Review

Gut Brain Axis and Neurodegenerative Diseases. Nutritional Interventions Targeting Gut Microbiome: A Systematic Review

Despoina Koumpouli , Varvara Koumpouli , Antonios E Koutelidakis *

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Gut Brain Axis and Neurodegenerative Diseases. Nutritional Interventions Targeting Gut Microbiome: A Systematic Review

Despoina Koumpouli [1], Varvara Koumpouli [2] and Antonios E. Koutelidakis [3,*]

[1] Laboratory of Microbiology, University General Hospital of Ioannina, Stavrou Niarchou Avenue, 45500 Ioannina, Greece; dkoub@hotmail.com

[2] Laboratory of Hematology, University General Hospital of Ioannina, Stavrou Niarchou Avenue, 45500 Ioannina, Greece; vana_koumpouli@yahoo.gr

[3] Unit of Human Nutrition, Laboratory of Nutrition and Public Health, Department of Food Science and Nutrition, University of the Aegean, Leoforos Dimokratias 66, 81400 Myrina, Greece

* Correspondence: akoutel@aegean.gr; Tel.: +30-225-408-3123; Fax: +30-225-408-3109

Abstract: The Microbiota-gut–brain axis (GBA) comprises a bidirectional communication between the gut and brain. Many neurodegenerative disorders (NDDs), such as Alzheimer's disease (AD), Parkinson's disease (PD), and Multiple sclerosis (MS) are characterized by a disfunction of the GBA, indicating a possible implication role in dis-ease pathogenesis. This systematic review was performed according to PRISMA guidelines, mainly using the key words gut–brain axis, gut microbiota, gut dysbiosis, neurodegenerative disorders, prebiotics and probiotics. The most recent scientific articles were searched from the Pubmed, Google Scholar, and Scopus databases. The main components and communication pathways of the GBA were discussed in this study and the aim was to investigate if therapeutic approaches, through dietary intervention targeting the gut microbiota, could ameliorate NDDs. The gut microbiota is a crucial constituent of the GBA, and an unbalanced microbiota, known as dysbiosis, has been related to GBA impairment and neurodegeneration. In most of the studies discussed, modulation of microbial constitution through nutritional intervention, probiotic and prebiotic supplementation, has shown promising outcomes. More research is essential for the full comprehension of the mechanisms studied.

Keywords: gut–brain axis; gut microbiota; gut dysbiosis; neurodegenerative disorders; prebiotics; probiotics

1. Introduction

Recent studies emphasize the impact of the gut microbiota via the Gut Brain Axis (GBA) on Neurodegenerative diseases (NDDs), such as Alzheimer's disease (AD), Parkinson's disease (PD) and Multiple sclerosis (MS) [1–4]. NDDs are a heterogeneous group of diseases, having as main clinical characteristic the impairment of the central and peripheral nervous systems [3,5]. Mostly older people are affected by NDDs, which are an important cause of mortality and comorbidity [1].

The World Health Organization (WHO) believe that by 2040, NDDs would become the second cause of mortality globally [5]. NDDs present a pathological aggregation of deficient proteins in the brain, like phosphorylated Tau proteins, extracellular amyloid β-protein (Aβ) and α-synuclein (α-Syn), that lead to the progression of AD and PD, respectively [3,6]. These accumulated proteins stimulating astrocytes and microglia, cause damage and influence synaptic activity [3]. Gut microbiota influencing vagus nerve activation lead to the accumulation of toxic proteins in the brain [3].

GBA is a two-way communication pathway between the gut and brain [2,3,5,7,8]. NDDs present a disfunction of the GBA, suggesting a probable involvement of GBA in disease pathogenesis [3]. In

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this bidirectional pathway, the gut microbiota interact with the immune system, enteric nervous system (ENS) and enteroendocrine system, supporting signal transmission via the vagus nerve and the blood circulation to the central nervous system (CNS). This involves various microorganism metabolites, neurotransmitters, hormones and cytokines, indicating the crucial role of the gut microbiota in keeping this communication in equilibrium [3,5,9].

Additionally, the gut microbiota preserve from the colonization of pathogens [3,5], is very important for the integrity of the gut barrier, the permeability of the blood–brain barrier (BBB), the homeostasis of the endocrine system, the modulation of the immune system, and the development of astrocyte cells and microglia **[1–3,5]**. The gut microbiota is a crucial constituent of the GBA and an unbalanced gut microbiota, known as dysbiosis, has been related with GBA impairment and neurodegeneration [1,3,4]. The type of diet, is a very important factor that can modify the constitution of the gut microbiota [8,10]. In this way, dietary interventions modulating gut microbiota could offer probable therapeutic strategies for controlling NDDs pathology [1].

