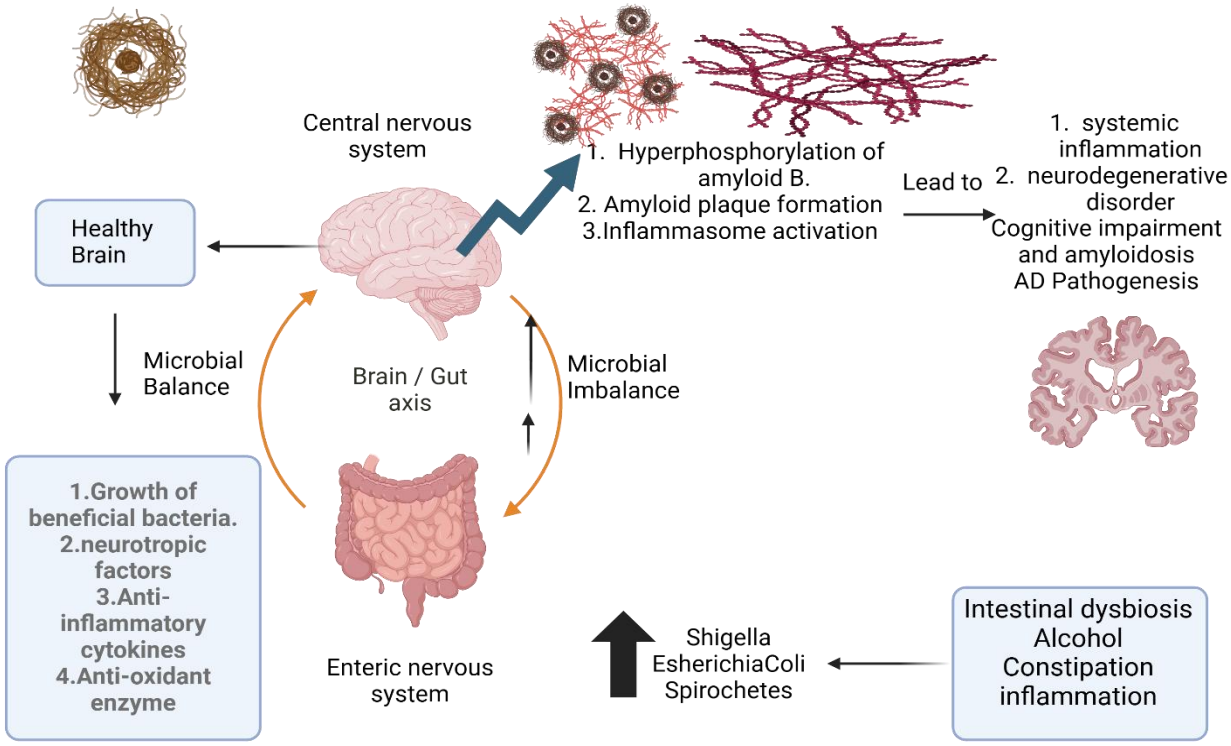

Figure (4): The gut microbiota actions in the GBA in the context of microbial balance and imbalance in the pathophysiology of Alzheimer disease.

7. Conclusion

In conclusion, there is growing evidence that the gut microbiota plays a critical role in the brain's normal growth and development. Besides, neurological and immunological mechanisms in the brain may be influenced by Products generated from microbiota. Moreover, numerous experimental and clinical investigations have determined that neurological dysfunctions such as PD and AD are associated with gut microbiota imbalance. As a result, microbiota-targeted therapies may potentially be an effective treatment to enhance the outcomes of patients with NDDs.

