

RECENT ADVANCES IN GUT MICROBIOTA- BRAIN INTERACTIONS: EMERGING INSIGHTS AND THERAPEUTIC IMPLICATIONS FOR NEURODEGENERATIVE AND NEUROPSYCHIATRIC DISORDERS

Priti Nandi¹, Subhasis Sarkar², Bidisha Ghosh^{*}

¹Department of Biotechnology, School of Life Sciences, Swami Vivekananda University, Telinipara, Barrackpore, Barasat, Kolkata- 700121

²Department of Microbiology, School of Life Sciences, Swami Vivekananda University, Telinipara, Barrackpore, Barasat, Kolkata- 700121

*Corresponding author: bidishag@svu.ac.in

ABSTRACT

Gut microbiota, also considered as the “second brain” play a pivotal role in regulating the physiological conditions as well as several neurochemical pathways through bidirectional communication in the gut-brain axis. The bidirectional pathway between microflora and the brain consists of vagus nerve, neuroendocrine, and immune system components. It indicates that a variety of neurodevelopmental, neurodegenerative, and neuropsychiatric disorders may be influenced by gut microorganisms, which may also affect behaviour, modify neurotransmission, and structure of brain development. The aim of this review article focused on the correlation between gut microflora and the brain and understand the significant role of gut microbiome in neurodegenerative disorder. The neuro-active metabolites such as short-chain fatty acids, neurotransmitters, and hormones derived from gut microbes can alter the enteric and central nervous system which causes various neurological diseases including Parkinson’s disease, Alzheimer’s disease, Huntington disease, multiple sclerosis, autism, and schizophrenia. It has been established that altering the gut microbiota has positive impacts on neural

networks, which delay the development of neurological diseases. Consequently, the adjustment of gut microbiota via tailored dietary approaches and oral bacteriotherapy could result in changes to gut microbiota and their byproducts. Therefore, this approach may offer a new therapeutic avenue for the medical treatment of neurodegenerative diseases.

Keywords: *Gut microbiota, Gut-brain axis, Neuro-active metabolites, Neurodegenerative disorder, Neuropsychiatric disorder.*

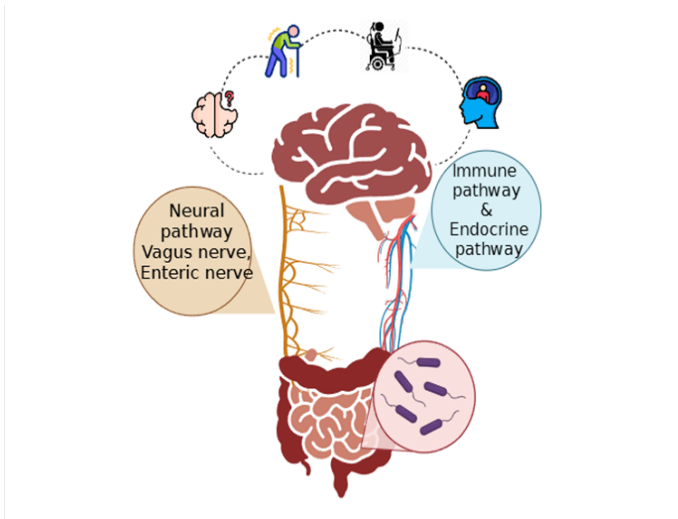


Figure 1.1:A Graphical representation of gut-brain axis(Image::BioRender)

1. Introduction:

The symbiotic bacteria that inhabit our gastrointestinal (GI) system, known as the gut microbiota, function as “metabolic machinery” (McGuinness et al., 2022). They affect multiple aspects of physiological condition through immunological, hormonal, and neurological pathways; in fact, certain individuals refer to the gut microbiota as a “virtual organ” (Clarke et al., 2014). Approximately 10^{14} microorganisms exist in the gastrointestinal tract (GIT) reported by Human Microbiome Project (HMP) and Metagenomics of Human

Intestinal Tract (MetaHIT) (Singh et al., 2022). Firmicutes and Bacteroidetes are the two phyla and Verrucomicrobia, Proteobacteria, Actinobacteria and Fusobacteria species that dominate the balanced proportions of the human GIT microflora (Martin et al., 2018). In past few years, gut microbes have drawn more attention among researchers, and several articles have been published on numerous diseases related to microflora such as irritable bowel syndrome, Crohn's disease, musculoskeletal diseases, neurodegenerative disorders, diabetes, obesity and colon cancer (Zhu et al., 2021). Correspond, studies shows that Actinobacteria, Firmicutes, Proteobacteria and Bacteroidetes are the most common microorganisms in the human the gastrointestinal tract, contributing for around 3%, 64%, 8%, and 23% of the overall microbial population, respectively (Zheng et al., 2020). Therefore, a number of studies are investigating the connections between gut microbiota and different diseases with the aim of developing novel diagnostic and treatment strategies (Lynch & Pedersen, 2016).

Chronic degradation of specific a group of neurons is an indicator of neurodegenerative diseases (Peilin et al., 2021). The main reason behind of the origin of neurodegenerative disease is environmental factors such as diet, lifestyle choice and xenobiotics exposure as well as genetic and aging is another key factor that influence the progression of neurodegenerative disorders (Dugger & Dickson, 2017). The emergence of accumulated proteins, such as amyloid-beta (Ab) and alpha-synuclein (a-syn), is a characteristic of the most common neurological disorders and significantly influences disease pathogenesis (Soto & Pritzkow, 2018). Surprisingly in the genesis of neurodegenerative diseases, the gut microbiota can communicate with these variables and function as an intermediary between the environment and the host. According to recent reports, gut microbes are thought to be crucial elements which communicate with both the extrinsic environmental factor and the central nervous system (CNS) (Jacob et al., 2021). Gut microorganisms use the sympathetic and parasympathetic nervous systems (SNS and PNS) as communication channels (Mohajeri et al., 2018). The diverse range of gut microbes influences both brain

functioning and behavioural patterns. The communication channel between gut microflora and brain, known as gut-brain axis (Wang et al., 2021). Its communication held through vagus nerve, hypothalamic-pituitary-adrenal (HPA) axis, tryptophane metabolism, immune system, peripheral nervous system, endocrine signalling pathway (Gubert et al., 2022). Through these pathways metabolites derived from gut microbiota including short-chain fatty acids (SCFA), gamma aminobutyric acid (GABA), norepinephrine, serotonin, histamine, kynurenines, etc., control a number of cerebral physiological functions in the brain (Kennedy et al., 2017; Rooks & Garrett, 2016). When the intestinal microflora composition get imbalance (i.e. dysbiosis) the brain receives signals which further contribute to the pathological mechanisms of various neurological diseases, especially neurodegeneration, by manifesting as low-grade inflammation, increased oxidative stress, disrupted energy metabolism, and increased cellular degeneration (Mulak & Bonaz, 2015; Noble et al., 2017). However, it has also been documented that major changes in the composition of the gut microbiota occur with human aging, and the aging gut also exhibits a decrease of microbial diversity (Cheng et al., 2013; Friedland, 2015). Additionally, the GI tracts of older people with neurological diseases showed a significant change in the composition of their microbiota (Claesson et al., 2011). Therefore, researchers suggested that changes in the human gut microbiota could be one of the underlying causes of neurodegenerative diseases.