This review aims to investigate the most recent literature about the impact of the gut microbiota through GBA on NDDs, to have a better knowledge about this communication pathway and about potential therapeutic approaches, through nutritional interventions, having as a target the gut microbiota. We also indicate the potential use of agents that ameliorate the constitution of the gut microbiota, such as prebiotics and probiotics.

2. Materials and Methods

The literature review was realized according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines using search engines PubMed, Scopus, and Google Scholar. The keywords used were GBA; gut microbiota; gut dysbiosis; NDDs; prebiotics; probiotics. The research articles used were published between 2011 and 2024 and only research articles written in English language were taken into consideration. Articles that included the above-mentioned keywords in the abstract or title were further studied. The selection criteria were research conducted in the last decade, in which there was an estimation of the influence of prebiotics and probiotics in NDDs through the gut microbiome. Articles that did not enclose information about prebiotics, probiotics regarding intestinal microbiome were excluded.

3. The Gut–Brain Axis (GBA)

GBA is a bidirectional communication among the gut and the brain [3,8,11]. It consists of neural, immune, and hormonal communication pathways between the gastrointestinal (GI) tract and the CNS and maintains the equilibrium inside the GI tract, CNS, and gut microbiome *[4,7,8,12,13]*. Some of the most considerable characteristics of the GBA are as follows:

3.1. Human Gut Microbiota

Human microbiota installation begins during the intrauterine period via the blood circulation from the placenta. After birth, diverse factors have an impact on colonization like vaginal birth or cesarean section, external environment, breastfeeding or formula, obesity, prematurity, infections and antibiotics [2,3,13]. The mode of delivery is a very important factor for the microbiota colonization. Vaginal birth offer a greater diversity in the gut microbiota, connected to the mother's vaginal microbiota, with a predominance of Lactobacillus and Prevotella [1]. On the other hand, when the delivery becomes by cesarean section the predominant microbiota is related to the environment and to mothers' skin bacteria, like Staphylococcus and Propionibacterium [1].

Another very important factor for the modulation of gut microbiota is breastfeeding, with abundant amounts of Lactobacillus and Bifidobacterium in breastfed childrens' feces [1]. These bacteria produce compounds that protect from installation of pathogenic bacteria. When babies pass to solid nutrition, the microbiota is modified so to be able to degrade complex sugars. The microbiota displays an adult like configuration at 3-6 years old [1].

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The gut microbiota contains up to 100 trillion bacteria, fungi, archaea, parasites, and viruses with the majority being bacteria [2,4,8,14] and it consists of about 22.000.000 genes, 1000 times more genes than our cells. There are four major phyla Firmicutes, Bacteroidetes, Actinobacteria and Proteobacteria and two minor phyla Verrucomicrobia and Fusobacteria. Firmicutes and Bacteroidetes represent almost 90% of the gut microbiota [2,3,5,13].

In the stomach and in the small intestine there is a high acidity, that restrict microbiota development and diversity. On the other hand, in the colon exist anaerobiosis, undigested food for fermentation and is densely inhabited with microbiota [15]. The colon presents a high diversity in the microbiome because of the fermentation of complex carbohydrates [1] and is very important because it can communicate with the rest of the body. Many factors have an impact on gut microbiotas' density, function and diversity such as genetics, [3] lifestyle, age, geography, health conditions, diet and drugs [1]. Each person carries a unique gut microbiota with only a limited proportion of the gut microbiota being shared [2].

A healthy microbiome is related to high diversity and balance of bacteria and consist of bacteria that produce short-chain fatty acids (SCFAs). Bacteria considered negative are potential pathogens or bacteria that produce bacterial toxins like lipopolysaccharide (LPS). *[16–18]*. The Firmicutes/Bacteroidetes ratio is an indicator of gut microbiota health. Reduced levels of Bacteroidetes and high levels of Firmicutes have been associated with obesity, diabetes, and dementia [11].

20 - 60% of microbiomes are not cultivable. So non-cultivable microbial taxa are identified with other methods [3] like next-generation sequencing (NGS), where DNA is extracted from faecal material, mostly sequencing the 16SrRNA gene, common to almost all bacteria [19]. Another technique is metagenomics, where the whole DNA is sequenced. [20]. Other techniques are metatranscriptomics (that detect functional genes in the microbiome), metabolomics (that examine the metabolic products) [21] and metaproteomics (that examine proteins present in the microbiome) [2].

3.2. Autonomic Nervous System Communication Pathway

The autonomic nervous system (ANS) consist of the sympathetic (SNS) and parasympathetic nervous systems (PNS), and include neurons allocated all through central and peripheral regions. ANS organizes involuntary activity like breathing, digestion and heartbeat. GBA's components interact with each other via this network [1,5,13].