Future perspectives

It's interesting to note that researchers can utilize interventional strategies such as prebiotics, probiotics, and fecal transplants to uncover more detailed reasons and how underlying processes affect. Longer follow-up studies, the right sample size, and It is important to consider more studies on the effects of microbial treatment interventions as well as possible drug combinations [76]. Since the beneficial effects on neurologic disorders vary and depend on the therapeutic bacterial strain, more research is required to determine the most advantageous microbiological or unique formulation for every specific neurologic condition [77]. Finding a healthy microbial flora is now one of the most challenging issues due to the significant interindividual variability in the GI microbiome. Microbiota-targeted treatments, however, can also be advantageous since they may represent a step toward precision medical techniques [78]. Furthermore, it will be crucial to identify the roles of the microbial products and any potential host interactions and comprehend the molecular mechanisms driving the bidirectional microbiota-gut-brain cross-talk. Confirming the impact of food components and microbe-derived metabolites on host physiology and health is necessary to develop treatment strategies [79]. Future studies in the field of neurotherapeutics will yield valuable insights into the gut microbiota as a novel barrier separating human health from a range of disorders.

Concerning microbiome-based therapeutics and the importance of probiotics and prebiotics, the alterations of the gut microbiome in neurodegenerative disease patients have prompted researchers to explore the clinical applications of microbiome-based therapeutics, including prebiotics, probiotics, and FMT. The rationale is further supported by several studies demonstrating that the human gut microbiome is a major determinant of plasma metabolome,

potentially playing a more dominant role than genetics. According to The International Scientific Association for Probiotics and Prebiotics (ISAPP), probiotics are defined as "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host". The administration of probiotics generally aims to introduce defined microbial strains to stimulate the health-promoting pathways in the microbiome and increase the production of beneficial metabolites. The development of new cultivation and sequencing technologies, along with the expansion of our knowledge of the human gut microbiota landscape, has enabled probiotics to move beyond the traditional *Lactobacillus* and *Bifidobacterium* to the next-generation probiotics (NGPs). Examples of NGPs include *A. muciniphila*, *Faecalibacterium prausnitzii*, *Roseburia intestinalis*, and *Bacteroides fragilis*. On the other hand, a prebiotic is defined by ISAPP as "a substrate that is selectively utilized by host microorganisms conferring a health benefit". Prebiotics are non-digestible substances that selectively stimulate the growth of beneficial bacteria to increase the production of associated metabolites. The most extensively documented prebiotics include inulin, FOS, and GOS, which promote the growth of *Lactobacillus* or *Bifidobacterium* spp. Nevertheless, technological advances have expanded the targets of prebiotics beyond *Lactobacillus* and *Bifidobacterium*, to other newly identified health-promoting gut microbes, such as *Roseburia, Eubacterium*, and *Faecalibacterium* spp. Probiotics and prebiotics prove effective in re-establishing beneficial gut microbiota and restoring metabolic functions, particularly the SCFA-producing species, resulting in elevated levels of SCFAs. The alleviation of biological barrier impairments and the reduction in systemic LPS levels attenuate systemic inflammation and glial activation, resulting in reduced neurodegenerative disease pathology. Furthermore, the administration of probiotics and prebiotics appears to contribute to restoring neurotransmitter systems in neurodegenerative disease models [24]. With the aid of cutting-edge technologies, we are beginning to delineate the intricate communication between gut microbiota and glial cells in neurodegenerative diseases. A dysregulated gut microbiome adversely affects glial cells by compromising the integrity of the intestinal barrier and BBB, with recent evidence also revealing the involvement of the meningeal barrier. The available preclinical evidence supports using probiotics, prebiotics, and FMT to attenuate glial activation and cognitive impairment by restoring the integrity of the intestinal barrier and BBB. Nevertheless, the clinical translation of microbiome-based therapeutics remains challenging, underscoring the need for continued research efforts to unravel the complexities of