In this review suggest aim to investigate the convergent mechanism in between neurological disorders and gut microbes, and focusing on remarkable biomarkers for a novel therapeutic approach in order treat, diagnose and prevent the neurodegenerative diseases and also to compile the knowledge currently available on the several approaches for gut microbe identification and counselling.

1.1 The Gut-Brain Microbial Axis: A Bidirectional Communication Pathway Between the Brain and Intestinal Microflora

The bidirectional communication between gut microbes and the central nervous system is known as the microbiota-gut-brain

axis (Veiga-Fernandes & Pachnis, 2017). Through hormones, immunological signals, and neurons, the brain can exchange information with intestine (Ceppa et al., 2020). Once in the bloodstream, microorganisms synthesize neuromodulators such as serotonin, short-chain fatty acids, host-derived vitamin B12, and choline (Nishiwaki et al., 2020). With the aid of G protein-coupled receptors, short-chain fatty acids like butyrate and acetate are crucial for altering brain behaviour (Mirzaei et al., 2021). These fatty acids play a major role in energy supply, production of regulatory T-cells (Treg) and activation of trophic factors, and simultaneously maintaining the unity of blood brain barrier and intestine barrier (Dalile et al., 2019; Vogt et al., 2017). It influences various mechanisms including a) development and stimulation of the glial cells of brain to remove any unnecessary connections between synapses or neurons (Batarseh et al., 2016), b) upregulation of anti-inflammatory cytokines and Treg cell production (Cattaneo et al., 2017), c) reduction of neuroinflammation by preventing monocytes, macrophages, and dendritic cells from maturing and differentiating, which lowers their capacity to generate pro-inflammatory cytokines including TNF- α and IL-12 (Sampson et al., 2016), d) maintaining the blood-brain barrier's (BBB) integrity via maintaining the quantity of protein at the tight junction (Shi et al., 2018), e) Neurotrophic factors, neurotransmitters, and neuropeptides in the brain: homeostatic regulation (Foster and Neufeld, 2013), f) maintenance of comprehension and persistent memory function in the brain through histone acetylation-mediated gene expression regulation (Albenberg and Wu, 2014). Immune cells in the GI tract establish cytokines, which travel through peripheral arteries to the brain and stimulate the hypothalamic-pituitary-adrenal (HPA) system. Cortisol is released by the HPA axis and regulates a number of brain processes (Breit et al., 2018). This signalling pathway helps macrophages attach to the α -7 nicotinic cholinergic receptor, which inhibits TNF- α and other cytokines that promote inflammation (Costantini et al., 2012). Additionally, SCFA regulated the expression of 5-HT (5-hydroxytryptophan) and tryptophan hydrolase enzymes (TPH1 & TPH2) which is responsible for serotonin production (Lepage et al., 2013).

Quinolic acid and kynurenic acid is a major metabolite derived by kynurenine pathway where tryptophan is related (Albenberg and Wu, 2014). Quinolic acid acts neurotoxically by attaching to the NMDA receptor, while kynurenic acid exerts neuroprotective effects by antagonistically binding to both the NMDA and the α -7 nicotinic cholinergic receptor (Li et al., 2014). Through the action of the enzyme tryptophanase, gut microbes also control these pathways and affect how tryptophan is converted to indole derivatives (Figure 2) (Goyal et al., 2020). These derivatives control the expression of inflammatory genes by acting on the aryl hydrocarbon receptor (Gulaj et al., 2010).

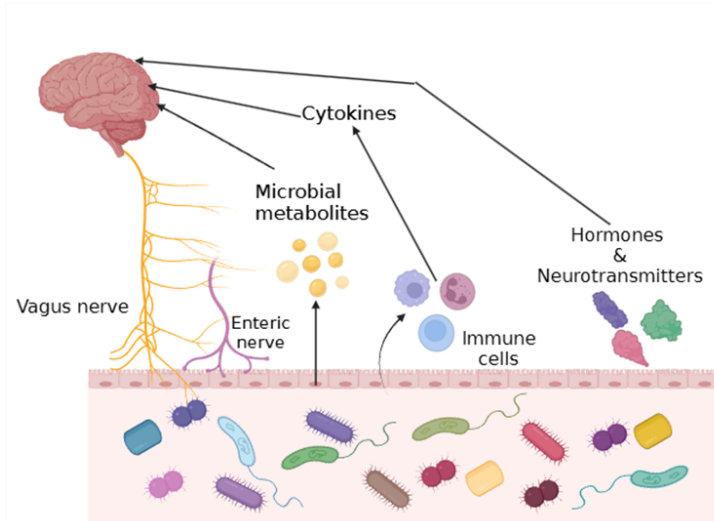


Fig 1.2: The pathways are involved in the Neurological disorders (Image :BioRender)

The direct stimulation of enterochromaffin cells to generate neuropeptides (such as neuropeptide Y, cholecystokinin, GLP-2, peptide YY, glucagon-like peptide-1, and substance P) or neurotransmitters (such as serotonin, GABA) by enteric bacteria and their byproducts (such as SCFA) can affect central nervous system function (Strandwitz et al., 2019). Hence, Myenteric neurons are directly activated by neurotransmitters

and neuropeptides generated from bacteria. These neurons then convey nerve signals to the brain via ascending fibres of the vagal nerve (Kaul et al., 2024). Eliminating the intestinal epithelium gives the gut bacteria and their byproducts the chance to enter and come into direct contact with VN, which activates the vagal afferent fibres via particular receptors or more straightforward means (Han et al., 2022). To trigger nodose ganglia (NG), *Edwardsiella tarda* can attach to the transient receptor potential ankyrin A1 (TRPA1) receptor, which is abundantly distributed on NG (Nodose Ganglia) (Strader & Woods, 2005). Through toll-like receptors (TLR) on their surface, enteroendocrine cells can identify bacterial compounds in the intestinal lumen, like LPS, or use other receptors to identify microbial metabolites, like SCFA. They can then send intestinal signals to vagal afferents via synaptic connections using glutamate as a neurotransmitter, or they can release more than 30 known peptides to stimulate vagal afferents (Ye et al., 2021). By activating enteroendocrine cells through the receptor transient receptor potential ankyrin A1 (TRPA1), *Edwardsiella tarda* can release the neurotransmitter 5-hydroxytryptamine (5-HT), which directly stimulates vagal sensory ganglia. When enteroendocrine cells get isovalerate stimulation, their olfactory receptor 558 can function as a sensory receptor for microbial compounds (Wu et al., 2021). The transmission of intestinal signals is then achieved by the production of 5-HT by enteroendocrine cells, which binds to the 5-HT receptors on vagal afferents (Bellono et al., 2017).