Afferent signals from the GI tract are send to the CNS and efferent signals from the CNS to the lumen, through both the SNS and the PNS. The ANS regulate the intestinal barrier integrity, intestinal motility and immune response. Gut microbiota metabolites which interact with gut ANS synapses, such as catecholamines, serotonin, and precursors of tryptophan and γ-aminobutyric acid (GABA) trigger gut autonomic nerves to send sensory messages to the brain. These neurotransmitters can interact with the CNS. Visceral information from the gut, send through the ANS, is processed by the CNS, that stimulates a response with effects on peripheral organs. So the ANS serves as a conductor for instantaneous neurological reactions via its innervation of the target organ [22].

3.3. Vagus Nerve

The vagus nerve is a crucial constituent of the PNS and has a very important role in the GBA. Its name derives from the Latin word meaning "wandering" [4,13]. It is made up of 80% afferent and 20% efferent neurons, which transmit information from visceral organs like the GI, cardiovascular and respiratory systems to the CNS and from CNS to the viscera [4]. Vagus nerve control appetite, inflammation, stress answers, reflex actions such as swallowing, sneezing, vomiting and cognitive reactions [3,4,12]. Vagal afferents consist of an abundance of receptors that can detect bacterial products, intestinal hormones, and neurotransmitters. Consequently, they respond to chemical, hormonal and mechanical signals [13].

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3.4. Enteric Nervous System

A crucial constituent of the ANS is the ENS situated in the GI tract. It is made of 200 to 600 million neurons. ENS regulate gut activity, secretion and absorption, immune defense, motor activity and preserves gut equilibrium and communication with gut microbiota [5]. The ENS is made of two ganglionated plexuses, the submucosal and myenteric plexus, that contain nitrergic and cholinergic neurons. These plexuses are established in the intestinal wall from the esophagus to the anus [11,12]. The submucosal plexus control gastrointestinal blood circulation and epithelial cell activity, and the myenteric plexus control the contraction and repose of the intestinal wall [12].

The ENS interact with the CNS via the SNS (prevertebral ganglia) and the PNS (the vagus nerve) [11,12]. The gut microbiota control the ENS functions and development by stimulating toll-like receptors (TLR), which have the ability to identify microbial peptidoglycan, LPS and viral RNA. Germ-free (GF) mice have a damaged ENS structure and gut motility, diminished enteric neurons and damaged sensory communication. Furthermore, gut microbiota control the ENS by producing metabolites and neurotransmitters such as SCFAs, catecholamines, GABA and acetylcholine [3,12]. On the other hand, the ENS exhibits an influence on the gut microbiota [12].

3.5. Hypothalamic–Pituitary–Adrenal Axis Communication Pathway

The hypothalamic–pituitary–adrenal (HPA) axis is a neuroendocrine pathway crucial for GBA communication, that regulate adaptation to stress. In condition of stress, corticotropin-releasing hormone (CRH), is produced and released from the paraventricular nucleus of the hypothalamus, and then binds to its corticotropin receptor in the anterior pituitary gland and stimulate the release of adrenocorticotropic hormone (ACTH) into the blood circulation. ACTH enter to the zona fasciculata of the adrenal gland and triggers the production and release of glucocorticoids (cortisol in humans and corticosterone in mice) [12,23].

Recent studies on GF mice have shown the HPA axis influence on microbiota constitution and metabolites. On the other hand, the microbial impact on the HPA axis also regulate glucocorticoid concentrations [12]. Glucocorticoid receptors are allocated in multiple organs, such as the CNS and the GI tract, including various cells like endocrine cells, epithelial cells, neurons, and immune cells [23]. Cortisol is a stress hormone that regulate body fat, muscles, bones, and brain. Adequate levels of glucocorticoids are vital for neurodevelopment and cognitive mechanisms like memory and learning [12]. Glucocorticoids are important for gut and brain function via endocrine, metabolic, neural, and immunological pathways. Extended periods with stress lead to HPA axis dysregulation. Elevated levels of cortisol lead to cognitive dysregulation and elevated AD risk [23].

3.6. Neurotransmitters

Neurotransmitters control signal transportation through neuronal and glial cells, influencing memory, learning and movement activity. There are two categories of Neurotransmitters. Excitatory like dopamine, acetylcholine, glutamate, norepinephrine and inhibitory, like serotonin, GABA and glycine [2]. Their production and modulation are controlled by neurons and glial cells with the assistance of enzymes, and their impairment is related to NDDs, including AD, PD, in anxiety and depression. Enzymes and metabolites of the gut microbiota promote the production of neurotransmitters and their precursors, so in this mode they regulate brain activity *[3–5,9,13,14]*.

However, only a limited number of neurotransmitters pass through the BBB and operate on the CNS. They can indirectly modulate brain activity with local interaction with the ENS or rapid signal transportation to the brain via the vagus nerve [4,13].