the microbiota–gut–brain axis and fully harness their potential. Establishing a definitive causal relationship between the altered gut microbiome and disease remains challenging as it is difficult to determine whether the observed microbiome alterations are causative, consequential, or merely a bystander response to the disease. Moreover, existing animal models do not fully recapitulate the intricacies of the human microbiome and pathobiology. Thus, the excessively high rate (95%) of positive results and causal claims in human microbiota-associated rodents demands caution against overinterpreting and overstating the causal implications of these findings. Nevertheless, when combined with single-cell technologies and computational techniques, animal models remain essential complementary tools as they offer valuable mechanistic insights that are difficult to obtain through human studies [24]. The increasing maturity of technical and methodological innovations has enabled us to unravel numerous aspects of the microbiota–gut–brain axis and discover opportunities for therapeutic development. Notably, the recent development of non-invasive, ingestible sampling devices has made it possible to collect luminal contents throughout the intestinal tract, potentially overcoming the limitations of stool samples in reflecting the regional variation of gut microbiota. In addition, the intricate cell-to-cell signaling mechanisms of gut microbiota that regulate community behaviors have been understood. Ultimately, the malleability of the human gut microbiome presents exciting opportunities for the development of personalized microbiome-based therapeutics for neurodegenerative diseases [24].

List of abbreviations:

Abbreviation	Full term
α-syn	α-synuclein
AD	Alzheimer's disease
ALP	Autophagy-lysosome pathway
ALS	Amyotrophic lateral sclerosis
ANS	Autonomic nervous system
ASD	Autism spectrum disorder
BACE1	β-secretase
BDNF	Brain-derived neurotrophic factor
CNS	Central nervous system
EECs	Enteric endocrine cells
ENS	Enteric nervous system
GABA	Gamma-aminobutyric acid

GBA	Gut-brain axis
GIT	Gastrointestinal tract
GM	Gut microbiota
HD	Huntington's disease
IBS	Irritable bowel syndrome
IGF-1	Insulin-like growth factor-1
ISAPP	International Scientific Association for Probiotics and Prebiotics
NDDs	Neurodegenerative disorders
NFTs	Neurofibrillary tangles
PD	Parkinson's disease
PNS	Parasympathetic nervous system
PSP	Progressive supranuclear palsy
ROS	Reactive oxygen species
SCFA	Short-chain fatty acid
SNS	Sympathetic nervous system
TLRs	Toll-like receptors
UPS	Ubiquitin-proteasome system
VN	Vagus nerve

Acknowledgments

Not applicable

Competing interests

The authors report that they have no conflict of interest.

8. References:

1. Wilson DM, Cookson MR, Van Den Bosch L, Zetterberg H, Holtzman DM, Dewachter I. Hallmarks of neurodegenerative diseases. Cell. 2023;186(4):693-714.
2. Hao P, Yang Z, So K-F, Li X. A core scientific problem in the treatment of central nervous system diseases: newborn neurons. Neural Regeneration Research. 2024;19(12):2588-601.
3. Abrahams S, Haylett WL, Johnson G, Carr JA, Bardien S. Antioxidant effects of curcumin in models of neurodegeneration, aging, oxidative and nitrosative stress: A review. Neuroscience. 2019;406:1-21.
4. Milošević M, Arsić A, Cvetković Z, Vučić V. Memorable food: fighting age-related neurodegeneration by precision nutrition. Frontiers in Nutrition. 2021;8:688086.
5. Kayama H, Okumura R, Takeda K. Interaction between the microbiota, epithelia, and immune cells in the intestine. Annual review of immunology. 2020;38:23-48.