1.2 Role of gut microbiota in neurodegenerative and neuropsychiatric diseases:

Amyotrophic Lateral Sclerosis:

The progressive neurodegenerative disease, amyotrophic lateral sclerosis (ALS) is typified by the degeneration of motor neurons (Kaul et al., 2024). This eventually causes paralysis, muscle weakness, and breathing failure (Jain et al., 2023). A small number of ALS cases are inherited due to mutations in genes like SOD1 and C9orf72, but the majority are random (Kaul et al., 2024). Activated glial cells, impaired axonal transport, and improper protein folding all contribute to neurodegeneration in ALS (Jain et al., 2023).

In ALS, Bacteroidetes and Firmicutes two phyla ratio shown decreased, reported by Zeng et al., 2020 & Zhai et al., 2019. Recent studies discovered that ALS patients had higher levels of *Prevotella copri* and lower levels of eight prominent butyrate-producing bacteria, such as *Eubacterium rectale* and *Roseburia intestinalis* (Nicholson et al., 2021). Also, it revealed that OTU10032 unclassified Acidaminococcaceae and Enterobacteriaceae were linked to an increased incidence of ALS (Zhang et al., 2022). Another study demonstrated alterations in the microbiota composition of ALS patients, with a decline in the relative abundances of Streptococcaceae and Ruminococcaceae in the patients, while the prominent families in healthy controls were Bacteroidaceae and Succinivibrionaceae (Ozaydin et al., 2024). Guo et al., 2024 revealed that microflora derived metabolites accumulation cause the ALS. This research may improve the reliability of putative biomarkers and provide mechanistic understanding of when ALS develops. According to a study by Davis and colleagues, cyanobacteria, or blue green algae, are connected to ALS and can cause the disease due to toxins in the algae blooms (Torbick et al., 2014). They suggested that the cyanotoxin *b*-N-methylamino-L-alanine (BMAA) would cause a similar pathology because microglial activation and protein aggregation in motor neurons are recognized to be the main pathology accompanying this disease. Degeneration of motor neurons was observed in BMAA-dosed vervets due to reactive astrogliosis, activated microglia, TDP-43 proteinopathy in anterior horn cells, and damage to myelinated axons in the lateral corticospinal tracts (Hertzberg et al., 2022). Interestingly, vervets administered BMAA þ L-serine showed fewer neuropathological alterations, indicating that long-term nutritional exposure to BMAA results in pathological alterations of the ALS/MND type within the vervet and that coadministration of L-serine lowers the degree of development and motor cortex damage (Kaul et al., 2024).

Parkinson Disease:

The primary neuropathological biomarker that emerged in Parkinson's disease was the accumulation of α -Synuclein in the stomach, nerve fiber, and ganglionic α mucosa and

submucosa (Rai et al., 2017). Through the vagus nerve, the intestine's synuclein protein contributes to communication between the gut and the brain (Fitzgerald et al., 2019). Parkinson's disease is most consistently associated with changes in the gut microbiota. There has been a decrease in bacteria belonging to the genus *Faecalibacterium* and an increase in the populations of bacteria belonging to the genera *Lactobacillus*, *Bifidobacterium*, and *Akkermansia* (Romano et al., 2021). There were fewer Parkinson's disease patients with *Lactobacillus*, *Bacteroides*, *Prevotella*, and *Bifidobacterium*, among other helpful microorganisms. In addition, patients with Parkinson's disease had higher populations of harmful bacteria, including *Enterobacteria*, *Streptococci*, *Staphylococci*, *Shigella*, and *Helicobacter* (Vamanu & Rai, 2021). Additionally, the microorganisms in the gut affect the generation of dopamine, the buildup of α -synuclein, oxidative stress, local inflammation, intestinal permeability, and constipation (Doroszkiewicz et al., 2021). Through reducing pro-inflammatory nuclear factor- κ B (NF- κ B) signalling, the Pirin-like protein found in *B. thetaiotaomicron*'s anti-inflammatory effect shields epithelial cells (Singh et al., 2022). Additionally, an increase in *Lactobacillaceae* and a decline in the population of *Prevotellaceae* in the gut microbiome are linked to lower levels of the gut hormone ghrelin, which controls the activity of nigrostriatal dopamine (Caputi & Giron, 2018). The bacteria *Prevotella* controls the intestinal layer's mucin production process. As a result, the Parkinson's disease patient is disturbed by the intestinal production of mucin. Moreover, Parkinson's disease patients' microbiomes are characterized by a decrease in butyrate-producing bacteria like *Blautia*, *Coprococcus*, and *Roseburia* and an increase in proinflammatory *Proteobacteria*, which may lead to inflammation-induced misfolding of α -syn (Singh et al., 2022).

Alzheimer disease:

Alzheimer's disease (AD) is a multifaceted, intricate illness that includes both neurodegeneration and persistent neuroinflammation (Goyal et al., 2020). The accumulation of amyloid beta ($A\beta$), hyperphosphorylated tau proteins, and

neurofibrillary tangles (NFTs) in brain tissue are pathogenic characteristics of AD (Zhu et al., 2020). Microbiota-derived compounds in patients' cerebral spinal CSF make gut microbiota a dynamic element in the aetiology of disease (Zhu et al., 2020). Both amyloid and lipopolysaccharides (LPS), which impair the gastrointestinal tract's permeability and the BBB's function, are produced when the gut microbial population experiences dysbiosis (Kowalski & Mulak, 2019). Amyloid molecules can be detected and eliminated by microglia's TLR4 and TLR2 receptors. The activation of nuclear factor kappa B and TNF α is caused by the production of a signal of myeloid differentiation main response 88 (MyD88) by microglial TLR2. A β is also stimulated by α MyD88 through the upregulation of β -secretase and -secretase (Kaul et al., 2024). The gut microflora distribution has been visualized in **Table 1**.