3.7. Immune System Communication Pathway

Enterocytes have immune receptors and can release cytokines and chemokines. Gut-associated lymphoid tissue (GALT) utilize lymphocytes to start a specific immune response that involves immunoglobulins. TLRs identify microorganism associated molecular patterns (MAMPs), LPS,

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polysaccharide A (Gram-negative bacteria) and peptidoglycan (Gram-positive bacteria) and that's how immune system cells identify and react to microorganisms, identify alterations in microbial balance and preserve gut equilibrium [24].

Immune cells stimulation lead to the employment of chemical messengers, cytokines and chemokines [24] and promote the intercommunication between the immune system, gut microbiota, and CNS. Appropriate intestinal cytokine production maintain intestinal equilibrium and microbial abundance under control. While not balanced cytokines could pass the BBB and modulate brain function. Dysbiosis can impair the integrity of the intestinal barrier and the BBB, allowing the entry of microbes and their metabolites into the CNS, triggering microglia, and leading to a proinflammatory condition. Chronic inflammation promote cognitive deficiency and behavioral modifications [25]. Monocyte transfer from the periphery to the CNS is regulated by tumor necrosis factor-alpha (TNF-α) produced by microglia and can be modified by the gut microbiota. So the gut microbiota can regulate neuroinflammation [26,27].

3.8. Enteroendocrine Communication Pathway

Enteroendocrine cells (EECs) are situated in the GI tract. They constitute a big endocrine organ and exhibit a regulatory function on the GBA. Ten specific EEC subtypes have been discovered. L-cells release glucagon-like peptide-1 (GLP-1), I-cells release cholecystokinin (CCK) and K-cells release glucose-dependent insulinotropic polypeptide (GIP) [28,29]. EECs have a bottleneck architecture with an apical membrane that is connected with the gut lumen and a basolateral membrane adjacent to blood vessels and neurons. EECs exhibit transporters and specific G protein-coupled receptors (GPCRs), that permit to the EECs to identify alterations in the gut lumen nutrients, gut microbiota and metabolites [28,30].

After neural or mechanical stimulation, there is a release of gut molecules through the basolateral membrane into the outer environment, where these peptides trigger vagal afferent neurons [5]. Vagal afferent neurons can be triggered by the ENS via neurotransmitters produced by the gut, like 5-hydroxytryptamine (5-HT) known as serotonin [28], that is a neurotransmitter that regulate the GBA. 90% of serotonin occurs in the enterochromaffin cells, that are influenced by gut microbiota. The serotonin that derives from the gut does not have the ability to pass the BBB, but its precursor 5-hydroxytryptophan that derives from the diet, could pass the BBB and affect the CNS [1,4].

Many gut hormones, GLP-1, ghrelin, peptide YY (PYY), GIP and CCK, are associated with the activity of GBA. GLP-1 ameliorates memory, learning, motor activity and displays potential neuroprotective function in NDDs such as AD and PD. Gut microbiota regulates the release of GLP-1 [31]. Ghrelin influences glucose and lipid metabolism and modulate memory and learning [32].

Bacteria metabolites trigger EECs to produce neuropeptides that pass into the blood circulation and affect the ENS. The consequent stimulation of the immune system provoke the release of cytokines or the stimulation of the vagal nerve. This process affect neurotransmission and neurogenesis and can be involved in neuroinflammation [3,5].

3.9. Intestinal Barrier

The intestinal barrier is a selective barrier that promotes the absorption of nutrients and immune supervision and limits the entry of pathogenic microorganisms [33]. The intestinal barrier consists of the external mucus layer and the internal lamina propria. The external mucus layer is composed by epithelial cells and presents mucins, that invest the epithelium and consist a physical defense against bacteria. The external mucus layer provide the optimal environment and nutriment to the gut microbiota [33,34].

The gut microbiota regulate the mucus gel and the constitution of the mucus layer has an impact on the microbiota. Intestinal epithelial cells, beneath the mucus layer, are linked to each other with firm junctional structures. Tight junctions are situated at the apical side of the cells controlling in this mode the transportation of small particles and ions. They consist of transmembrane proteins,

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occludins and claudins and membrane proteins, zonula occludens (ZO). Adherent junctions are situated under the tight junctions so to form adhesion links and guarantee the integrity of the intestinal barrier. The inner lamina propria contain macrophages, B cells and T cells, responsible of the immune defense system of the intestinal barrier [33].

When the intestinal permeability rises (leaky gut), microbiome metabolites and toxins can enter into the blood circulation and induce the production of pro-inflammatory cytokines and initiate an inflammatory cascade [10]. Gut dysbiosis allow bacterial toxins like LPS to enter the blood circulation and induce the production of pro-inflammatory cytokines as well [10]. Leaky gut is associated with various human diseases, like irritable bowel, obesity, depression, AD, PD, and diabetes [35].