6. Toledo ARL, Monroy GR, Salazar FE, Lee J-Y, Jain S, Yadav H, Borlongan CV. Gut–brain axis as a pathological and therapeutic target for neurodegenerative disorders. International Journal of Molecular Sciences. 2022;23(3):1184.
7. Bistoletti M, Bosi A, Banfi D, Giaroni C, Baj A. The microbiota-gut-brain axis: Focus on the fundamental communication pathways. Progress in molecular biology and translational science. 2020;176:43-110.
8. Agnihotri TG, Gomte SS, Peddinti V, Rout B, Shewale RS, Janjal P, Jain A. Role of Microbiota-Derived Exosomes in Gut–Brain Communication for the Treatment of Brain Disorders. Exosomes Based Drug Delivery Strategies for Brain Disorders: Springer; 2024. p. 227-56.
9. Steinman G. The putative etiology and prevention of autism. Progress in molecular biology and translational science. 2020;173:1-34.
10. Cacciatore M, Grasso EA, Tripodi R, Chiarelli F. Impact of glucose metabolism on the developing brain. Frontiers in endocrinology. 2022;13:1047545.
11. Sharkey KA, Mawe GM. The enteric nervous system. Physiological reviews. 2023;103(2):1487-564.
12. Costa M, Spencer NJ, Brookes SJ. The role of enteric inhibitory neurons in intestinal motility. Autonomic Neuroscience. 2021;235:102854.
13. Abg Abd Wahab DY, Gau CH, Zakaria R, Muthu Karuppan MK, Abdullah Z, Alrafiah A, Abdullah JM, Muthuraju S. Review on cross talk between neurotransmitters and neuroinflammation in striatum and cerebellum in the mediation of motor behaviour. BioMed research international. 2019;2019.
14. Tang H, Chen X, Huang S, Yin G, Wang X, Shen G. Targeting the gut–microbiota–brain axis in irritable bowel disease to improve cognitive function–recent knowledge and emerging therapeutic opportunities. Reviews in the Neurosciences. 2023;34(7):763-73.
15. Sánchez Aragón S. The microbiota-gut-brain axis: from dysbiosis to neurodegenerative disease. 2022.
16. Vijay A, Valdes AM. Role of the gut microbiome in chronic diseases: a narrative review. European journal of clinical nutrition. 2022;76(4):489-501.
17. Johnson KV-A, Foster KR. Why does the microbiome affect behaviour? Nature reviews microbiology. 2018;16(10):647-55.
18. Van de Wiele T, Van Praet JT, Marzorati M, Drennan MB, Elewaut D. How the microbiota shapes rheumatic diseases. Nature Reviews Rheumatology. 2016;12(7):398-411.
19. Erkkinen MG, Kim M-O, Geschwind MD. Clinical neurology and epidemiology of the major neurodegenerative diseases. Cold Spring Harbor perspectives in biology. 2018;10(4):a033118.
20. Wang F, Pritzkow S, Soto C. PMCA for ultrasensitive detection of prions and to study disease biology. Cell and Tissue Research. 2023;392(1):307-21.
21. Saier Jr MH, Baird SM, Reddy BL, Kopkowski PW. Eating Animal Products, a Common Cause of Human Diseases. Microbial Physiology. 2022;32(5-6):146-57.
22. Wilhelm T, Said M, Naim V. DNA replication stress and chromosomal instability: dangerous liaisons. Genes. 2020;11(6):642.
23. Wendimu MY, Hooks SB. Microglia phenotypes in aging and neurodegenerative diseases. Cells. 2022;11(13):2091.