Schizophrenia:

Schizophrenia is a diverse neurodevelopmental condition that results from an accumulation of environmental risk factors throughout gestation and after delivery, as well as a complex and dynamic bidirectional interaction of genetic expression (Kelly et al., 2020). Remarkably, GI comorbidities are common in schizophrenia patients, and they also have a greater frequency of intestinal barrier failure and increased bacterial translocation (Socolata et al., 2021). Additionally, the chronic schizophrenia individuals had significantly increased level of the genera *Lactobacillus* and *Prevotella* and the orders *Clostridiales*, *Lactobacillales*, and *Bacteroidales*. In the phylum level, *Proteobacteria* and genus level *Succinivibrio*, *Megasphaera*, *Mogibacterium*, *Corynebacterium*, *Collinsella*, *Clostridium*, *Klebsiella*, and *Methanobrevibacter*, *Anaerococcus*, *Ruminococcus* and *Eubacterium* were shown an increased abundance whereas, *Bifidobacterium* spp., *Escherichia coli*, *Lactobacillus* spp., *Haemophilus*, *Sutterella*, *Clostridium*, *Adlercreutzia*, *Anaerostipes*, *Ruminococcus* and *Faecalibacterium* of abundance in microbial diversity were decreased in schizophrenia patients (Socolata et al., 2021). Notably, the degree of symptoms associated with schizophrenia was linked to *Succinivibrio* and

Corynebacterium, which could offer some new biomarkers for the diagnosis of schizophrenia (Li et al., 2020).

Table 1: Distribution of gut microbiota in neurological disorders.

Neurological disease	Gut microflora distribution		References
	Higher expression	Lower expression	
Parkinson's Disease	<i>Oscillospira</i> , <i>Ralstonia</i> , <i>Serratia</i> , <i>Enterobacteriaceae</i> , <i>Bifidobacterium</i> , <i>Akkermansia</i> , <i>Lactobacillus</i> , <i>Butyrivibrio</i> , <i>Clostridium</i> , <i>Escherichia coli</i> , <i>Helicobacter pylori</i>	<i>Shigella</i> , <i>Lachnospiraceae</i> , <i>Faecalibacterium</i> , <i>Coprococcus</i> , <i>Blautia</i> , <i>Prevotellaceae</i> , <i>Roseburia</i> .	Singh et al, 2022; Kaul et al., 2024
Alzheimer Disease	<i>E. coli</i> , <i>Bacteroidetes</i> , <i>Salmonella</i> , <i>Bacillus</i> <i>subtilis</i> , <i>Streptomyces</i> <i>coelicolor</i> , <i>Staphylococcus</i> <i>aureus</i> , <i>Bacteroidetes</i> , <i>Ruminococcaceae</i> , <i>Blautia</i> , <i>Prevotella</i> ,	<i>Eubacterium</i> <i>rectale</i> , <i>Firmicutes</i> , <i>Bifidobacterium</i> , <i>Firmicutes</i> , <i>Ruminococcaceae</i> , <i>Lachnospiraceae</i> , <i>Faecalibacterium</i>	Wang et al., 2022; Heravi et al., 2023;
Amyotrophic Lateral Sclerosis	<i>Methanobrevibacter</i> , <i>Streptococcus</i> <i>salivarius</i> , <i>Citrobacter</i> , <i>Coprococcus</i> , <i>Lactobacillus</i> , <i>Ruminococcaceae</i> , <i>Sphingomonas</i> , <i>Erysipelotrichaceae</i> , <i>Atopobiaceae</i> .	<i>Eubacterium eligens</i> , <i>Bifidobacterium</i> , <i>rectale</i> , <i>Oscillibacter</i> , <i>Roseburia</i> , <i>Firmicutes</i> , <i>Lachnospiraceae</i> , <i>Anaerostipes</i> , <i>Faecalibacterium</i> , <i>E. coli</i> , <i>Megamonas</i> , <i>Butyrivibrio</i> <i>fibrisolvens</i> .	Kaul et al., 2024; Singh et al, 2022

Schizophrenia	<i>Prevotella</i> , <i>Veillonella</i> , <i>Shigella</i> , <i>Escherichia coli</i> , <i>Megasphaera</i> , <i>Eggerthella</i> , <i>Lactobacillus</i> , <i>Alisipipes</i> , <i>Proteobacteria</i> .	<i>Streptococcus</i> , <i>Haemophilus</i> , <i>Bacteroides</i> , <i>Roseburia</i> , <i>Coprococcus</i> , <i>Ruminococcus</i> , <i>Bifidobacterium</i>	McGuinness et al., 2022
Huntington’s Disease	<i>Actinobacteria</i> , <i>Bacteroidetes</i> , <i>Proteobacteria</i>	<i>Firmicutes</i> , <i>Deferibacteres</i> .	Zhu et al., 2021
Multiple Sclerosis	<i>Patescibacteria</i> , <i>Methanobrevibacter</i> , <i>Akkermansia muciniphila</i> , <i>Bacillusfusiformis</i> (<i>Caproic acid producer</i>)	<i>Lachnospiraceae</i> , <i>Ruminocicaceae</i> , <i>Provotella</i> , <i>Fecalibacterium</i> , <i>Clostridium</i> , <i>Oscillibacter</i> .	Wang et al., 2022; Doroszkiewicz et al., 2021
Autism	<i>Clostridium</i> , <i>Lactobacillus</i> , <i>Bacteroidetes</i>	<i>Coprococcus</i> , <i>Provotella</i> , <i>Firmicutes</i>	Doroszkiewicz et al., 2021
Bipolar Disorder	<i>Desulfosporosinus</i> , <i>Desulfotomaculum</i> , <i>Desulfovibrio</i> , <i>Methanobrevibacter</i> , <i>Bifidobacterium</i> , <i>Oscillibacter</i> , <i>Enterococcus</i> , <i>Strptococcus</i> , <i>Flavonifractor</i>	<i>Faecalibacterium</i> , <i>Ruminococcus</i>	McGuinness et al., 2022

2. Implication of Microbiota- gut axis in neurological diseases:

Role of Gut Microbes as Potential Biomarkers:

The relationship between neurodegenerative diseases and the gut microbiota may lead to new avenues for early detection and therapy. According to recent studies, changes in the composition of gut bacteria and metabolite profiles could

serve as markers for neurodegenerative diseases (Jain et al., 2023). This study concludes that many bacteria (at phyla level or genus level) share common abundance in different neurological disorders. It might be higher possibility to applied them as per diagnosis and to build an early prevention method. In order to genus level Prevotella has been decreased in PD, AD, ALS, MS, HD, autism, bipolar and schizophrenia. It is implied as a biomarker for all different neurological diseases. Additionally, the increased level of Megasphaera, Eggerthella, Lactobacillus, Escherichia, Shigella, Veillonella were note as a biomarker for neuropsychiatric disorders whereas decreased level of Roseburia, Coprococcus were also reported (McGuinness et al., 2022). Incase of PD and AD, the abundance of Akkermansia, Bifidobacterium, Ruminococcaeae, Verrucomicrobia, Allistipes, Lachnospiraceae bacterial communities sever as a biomarker for diagnosis purpose (Heravi et al., 2023). Therefore, the relation between gut microflora and brain possesses several pivotal roles in diagnosis, early treatment, and prevention of neurological diseases.

3. Emerging and Future Therapeutic Approaches:

Complex disorders associated with neurodegenerative illnesses typically encompass motor, systemic, and cognitive dysfunctions. Their pathogeneses are thought to be influenced by both genetic and environmental factors, with gut microbiota potentially playing a role. Although there is little evidence, the manipulation of intestinal microbiota by FMT may influence the possible symptoms of diseases through metabolic, endocrine, immune, and neural pathways mediated by intestinal microorganisms. As a result, it may be a viable treatment opportunity for a number of neurodegenerative and neuropsychiatric conditions. Recent studies reveal that biopeptides play a pivotal role to treat the neurodegenerative disease by improving the gut dysbiosis. The impair arrangement of gut microflora has been influenced by the biopeptides. Low molecular weight peptides often display superior structural stability and increased bioavailability in the stomach. Gly-Pro-Hyp and Pro-Hyp, for instance, were able to penetrate the intestinal cell monolayer and remained

stable in simulated gastrointestinal fluid for two hours. These characteristics, such as intestinal permeability and stability against further enzymatic hydrolysis, are crucial for ensuring the functional performance of peptides. As for example, walnut, sesame cake and soyabean peptides suggest a beneficial approach to treat the AD, PD in human (Wu et al., 2021). These peptides regulate gut homeostasis in the initial phases of CNS ailments, which can help cure the unfavourable signs associated with neurodegenerative diseases. Other than that, probiotics and prebiotics intake, fecal microbiota transplantation are also involved to prevent and treat the gut-microbiota's distribution in neurological diseases.

Conclusion:

Since, the ratio of pollution and highly refined food intake was increased day by day, neurological diseases have become emerged as the most common adolescent life-threatening illnesses. A precise coordination of gut microflora is required for optimal health, according to a multitude of research, and any disturbance of this equilibrium may result in neuropsychiatric disorders. In this review, describe the correlation between gut microbes and neurodegenerative and neuropsychiatric disease, and their various pathway involved in gut-brain axis, which modulation led to various neurological diseases. Also, this study summarizes the biomarkers present in both neurological disorders provide a suitable treatment approach as per futuristic possibility. As previously reported, peptides have the ability to control gut microbiota, which may play a useful part in daily dietary intake to fend against neurodegenerative illnesses. Additionally, it offers insight into whether changes in a single gut microbe impact host immunity.

CONFLICT OF INTEREST: There is no conflict of interest related to the study.

AUTHOR CONTRIBUTIONS: Acquisition and interpretation of data is done by Priti Nandi. Conception, design and revising of the article are done by Dr. Bidisha Ghosh.

ACKNOWLEDGEMENT: I would like to express my special thanks of gratitude to the higher dignitaries of Swami

Vivekananda University for allowing me to carry out this study.

References:

Albenberg, L. G., & Wu, G. D. (2014). Diet and the intestinal microbiome: associations, functions, and implications for health and disease. *Gastroenterology*, 146(6), 1564-1572. DOI: 10.1053/j.gastro.2014.01.058

Batarseh, Y. S., Duong, Q. V., Mousa, Y. M., Al Rihani, S. B., Elfakhri, K., & Kaddoumi, A. (2016). Amyloid- β and astrocytes interplay in amyloid- β related disorders. *International journal of molecular sciences*, 17(3), 338. DOI: 10.3390/ijms17030338

Bellono, N. W., Bayrer, J. R., Leitch, D. B., Castro, J., Zhang, C., O'Donnell, T. A., Brierley, S. M., Ingraham, H. A., & Julius, D. (2017). Enterochromaffin cells are gut chemosensors that couple to sensory neural pathways. *Cell*, 170(1), 185-198. DOI: 10.1016/j.cell.2017.05.034

Breit, S., Kupferberg, A., Rogler, G., & Hasler, G. (2018). Vagus nerve as modulator of the brain-gut axis in psychiatric and inflammatory disorders. *Frontiers in psychiatry*, 9, 44. DOI: 10.3389/fpsy.2018.00044

Caputi, V., & Giron, M. C. (2018). Microbiome-gut-brain axis and toll-like receptors in Parkinson's disease. *International journal of molecular sciences*, 19(6), 1689. DOI: 10.3390/ijms19061689

Cattaneo, A., Cattane, N., Galluzzi, S., Provasi, S., Lopizzo, N., Festari, C., Ferrari, C., Guerra, U. P., Paghera, B., Muscio, C., Bianchetti, A., Volta, G. D., Turla, M., Coteli, M., Gennuso, M., Prella, A., Zanetti, O., Lussignoli, G., Mirabile, D., Bellandi, D., Gentile, S., Belotti, G., Villani, D., Harach, T., Bolmont, T., Padovani, A., Boccardi, M., Frisoni, G. B., & Group, I. F. (2017). Association of brain amyloidosis with pro-inflammatory gut bacterial taxa and peripheral inflammation markers in cognitively impaired elderly. *Neurobiology of aging*, 49, 60-68. DOI: 10.1016/j.neurobiolaging.2016.08.019

Ceppa, F. A., Izzo, L., Sardelli, L., Raimondi, I., Tunesi, M., Albani, D., & Giordano, C. (2020). Human gut-microbiota interaction in neurodegenerative disorders and current engineered tools for its modeling. *Frontiers in cellular and infection microbiology*, 10, 297. DOI: 10.3389/fcimb.2020.00297

Cheng, J., Palva, A. M., de Vos, W. M., & Satokari, R. (2013). Contribution of the intestinal microbiota to human health: from birth to 100 years of age. Between pathogenicity and commensalism, 323-346.DOI:10.1007/82_2011_189