3.10. Blood Brain Barrier

The BBB subdivides CNS from the systemic circulation, and preserve brain homeostasis. The BBB is a selective barrier that allow oxygen, vital nutrients and waste metabolites to entry, while impede entry to pathogens and harmful products. The impairment of the BBB integrity is involved in the pathology and development of NDDs. The BBB consists of endothelial cells that cover cerebral vessels, tight junction proteins and basement membranes [36].

Endothelial cells in the CNS are characterized by low level of transcytosis and display many enzymes and transporters. In that mode there is a selective translocation of elements in and out of the CNS parenchyma, maintaining an equilibrium for optimal neuronal function [36,37]. Additionally, tight junction proteins preserve the stability of the BBB. Tight junction proteins are membrane-associated cytoplasmic proteins like ZO and transmembrane proteins like claudins and occludins. Alterations in tight junction proteins, leads to BBB damage and development of NDDs [38]. Brain analysis with MRI have shown the impairment of the BBB [39].

The dysbiosis that exists in NDDs could lead to the BBB impairment and disease development. In GF mice BBB is more permeable than in mice with a normal constitution of gut microbiota and transferring gut microbiota to GF mice partially ameliorates the barrier activity [40].

4. Neurodegenerative Diseases

4.1. Alzheimer Disease

AD is the most common type of dementia, more frequent in old age, discovered in 1907. Almost 50 million people are affected by dementia and is predicted to quadruple by 2050 [6,41]. AD is an irreversible and developing disorder characterized by memory loss, personality modification, behavioral matters and an impairment in thinking capacity [6,42]. AD brains, display extracellular gathering of insoluble Aβ peptide and intraneuronal neurofibrillary tangles produced by pathological alterations of tau protein [4,6,7,41,42].

Amyloid precursor protein (APP) is a transmembrane protein located in synapses [6] that normally forms the Aβ peptide, that is processed and cleared. In physiological conditions, this peptide protect synapses [43]. In the AD, APP create aggregates of Aβ fragments because they are not properly processed, conducing to aggregates of extracellular plaques. In the AD the hyperphosphorylation of Tau, a protein with a microtubule-stabilizing activity in neuronal axons, cause microtubule destabilization and neurofibrillary tangles. These proteins when accumulated cause inflammation, oxidative stress, microglia stimulation, deficits in neurotransmitters and death of neurons [7,44].

GBA may lead to the progress of AD. Gut microbiota due to its ability to produce proinflammatory cytokines (IFN-γ, IL-6, TNF-α, IL-18, IL-1β) and metabolites that pass through BBB, provoke neuroinflammation in the AD brain. High levels of IL-6 conduce to hyperphosphorylation of tau and neuronal degeneration. High levels of IL-1 are involved to elevated production of APP in vivo and in vitro [45]. Furthermore, gut microbiota produces insoluble amyloids, that could increment the development of plaques and contribute to the pathogenesis of AD [46,47].

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Additionally, in AD patients' feces, bacteria with the ability to produce butyrate, a SCFA with anti-inflammatory and immunomodulatory features, were reduced compared to controls feces [48].

AD patients display in their feces great amounts of Escherichia spp. and Shigella spp., which are pro-inflammatory bacteria and low concentrations of Eubacterium rectale, known as anti-inflammatory bacteria [4,8,9,13]. The bacteria found in AD patients are Actinobacteria, Bacteroides, Lachnospiraceae and Ruminococcus, with lower levels of Firmicutes and Bifidobacterium and higher levels of Bacteroidetes [9].

Dysbiosis of gut microbiota may consist one of the major causes of AD pathogenesis [4,5,13]. The ENS can be triggered to create and aggregate Aβ protein by various bacteria such as Escherichia coli, Klebsiella pneumoniae, Streptococcus, Staphylococcus aureus, Salmonella and Mycobacterium [49]. Metabolites produced from pro-inflammatory bacterial species increase brain neuroinflammation and worsen AD [9]. Furthermore, a leaky gut allows bacterial amyloids to pass into the blood circulation and intensify brain's neuroinflammation [9].

On the other hand, age-related decline of gut microbiota diversity is correlated to AD, with a decrease in Bifidobacterium spp. and an increase in Proteobacteria influencing lipid metabolism and memory function [5,9]. All these results discussed above indicate a relationship between GBA, microbial metabolism and the progress of AD.

4.2. Parkinson Disease

PD is the second most frequent NDD globally [1,7]. There is an increasing prevalence of PD as age advances and is predicted to arrive at 12.9 million in 2040 globally. Furthermore, is not common before the age of 50 and it is more frequent in men than women among 50 and 59 years old [13]. The risk factors of PD are age, genetic predisposition and environmental factors. If a family member is affected by PD the risk of being affected by PD rises by 2–3 folds [50]. In addition, contact with heavy metals and pesticides, provoke mitochondrial impairment and oxidative stress and leads to gene abnormalities in familial PD [50].