24. Loh JS, Mak WQ, Tan LKS, Ng CX, Chan HH, Yeow SH, Foo JB, Ong YS, How CW, Khaw KY. Microbiota–gut–brain axis and its therapeutic applications in neurodegenerative diseases. Signal transduction and targeted therapy. 2024;9(1):37.
25. Fukushi Y, Golanov EV, Koizumi S, Thura M, Ihara H, Yamamoto S. The Cholinergic Pathway and MitoKATP Induce UCP4 Expression Involved in Neuroprotection of FN Stimulation in Rats. Stroke: Vascular and Interventional Neurology. 2022;2(6):e000362.
26. Liu J, Duan W, Deng Y, Zhang Q, Li R, Long J, Ahmed W, Gu C, Qiu Y, Cai H. New insights into molecular mechanisms underlying neurodegenerative disorders. Journal of Integrative Neuroscience. 2023;22(3):58.
27. Zhang Y-m, Qi Y-b, Gao Y-n, Chen W-g, Zhou T, Zang Y, Li J. Astrocyte metabolism and signaling pathways in the CNS. Frontiers in Neuroscience. 2023;17:1217451.
28. Sies H, Jones DP. Reactive oxygen species (ROS) as pleiotropic physiological signalling agents. Nature reviews Molecular cell biology. 2020;21(7):363-83.
29. Sadiq IZ. Free radicals and oxidative stress: Signaling mechanisms, redox basis for human diseases, and cell cycle regulation. Current Molecular Medicine. 2023;23(1):13-35.
30. Muñoz-Lasso DC, Romá-Mateo C, Pallardó FV, Gonzalez-Cabo P. Much more than a scaffold: cytoskeletal proteins in neurological disorders. Cells. 2020;9(2):358.
31. Bason M. Cell-autonomous and non-cell autonomous protection of DNAJB6 in Huntington's disease. 2019.
32. Kaur R, Kaur H, Rajput R, Kumar S, Rachana R, Singh M. Neurodegenerative Disorders Progression: From Synaptic Dysfunction to Transmission Failure. Handbook of Research on Critical Examinations of Neurodegenerative Disorders: IGI Global; 2019. p. 129-52.
33. Dash S, Syed YA, Khan MR. Understanding the role of the gut microbiome in brain development and its association with neurodevelopmental psychiatric disorders. Frontiers in Cell and Developmental Biology. 2022;10:880544.
34. Morais LH, Schreiber IV HL, Mazmanian SK. The gut microbiota–brain axis in behaviour and brain disorders. Nature Reviews Microbiology. 2021;19(4):241-55.
35. Lynch CM, Nagpal J, Luczynski P, Neufeld K-AM, Dinan TG, Clarke G, Cryan JF. Germ-Free Animals: A Key Tool in Unraveling How the Microbiota Affects the Brain and Behavior. The Gut-Brain Axis: Elsevier; 2024. p. 401-54.
36. Almada AE, Wagers AJ. Molecular circuitry of stem cell fate in skeletal muscle regeneration, ageing and disease. Nature reviews Molecular cell biology. 2016;17(5):267-79.
37. Carabotti M, Scirocco A, Maselli MA, Severi C. The gut-brain axis: interactions between enteric microbiota, central and enteric nervous systems. Annals of gastroenterology: quarterly publication of the Hellenic Society of Gastroenterology. 2015;28(2):203.
38. Rajanala K, Kumar N, Chamallamudi MR. Modulation of gut-brain axis by probiotics: a promising anti-depressant approach. Current Neuropharmacology. 2021;19(7):990-1006.
39. Galley JD, Nelson MC, Yu Z, Dowd SE, Walter J, Kumar PS, Lyte M, Bailey MT. Exposure to a social stressor disrupts the community structure of the colonic mucosa-associated microbiota. BMC microbiology. 2014;14:1-13.
40. Takiishi T, Fenero CIM, Câmara NOS. Intestinal barrier and gut microbiota: Shaping our immune responses throughout life. Tissue barriers. 2017;5(4):e1373208.
41. Karl JP, Margolis LM, Madslien EH, Murphy NE, Castellani JW, Gundersen Y, Hoke AV, Levangie MW, Kumar R, Chakraborty N. Changes in intestinal microbiota composition and metabolism coincide with increased intestinal permeability in young adults under prolonged