Claesson, M. J., Cusack, S., O'Sullivan, O., Greene-Diniz, R., de Weerd, H., Flannery, E., Marchesi, J. R., Falush, D., Dinan, T., Fitzgerald, G., Stanton, C., Sinderen, D. V., O'Connor, M., Harnedy, N., O'Connor, K., Henry, C., O'Mahony, D., P. Fitzgerald, A., Shanahan, F., Twomey, C., Hill, C., Ross, R. P., & O'Toole, P. W. (2011). Composition, variability, and temporal stability of the intestinal microbiota of the elderly. *Proceedings of the National Academy of Sciences*, 108(supplement_1), 4586-4591.DOI: 10.1073/pnas.1000097107

Clarke, G., Stilling, R. M., Kennedy, P. J., Stanton, C., Cryan, J. F., & Dinan, T. G. (2014). Minireview: gut microbiota: the neglected endocrine organ. *Molecular endocrinology*, 28(8), 1221-1238.DOI: 10.1210/me.2014-1108

Costantini, T. W., Krzyzaniak, M., Cheadle, G. A., Putnam, J. G., Hageny, A. M., Lopez, N., Eliceriri, B. P., Bansal, V., & Coimbra, R. (2012). Targeting α -7 nicotinic acetylcholine receptor in the enteric nervous system: a cholinergic agonist prevents gut barrier failure after severe burn injury. *The American journal of pathology*, 181(2), 478-486.DOI: 10.1016/j.ajpath.2012.04.005

Dalile, B., Van Oudenhove, L., Vervliet, B., & Verbeke, K. (2019). The role of short-chain fatty acids in microbiota-gut-brain communication. *Nature reviews Gastroenterology & hepatology*, 16(8), 461-478.DOI: 10.1038/s41575-019-0157-3

Doroszkiewicz, J., Groblewska, M., & Mroczko, B. (2021). The role of gut microbiota and gut-brain interplay in selected diseases of the central nervous system. *International journal of molecular sciences*, 22(18), 10028.DOI: 10.3390/ijms221810028

Dugger, B. N., & Dickson, D. W. (2017). Pathology of neurodegenerative diseases. *Cold Spring Harbor perspectives in biology*, 9(7), a028035.DOI: 10.1101/cshperspect.a028035

Fitzgerald, E., Murphy, S., & Martinson, H. A. (2019). Alpha-synuclein pathology and the role of the microbiota in Parkinson's disease. *Frontiers in neuroscience*, 13, 369.DOI: 10.3389/fnins.2019.00369

Foster, J. A., & Neufeld, K. A. M. (2013). Gut-brain axis:

how the microbiome influences anxiety and depression. *Trends in neurosciences*, 36(5), 305-312.DOI: 10.1016/j.tins.2012.12.010

Friedland, R. P. (2015). Mechanisms of molecular mimicry involving the microbiota in neurodegeneration. *Journal of Alzheimer's Disease*, 45(2), 349-362.DOI:10.3233/JAD-142841

Goyal, D., Ali, S. A., & Singh, R. K. (2021). Emerging role of gut microbiota in modulation of neuroinflammation and neurodegeneration with emphasis on Alzheimer's disease. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 106, 110112.DOI: 10.1016/j.pnpbp.2020.110112

Gubert, C., Gasparotto, J., & H. Morais, L. (2022). Convergent pathways of the gut microbiota-brain axis and neurodegenerative disorders. *Gastroenterology Report*, 10, goac017.DOI: 10.1093/gastro/goac017

Gulaj, E., Pawlak, K., Bien, B., & Pawlak, D. (2010). Kynurenine and its metabolites in Alzheimer's disease patients. *Advances in medical sciences*, 55(2), 204-211.DOI: 10.2478/v10039-010-0023-6

Guo, K., Figueroa-Romero, C., Noureldein, M. H., Murdock, B. J., Savelieff, M. G., Hur, J., Goutman, S. A., & Feldman, E. L. (2024). Gut microbiome correlates with plasma lipids in amyotrophic lateral sclerosis. *Brain*, 147(2), 665-679. DOI: 10.1093/brain/awad306

Han, Y., Wang, B., Gao, H., He, C., Hua, R., Liang, C., Zhang, S., Wang, Y., & Xu, J. (2022). Vagus nerve and underlying impact on the gut microbiota-brain axis in behavior and neurodegenerative diseases. *Journal of inflammation research*, 6213-6230.DOI: 10.2147/JIR.S384949

Heravi, F. S., Naseri, K., & Hu, H. (2023). Gut microbiota composition in patients with neurodegenerative disorders (Parkinson's and Alzheimer's) and healthy controls: a systematic review. *Nutrients*, 15(20), 4365.DOI: 10.3390/nu15204365

Hertzberg, V. S., Singh, H., Fournier, C. N., Moustafa, A., Polak, M., Kuelbs, C. A., Torralba, M. G., Tansey, M. G., Nelson, K. E., & Glass, J. D. (2022). Gut microbiome differences between amyotrophic lateral sclerosis patients and spouse controls. *Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration*, 23(1-2), 91-99.DOI: : 10.1080/21678421.2021.1904994

Jacobs, B. M., Noyce, A. J., Bestwick, J., Belete, D.,

Giovannoni, G., & Dobson, R. (2021). Gene-environment interactions in multiple sclerosis: a UK Biobank study. *Neurology: Neuroimmunology & Neuroinflammation*, 8(4), e1007.DOI: 10.1212/NXI.0000000000001007

Jain, A., Madkan, S., & Patil, P. (2023). The role of gut microbiota in neurodegenerative diseases: Current insights and therapeutic implications. *Cureus*, 15(10).DOI:10.7759/cureus.47861

Kelly, J. R., Minuto, C., Cryan, J. F., Clarke, G., & Dinan, T. G. (2021). The role of the gut microbiome in the development of schizophrenia. *Schizophrenia Research*, 234, 4-23.DOI: 10.1016/j.schres.2020.02.010

Kennedy, P. J., Cryan, J. F., Dinan, T. G., & Clarke, G. (2017). Kynurenine pathway metabolism and the microbiota-gut-brain axis. *Neuropharmacology*, 112, 399-412.DOI:10.1016/j.neuropharm.2016.07.002

Kowalski, K., & Mulak, A. (2019). Brain-gut-microbiota axis in Alzheimer's disease. *Journal of neurogastroenterology and motility*, 25(1), 48.DOI: 10.5056/jnm18087