In PD there is an accumulation of misfolded α-Syn protein (known as Lewy bodies) in dopaminergic neurons of the substantia nigra, considered as a biomarker in PD [7,11,13]. The accumulation of α-Syn protein conduce to motor symptoms (bradykinesia, postural instability, resting tremors, stiffness) *[11,50]* and non-motor symptoms in the GI tract, like constipation that affects 80% of the individuals [1,6,8,11,13,41] cognitive deficits, urinogenital complications and olfactory damage (hyposmia). Hyposmia, often anticipate the diagnosis by years, suggesting an early accumulation of α-Syn protein, in the olfactory bulb [11].

The ENS could be the way of communication between gut microbiota and the CNS and could contribute to the development of PD [11,13]. GI impairment anticipate motor symptoms, suggesting that α-Syn accumulation firstly take place in the ENS and then advance to the CNS [11] indicating a potential connection to the GBA [2,13]. Furthermore, in vivo studies evidenced that α-Syn is disseminated from the intestine via the vagus nerve to the brain [5,8,11]. Other studies indicate that dysbiosis in mice conduce to accumulation of α-Syn in the brain, with neuroinflammation related to low quantities of SCFAs in feces [11].

In addition, PD patients present modifications of the gut microbiota as well as an increased permeability of the intestinal barrier [2,5] permitting the access in toxins that may impair the neuroendocrine system and GBA [5,11,13]. Dysbiosis has been suggested being an early marker in PD because the aggregation of α-Syn in the ENS anticipate the symptoms of PD [13].

PD patients, present low quantities of Prevotellaceae [4,11] that are SCFA producers, which contribute to intestinal barrier's impairment and low quantities of Lachnospiraceae (SCFA producers as well) such as Ruminococcus, Roseburia and Blautia. On the other hand, PD patients, present increased Enterobacteriaceae, that increase LPS, lead to neuroinflammation and are related with postural instability [4,13] and increased pro-inflammatory genera such as Proteobacteria [13].

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4.3. Multiple Sclerosis

MS is a chronic demyelinating inflammatory disease of the CNS, where immune system's impairment plays a crucial role [1,13,14,41,42,51]. Having the knowledge that gut microbiota is very important for the growth and development of the immune system, we can comprehend why gut microbiota is involved in the pathogenesis of MS, an immune related neurological disorder [8,52].

Globally, is most common to women than men [13,52] with a ratio woman to men 4:1. Worldwide, MS affects about 2.3 million people [1,13,52]. There is an association between higher latitudes such as in European countries and MS, probably because of lower sun exposure and different nutritional reasons like variations in vitamin D quantities [53]. Various environmental factors have been related to the growth of MS. Besides vitamin D mentioned above, other factors are Epstein–Barr virus, obesity, smoking that provokes lung irritation and consequent inflammatory responses and autoimmunity *[10,14,51–53]*. MS can also be triggered by environmental factors in persons with specific genetic factors [53].

The principal symptoms are diplopia associated with optic neuritis, gastrointestinal symptoms such as dysphagia, constipation or incontinence (gastrointestinal impairment modify the composition of gut microbiota), motor sensory symptoms, vestibular symptoms like vertigo, memory impairment and even psychiatric symptoms like anxiety and depression [51].

MS display demyelination of neurons, axonal impairment and impairment in neurological activity [1,13,14,42,52,53]. MS presents inflammation, BBB impairment and neurodegeneration [8,13]. The BBB's increased permeability leads to the transportation of CD4+ and CD8+ T lymphocyte into the CNS and the growth of demyelinating plaques [13]. Cellular autoimmunity play an important role in MS pathogenesis [51]. It is suggested that MS pathogenesis includes an autoimmune reaction where T cells react against myelin autoantigens [51].

Lymphocytes produce cytokines. Th1 lymphocytes release interferon γ (IFN-γ) which stimulates macrophage and release of reactive oxygen species (ROS) that damage surrounding tissues [13]. Furthermore, they produce IL-12, that increase IFN-γ and TNF-α [13]. Th17 lymphocytes, produce IL-17, IL-22, IL-21, that increase inflammation [13,51]. Neurodegeneration in MS is associated with the production of proteolytic enzymes and modulation of mitochondrial function that leads to an increased quantity of ROS, and damage of neurons and glia [53].

GF mice resist to neuroinflammation, and this information triggered an interest in analyzing the relation between the gut microbiota and MS [53]. The gut microbiota take part in the etiopathogenesis of MS because it modulates the immune system, modifies the permeability of the BBB and is implicated in the autoimmune demyelination [8,13].