physiological stress. American Journal of Physiology-Gastrointestinal and Liver Physiology. 2017;312(6):G559-G71.
42. Gupta S, Dinesh S, Sharma S. Bridging the Mind and Gut: Uncovering the Intricacies of Neurotransmitters, Neuropeptides, and their Influence on Neuropsychiatric Disorders. Central Nervous System Agents in Medicinal Chemistry (Formerly Current Medicinal Chemistry-Central Nervous System Agents). 2024;24(1):2-21.
43. Manoharan N, Jayamurali D, Parasuraman R, Govindarajulu SN. Brain Related Gut Peptides–A Review. Protein and Peptide Letters. 2022;29(12):1016-30.
44. Woźniak D, Cichy W, Przysławski J, Drzymała-Czyż S. The role of microbiota and enteroendocrine cells in maintaining homeostasis in the human digestive tract. Advances in medical sciences. 2021;66(2):284-92.
45. Roura E, Depoortere I, Navarro M. Chemosensing of nutrients and non-nutrients in the human and porcine gastrointestinal tract. Animal. 2019;13(11):2714-26.
46. Latorre R, Sternini C, De Giorgio R, Greenwood-Van Meerveld B. Enteroendocrine cells: a review of their role in brain–gut communication. Neurogastroenterology & Motility. 2016;28(5):620-30.
47. Agrawal S, Kumar V, Singh V, Singh C, Singh A. A review on pathophysiological aspects of sleep deprivation. CNS & Neurological Disorders-Drug Targets (Formerly Current Drug Targets-CNS & Neurological Disorders). 2023;22(8):1194-208.
48. Raise-Abdullahi P, Meamar M, Vafaei AA, Alizadeh M, Dadkhah M, Shafia S, Ghalandari-Shamami M, Naderian R, Afshin Samaei S, Rashidy-Pour A. Hypothalamus and post-traumatic stress disorder: a review. Brain sciences. 2023;13(7):1010.
49. Sittipo P, Choi J, Lee S, Lee YK. The function of gut microbiota in immune-related neurological disorders: A review. Journal of Neuroinflammation. 2022;19(1):154.
50. Antonini M, Lo Conte M, Sorini C, Falcone M. How the interplay between the commensal microbiota, gut barrier integrity, and mucosal immunity regulates brain autoimmunity. Frontiers in immunology. 2019;10:474135.
51. McDonell AF. Effects of the Gut Microbiota on Intestinal Function: Queen's University (Canada); 2020.
52. Piancone F, La Rosa F, Marventano I, Saresella M, Clerici M. The role of the inflammasome in neurodegenerative diseases. Molecules. 2021;26(4):953.
53. Kip E, Parr-Brownlie LC. Reducing neuroinflammation via therapeutic compounds and lifestyle to prevent or delay progression of Parkinson's disease. Ageing Research Reviews. 2022;78:101618.
54. Cannon T, Sinha A, Trudeau L-E, Maurice CF, Gruenheid S. Characterization of the intestinal microbiota during Citrobacter rodentium infection in a mouse model of infection-triggered Parkinson's disease. Gut Microbes. 2020;12(1):1830694.
55. Balani GF, dos Santos Cortez M, da Silveira Freitas JEP, de Melo FF, Zarpelon-Schutz AC, Teixeira KN. Immune response modulation in inflammatory bowel diseases by Helicobacter pylori infection. World Journal of Gastroenterology. 2023;29(30):4604.
56. Sorboni SG, Moghaddam HS, Jafarzadeh-Esfehani R, Soleimanpour S. A comprehensive review on the role of the gut microbiome in human neurological disorders. Clinical Microbiology Reviews. 2022;35(1):e00338-20.
57. Mohammed OA, Elballal MS, El-Husseiny AA, Khidr EG, El Tabaa MM, Elazazy O, Abd-Elmawla MA, Elesawy AE, Ibrahim HM, Abulsoud AI. Unraveling the role of miRNAs in