Li, J., Jia, H., Cai, X., Zhong, H., Feng, Q., Sunagawa, S., Arumugam, M., Kultima, J. R., Prift, E., Nielsen, T., Juncker, A. S., Manichanh, C., Chen, B., Zhang, W., Levenez, F., Wang, J., Xu, X., Xiao, L., Liang, S., Zhang, D., Zhang, Z., Chen, W., Zhao, H., Al-Aama, J. Y., Edris, S., Yang, H., Wang, H., Wang, J., Hansen, T., Nielsen, H. B., Brunak, S., Kristiansen, K., Guarner, F., Pedersen, O., Doré, J., Ehrlich, S. D., Consortium, M., Bork, P., & Wang, J. (2014). An integrated catalog of reference genes in the human gut microbiome. *Nature biotechnology*, 32(8), 834-841.DOI:10.1038/nbt.2942

Li, S., Zhuo, M., Huang, X., Huang, Y., Zhou, J., Xiong, D., Li, J., Liu, Y., Pan, Z., Li, H., Chen, J., Li, X., Xiang, Z., Wu, F., Wu, K., & Wu, K. (2020). Altered gut microbiota associated with symptom severity in schizophrenia. *PeerJ*, 8, e9574.DOI: 10.7717/peerj.9574

Lynch, S. V., & Pedersen, O. (2016). The human intestinal microbiome in health and disease. *New England journal of medicine*, 375(24), 2369-2379.DOI:10.1056/NEJMr1600266

Martin, C. R., Osadchiy, V., Kalani, A., & Mayer, E. A. (2018). The brain-gut-microbiome axis. *Cellular and molecular*

gastroenterology and hepatology, 6(2), 133-148.DOI: 10.1016/j.jcmgh.2018.04.003

McGuinness, A. J., Davis, J. A., Dawson, S. L., Loughman, A., Collier, F., O'hely, M., Simpson, C. A., Green, J., Marx, W., Hair, C., Guest, G., Mohebbi, M., Berk, M., Stupart, D., Watters, D., & Jacka, F. N. (2022). A systematic review of gut microbiota composition in observational studies of major depressive disorder, bipolar disorder and schizophrenia. *Molecular psychiatry*, 27(4), 1920-1935.DOI:10.1038/s41380-022-01456-3

Mirzaei, R., Bouzari, B., Hosseini-Fard, S. R., Mazaheri, M., Ahmadyousefi, Y., Abdi, M., Jalalifar, S., Karimitabar, Z., Teimoori, A., Keyvani, H., Zamani, F., Yousefimashouf, R., & Karampoor, S. (2021). Role of microbiota-derived short-chain fatty acids in nervous system disorders. *Biomedicine & Pharmacotherapy*, 139, 111661.DOI: 10.1016/j.biopha.2021.111661

Mohajeri, M. H., La Fata, G., Steinert, R. E., & Weber, P. (2018). Relationship between the gut microbiome and brain function. *Nutrition reviews*, 76(7), 481-496.DOI: 10.1093/nutrit/nuy009

Mulak, A., & Bonaz, B. (2015). Brain-gut-microbiota axis in Parkinson's disease. *World journal of gastroenterology: WJG*, 21(37), 10609.DOI: 10.3748/wjg.v21.i37.10609

Nicholson, K., Bjornevik, K., Abu-Ali, G., Chan, J., Cortese, M., Dedi, B., ... & Berry, J. D. (2021). The human gut microbiota in people with amyotrophic lateral sclerosis. *Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration*, 22(3-4), 186-194.DOI: 10.1080/21678421.2020.1828475

Nishiwaki, H., Hamaguchi, T., Ito, M., Ishida, T., Maeda, T., Kashihara, K., Tsuboi, Y., Ueyama, J., Shimamura, T., Mori, H., Kurokawa, K., Katsuno, M., Hirayama, M., & Ohno, K. (2020). Short-chain fatty acid-producing gut microbiota is decreased in Parkinson's disease but not in rapid-eye-movement sleep behavior disorder. *MSystems*, 5(6), 10-1128.DOI: 10.1128/mSystems.00797-20

Noble, E. E., Hsu, T. M., & Kanoski, S. E. (2017). Gut to brain dysbiosis: mechanisms linking western diet consumption, the microbiome, and cognitive impairment. *Frontiers in behavioral neuroscience*, 11, 9.DOI: 10.3389/fnbeh.2017.00009

ÖZAYDIN AKSUN, Z. E. R. İ. N., Erdoğan, S., Kalkanci,

A., Şahin, E. A., Çuhadar, T., & Şener, H. Ö. (2024). Is gut microbiota of patients with ALS different from that of healthy individuals?. *Turkish Journal of Medical Sciences*, 54(3), 579-587.DOI: 10.55730/ 1300-0144.5825

Rai, S. N., Birla, H., Zahra, W., Singh, S. S., & Singh, S. P. (2017). Immunomodulation of Parkinson's disease using *Mucuna pruriens* (Mp). *Journal of Chemical Neuroanatomy*, 85, 27-35.DOI: 10.1016/j.jchemneu.2017.06.005

Romano, S., Savva, G. M., Bedarf, J. R., Charles, I. G., Hildebrand, F., & Narbad, A. (2021). Meta-analysis of the Parkinson's disease gut microbiome suggests alterations linked to intestinal inflammation. *npj Parkinson's Disease*, 7(1), 27.DOI: 10.1038/s41531-021-00156-z

Rooks, M. G., & Garrett, W. S. (2016). Gut microbiota, metabolites and host immunity. *Nature reviews immunology*, 16(6), 341-352.DOI:10.1038/nri.2016.42

Sampson, T. R., Debelius, J. W., Thron, T., Janssen, S., Shastri, G. G., Ilhan, Z. E., Challis, C., Schretter, C. E., Rocha, S., Gradinaru, V., Chesselet, M. F., Keshavarzain, A., Shannon, K. M., Krajmalnik-Brown, R., Wittung-Stafshede, P., Knight, R., & Mazmanian, S. K. (2016). Gut microbiota regulate motor deficits and neuroinflammation in a model of Parkinson's disease. *Cell*, 167(6), 1469-1480.DOI: 10.1016/j.cell.2016.11.018

Shi, Y., Kellingray, L., Zhai, Q., Gall, G. L., Narbad, A., Zhao, J., Zhang, H., & Chen, W. (2018). Structural and functional alterations in the microbial community and immunological consequences in a mouse model of antibiotic-induced dysbiosis. *Frontiers in microbiology*, 9, 1948.DOI: 10.3389/fmicb.2018.01948