MS patients may more frequently display dysbiosis than healthy controls [1,4,10]. 16S rRNA gene sequencing revealed that MS patients have a diverse microbiome than healthy controls [53]. All these suggest that the main target of therapies should be to lessen oxidative and inflammatory stress. The inflammation of the CNS is the main cause of damage in MS. The pathology of MS could be handled via regulation of gut microbiota constitution through specific dietary interventions [14].

5. Prebiotics

The prebiotics were first presented in 1995 by Glenn Gibson and Marcel Roberfroid [54,55]. In 2008, prebiotics were reported as a fermented constituent that led to specific modifications of the composition and activity of the gut microbiota, for the benefit of the host's health [54,56,57]. Prebiotic fermentation by gut microbiota, induce to the production of SCFAs and lactic acid. SCFAs, mainly butyrate, affect barrier function and present anti-inflammatory effects. Inulin and fructo-oligosaccharides (FOS) induce the growth of Bifidobacteria that leads to the production of acetic and lactic acids, produce antimicrobial substances that remove pathogens, and trigger development of the immune system *[57–59]*.

The consequent criteria are used for defining a compound as a prebiotic: a) it is resistant to acidic pH of stomach, it can't be absorbed in the GI tract and it can't be hydrolyzed by human enzymes b)

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it has the capacity to be fermented by gut microbiota and c) promotes growth and activities of the gut microbiota helping host's health [54,56].

Types of Prebiotics

Fructans

This category contains FOS or oligofructose and inulin. Fructans can selectively stimulate lactic acid bacteria [54,56]. FOS is included in many fruits and vegetables and can be produced by microbial fermentation [56].

Galacto-Oligosaccharides (GOS)

GOSs stimulate Bifidobacteria and Lactobacilli. GOS also stimulate Bacteroidetes, Firmicutes and Enterobacteria. There is a type of starch, named resistant starch (RS), that resist the upper gut digestion. RS produce high levels of butyrate, contributing to health and so it is classified as a prebiotic [54].

Non-Carbohydrate Oligosaccharides

There are some constituents that don't belong to carbohydrates but is proposed to be classified as prebiotics, like cocoa flavanols. In vivo and in vitro studies showed that flavanols stimulate lactic acid bacteria [54].

6. Probiotics

Probiotics are live microorganisms that have profitable effect on the body when consumed in adequate abundance [60,61]. These microorganisms can't colonize the gut permanently and have to survive through the digestive system. Probiotics modulate the constitution of the gut microbiota and the production of healthful products that derive from fermentation [62]. The main probiotic genera are Bifidobacterium and Lactobacillus [60]. The probiotic bacteria mainly included in dairy products are Lactobacillus acidophilus, Lactobacillus casei and Bifidobacterium. Antagonistic attachment to epithelium and mucosa with pro-inflammatory microbes ameliorate the intestinal barrier's integrity and activity via SCFA production [60,61].

7. Microbiome Modification as a Therapeutic Target for Neurodegenerative Diseases

Results

7.1. Effects of Prebiotics on the Microbiome Modification

In a randomized, double-blind, placebo-controlled, 3-period, crossover trial, 29 healthy adults of 20–40 years old, received 0, 5.0, or 7.5 g agave inulin/day for 21 days with 7-day washouts among periods. Agave inulin and control supplementations were given as chocolate chews in identical coded boxes. Agave inulin, used in this study, was composed of fructose chains. Fecal samples were collected and examined by 16S Illumina sequencing. This in vitro study has proven that agave inulin is fermented by Bifidobacteria and Lactobacilli. Fecal Actinobacteria and Bifidobacterium were increased 3- and 4-fold after 5.0 and 7.5 g agave inulin/d respectively in comparison to control, while Desulfovibrio were diminished 40% with agave inulin compared with control. Dietary fiber consumption (total fiber plus 0, 5.0, or 7.5 g agave inulin/d) per kilocalorie was related to fecal butyrate, tended to be related to Bifidobacterium and was negatively associated to Desulfovibrio abundance. Four species in the Bifidobacterium genera were highly increased after intake of 5.0 and 7.5 g agave inulin/d compared with control: B. adolescentis, B. breve, B. longum, and B. pseudolongum [57].

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In another open-label, non-randomized study, the participants were: 20 PD patients newly diagnosed, 10 treated PD patients and 10 non-medicated PD patients. Prebiotics were given in the form of a bar (one bar contained 10 g fiber), consisting of rice bran, inulin resistant starch, and resistant maltodextrin, for 10 days. Participants consumed one bar daily for the first 3 days, and then one bar twice a day for the next 7 days. The fiber mixture constitution used was: 10% agave branched inulin, 30% resistant maltodextrin, 30% resistant starch, 30% stabilized rice bran. This intervention reduced the pro-inflammatory phylum Proteobacteria and Escherichia coli and increased SCFA-producing species like Fusicatenibacter saccharivorans and Parabacteroides merdae, Bifidobacterium adolescentis, Faecalibacterium prausnitizii and Ruminococcus bicirculans, with a simultaneous increase in plasma SCFA. The prebiotic intervention also diminished plasma zonulin a marker of intestinal barrier integrity and calprotectin, a marker of neutrophils in the intestinal mucosa [63].