the diagnosis, progression, and therapeutic intervention of Parkinson's disease. Pathology-Research and Practice. 2024;253:155023.
58. Baldereschi M, Di Carlo A, Rocca WA, Vanni P, Maggi S, Perissinotto E, Grigoletto F, Amaducci L, Inzitari D. Parkinson's disease and parkinsonism in a longitudinal study: two-fold higher incidence in men. Neurology. 2000;55(9):1358-63.
59. Kumari S, Taliyan R, Dubey SK. Comprehensive review on potential signaling pathways involving the transfer of α-synuclein from the gut to the brain that leads to Parkinson's disease. ACS Chemical Neuroscience. 2023;14(4):590-602.
60. Ahlawat S, Asha, Sharma K. Gut–organ axis: a microbial outreach and networking. Letters in applied microbiology. 2021;72(6):636-68.
61. Chalazonitis A, Rao M. Enteric nervous system manifestations of neurodegenerative disease. Brain research. 2018;1693:207-13.
62. Mirzaei R, Bouzari B, Hosseini-Fard SR, Mazaheri M, Ahmadyousefi Y, Abdi M, Jalalifar S, Karimitabar Z, Teimoori A, Keyvani H. Role of microbiota-derived short-chain fatty acids in nervous system disorders. Biomedicine & Pharmacotherapy. 2021;139:111661.
63. Scheperjans F, Aho V, Pereira PA, Koskinen K, Paulin L, Pekkonen E, Haapaniemi E, Kaakkola S, Eerola-Rautio J, Pohja M. Gut microbiota are related to Parkinson's disease and clinical phenotype. Movement Disorders. 2015;30(3):350-8.
64. Haque RU, Levey AI. Alzheimer's disease: A clinical perspective and future nonhuman primate research opportunities. Proceedings of the national Academy of Sciences. 2019;116(52):26224-9.
65. DeTure MA, Dickson DW. The neuropathological diagnosis of Alzheimer's disease. Molecular neurodegeneration. 2019;14(1):32.
66. Cacabelos R, Carrera I, Martínez-Iglesias O, Cacabelos N, Naidoo V. What is the gold standard model for Alzheimer's disease drug discovery and development? Expert Opinion on Drug Discovery. 2021;16(12):1415-40.
67. Breijyeh Z, Karaman R. Comprehensive review on Alzheimer's disease: causes and treatment. Molecules. 2020;25(24):5789.
68. Jellinger KA. Neuropathological assessment of the Alzheimer spectrum. Journal of Neural Transmission. 2020;127(9):1229-56.
69. Nalivaeva NN, Turner AJ. Targeting amyloid clearance in Alzheimer's disease as a therapeutic strategy. British journal of pharmacology. 2019;176(18):3447-63.
70. Hampel H, Hardy J, Blennow K, Chen C, Perry G, Kim SH, Villemagne VL, Aisen P, Vendruscolo M, Iwatsubo T. The amyloid-β pathway in Alzheimer's disease. Molecular psychiatry. 2021;26(10):5481-503.
71. Song M, Zhao X, Song F. Aging-dependent mitophagy dysfunction in Alzheimer's disease. Molecular Neurobiology. 2021;58(5):2362-78.
72. Borrero JAC, Aulestia JVM, Espinoza AC, Alcivar NMY, Mora RGV, Abarca FLP. Systematic analysis of the relationship between intestinal microbiota and neurological disorders: emerging perspective in neurogastroenterology. Sapienza: International Journal of Interdisciplinary Studies. 2024;5(2):e24031-e.
73. Padhi P, Worth C, Zenitsky G, Jin H, Sambamurti K, Anantharam V, Kanthasamy A, Kanthasamy AG. Mechanistic insights into gut microbiome dysbiosis-mediated neuroimmune dysregulation and protein misfolding and clearance in the pathogenesis of chronic neurodegenerative disorders. Frontiers in neuroscience. 2022;16:836605.

74. Holbrook JA, Jarosz-Griffiths HH, Caseley E, Lara-Reyna S, Poulter JA, Williams-Gray CH, Peckham D, McDermott MF. Neurodegenerative disease and the NLRP3 inflammasome. Frontiers in pharmacology. 2021;12:643254.
75. Paoli A, Mancin L, Bianco A, Thomas E, Mota JF, Piccini F. Ketogenic diet and microbiota: friends or enemies? Genes. 2019;10(7):534.
76. Tan Q, Orsso CE, Deehan EC, Kung JY, Tun HM, Wine E, Madsen KL, Zwaigenbaum L, Haqq AM. Probiotics, prebiotics, synbiotics, and fecal microbiota transplantation in the treatment of behavioral symptoms of autism spectrum disorder: A systematic review. Autism Research. 2021;14(9):1820-36.
77. Umbrello G, Esposito S. Microbiota and neurologic diseases: potential effects of probiotics. Journal of Translational Medicine. 2016;14:1-11.
78. Sharpton S, Schnabl B, Knight R, Loomba R. Current concepts, opportunities, and challenges of gut microbiome-based personalized medicine in nonalcoholic fatty liver disease. Cell metabolism. 2021;33(1):21-32.
79. Zhang LS, Davies SS. Microbial metabolism of dietary components to bioactive metabolites: opportunities for new therapeutic interventions. Genome medicine. 2016;8:1-18.