Singh, N., Singh, V., Rai, S. N., Mishra, V., Vamanu, E., & Singh, M. P. (2022). Deciphering the gut microbiome in neurodegenerative diseases and metagenomic approaches for characterization of gut microbes. *Biomedicine & Pharmacotherapy*, 156, 113958.DOI: 10.1016/j.biopha.2022.113958

Soto, C., & Pritzkow, S. (2018). Protein misfolding, aggregation, and conformational strains in neurodegenerative diseases. *Nature neuroscience*, 21(10), 1332-1340.DOI: 10.1038/s41593-018-0235-9

Strandwitz, P., Kim, K. H., Terekhova, D., Liu, J. K., Sharma, A., Levering, J., McDonald, D., Dietrich, D., Rwmadhar, T. R., Lekbua, A., Mroue, N., Liston, C., Stewart, E. J., Dubin, M. J., Zengler, K., Knight, R., Gilbert, J. A., Clardy, J., & Lewis, K. (2019). GABA-modulating bacteria of the human gut microbiota. *Nature microbiology*, 4(3), 396-403. DOI:10.1038/s41564-018-0307-3

Sun, P., Su, L., Zhu, H., Li, X., Guo, Y., Du, X., Zhang, L., & Qin, C. (2021). Gut microbiota regulation and their implication in the development of neurodegenerative disease. *Microorganisms*, 9(11), 2281. DOI: 10.3390/microorganisms9112281

Torbick, N., Hession, S., Stommel, E., & Caller, T. (2014). Mapping amyotrophic lateral sclerosis lake risk factors across northern New England. *International journal of health geographics*, 13, 1-15. DOI: 10.1186/1476-072X-13-1

Vamanu, E., & Rai, S. N. (2021). The link between obesity, microbiota dysbiosis, and neurodegenerative pathogenesis. *Diseases*, 9(3), 45. DOI:10.3390/diseases9030045

Veiga-Fernandes, H., & Pachnis, V. (2017). Neuroimmune regulation during intestinal development and homeostasis. *Nature immunology*, 18(2), 116-122. DOI: 10.1038/ni.3634

Venuta, F., & Rendina, E. A. (2008). Combined pulmonary artery and bronchial sleeve resection. *Operative Techniques in Thoracic and Cardiovascular Surgery*, 13(4), 260-273. DOI: 10.1053/j.gastro.2004.10.043

Vogt, N. M., Kerby, R. L., Dill-McFarland, K. A., Harding, S. J., Merluzzi, A. P., Johnson, S. C., Carlsson, C. M., Asthana, S., Zetterberg, H., Blennow, K., Bendlibn, B. B., & Rey, F. E. (2017). Gut microbiome alterations in Alzheimer's disease. *Scientific reports*, 7(1), 13537. DOI: :10.1038/s41598-017-13601-y

Wang, H., Yang, F., Zhang, S., Xin, R., & Sun, Y. (2021). Genetic and environmental factors in Alzheimer's and Parkinson's diseases and promising therapeutic intervention via fecal microbiota transplantation. *npj Parkinson's Disease*, 7(1), 70. DOI:10.1038/s41531-021-00213-7

Ye, L., Bae, M., Cassilly, C. D., Jabba, S. V., Thorpe, D. W., Martin, A. M., Lu, H. Y., Wang, J., Thompson, J. D., Lickwar, C. R., Poss, K. D., Keating, D. J., Jordt, S. E., Clardy, J., Liddle, R. A., & Rawls, J. F. (2021). Enteroendocrine cells sense bacterial tryptophan catabolites to activate enteric and vagal neuronal

pathways. *Cell host & microbe*, 29(2), 179-196.DOI: 10.1016/j.chom.2020.11.011

Zeng, Q., Shen, J., Chen, K., Zhou, J., Liao, Q., Lu, K., Yuan, J., & Bi, F. (2020). The alteration of gut microbiome and metabolism in amyotrophic lateral sclerosis patients. *Scientific reports*, 10(1), 12998.DOI: 1038/s41598-020-69845-8

Zhai, C. D., Zheng, J. J., An, B. C., Huang, H. F., & Tan, Z. C. (2019). Intestinal microbiota composition in patients with amyotrophic lateral sclerosis: establishment of bacterial and archaeal communities analyses. *Chinese Medical Journal*, 132(15), 1815-1822.DOI: 10.1097/CM9.0000000000000351

Zhang, L., Zhuang, Z., Zhang, G., Huang, T., & Fan, D. (2022). Assessment of bidirectional relationships between 98 genera of the human gut microbiota and amyotrophic lateral sclerosis: a 2-sample Mendelian randomization study. *BMC neurology*, 22, 1-10.DOI: 10.1186/s12883-021-02522-z.

Zheng, D., Liwinski, T., & Elinav, E. (2020). Interaction between microbiota and immunity in health and disease. *Cell research*, 30(6), 492-506.DOI: 10.1038/s41422-020-0332-7

Zhu, S., Jiang, Y., Xu, K., Cui, M., Ye, W., Zhao, G., Jin, L., & Chen, X. (2020). The progress of gut microbiome research related to brain disorders. *Journal of neuroinflammation*, 17, 1-20.DOI: 10.1186/s12974-020-1705-z

Zhu, X., Li, B., Lou, P., Dai, T., Chen, Y., Zhuge, A., Yaun, Y., & Li, L. (2021). The relationship between the gut microbiome and neurodegenerative diseases. *Neuroscience bulletin*, 37(10), 1510-1522. DOI:10.1007/s12264-021-00730-8

Wang, Y., Zhang, Z., Li, B., He, B., Li, L., Nice, E. C., Zhang, W., & Xu, J. (2022). New insights into the gut microbiota in neurodegenerative diseases from the perspective of redox homeostasis. *Antioxidants*, 11(11), 2287.DOI:10.3390/antiox11112287

Doroszkiwicz, J., Groblewska, M., & Mroczko, B. (2021). The role of gut microbiota and gut-brain interplay in selected diseases of the central nervous system. *International journal of molecular sciences*, 22(18), 10028.DOI: 10.3390/ijms221810028

Wu, S., Bekhit, A. E. D. A., Wu, Q., Chen, M., Liao, X., Wang, J., & Ding, Y. (2021). Bioactive peptides and gut microbiota: Candidates for a novel strategy for reduction and control of neurodegenerative diseases. *Trends in Food Science & Technology*, 108, 164-176.DOI:10.1016/j.tifs.2020.12.019