A randomized, double-blind, placebo-controlled, cross-over study, included 34 healthy participants 19-65 years old, divided into 2 groups, low dietary fibre (LDF) and high dietary fibre (HDF) consumers. After 3 weeks of daily prebiotic consumption or placebo, gut microbiota constitution (16S rRNA bacterial gene sequencing) and SCFA concentrations were investigated. The aim of this study was to examine whether LDF versus HDF consumption modify gut microbiota reaction, to an inulin-type fructan prebiotic. Only participants with the following dietary fibre intakes, low (<18 g/d for females and <22 g/d for males) or high (≥25 g/d for females and ≥30 g/d for males) participated to the study. Participants received 16 g/d of inulin-type fructan prebiotic in two doses for 3 weeks or 16 g/d of placebo maltodextrin; in two doses for 3 weeks. A washout period of 3 weeks was undertaken between the two interventions. In the LDF group, the prebiotic consumption increased Bifidobacterium. In the HDF group, the prebiotic consumption increased Bifidobacterium and Faecalibacterium and diminished Ruminococcus, Dorea and Coprococcus. This study found that HDF consumers had a higher gut microbiota reaction and a greater benefit from an inulin-type fructan prebiotic than LDF consumers [59].

In a double-blind placebo control clinical trial, 35 sedentary constipated adults were divided. 17 subjects into an experimental group and 18 subjects into the control group and were given 10 g GOS and sugar gummies respectively, for 30 days. The aim of the study was to investigate the effect of GOS gummy consumption on gut health and depression in constipated subjects. 30 days of GOS consumption increased Lactobacillus, Bifidobacterium and Bacteroides and considerably diminished the phyla Bacteroidetes, Firmicutes and the genus Clostridium. Firmicutes to Bacteroidetes (F/B) ratio also ameliorated in the GOS group. On day 30, the experimental group had a higher ratio of Firmicutes to Bacteroidetes (F/B) than the placebo group. The F/B ratio is an indicator of gut dysbiosis. GOS consumption ameliorated SCFA profile. Increased levels of acetic acid, butyric acid and propionic acid were found in the experimental group in comparison to the placebo. In conclusion, daily consumption of 10 g of GOS for 30 days improves gut dysbiosis, constipation and depression in subjects with functional constipation [58].

A cross-sectional study recruited 41 adult patients (25 males, 16 females) who were receiving exclusive enteral nutrition for at least 12 days. 4 different standard formulas were utilized and 3 different FOS/fibre-enriched formulas. The standard formulas included no fibre or FOS and the FOS/fibre-enriched formulas included six dietary sources of non-digestible carbohydrate (inulin, oligofructose, resistant starch, soy polysaccharides, arabic gum, and cellulose. 53% insoluble fibre and 47% soluble fibre. 25 Patients consumed FOS/fibre-enriched formulas, and 16 patients consumed standard formulas. Fluorescent in situ hybridization was utilized to examine faecal samples for main groups of microbiota and gas liquid chromatography was utilized to examine SCFA concentrations. There were low concentrations of the main bacterial groups, including Bifidobacteria, in all patients. Nevertheless, faecal butyrate concentrations were higher in patients consuming the FOS/fibre-enriched formula in comparison to standard formula [64].

A 24-h in vitro culturing method was used to investigate if FOS could provoke a different effect in 3 diverse adult age groups. Gut microbial communities were cultured to investigate whether FOS can alter the microbial communities and how it can change the communities based on age. The

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cultures were analyzed using 16S rRNA sequencing analysis, qPCR analysis, and gas chromatography-flame ionizing detection, so as to identify modifications in their structure and activity. Fecal samples were collected from 18 adults. 3 age groups participated, young adult (25–35 years old), adult (36–50 years old), and older adult (51–70 years old) with 6 subjects for each group. The plenitude of SCFAs was evaluated using Gas Chromatography-Flame Ionizing Detection and the results were analyzed using principal component analysis to evaluate the impact of FOS on SCFAs that are produced by the gut microbiota. qPCR was used to investigate the plenitude of the Bifidobacterium genus. Consequently to FOS addition, the genus Odoribacter diminished in the adult and older adult age groups after consumption of FOS. The genus Bilophila, decreased significantly in all age groups after 24 h of incubation with FOS. Bilophila stimulates the production of LPS that leads to inflammation. After 24 h of incubation, there is an increment of Bifidobacterium in all groups, which is very important because Bifidobacterium decreases as we get older and is related to good health of the gut microbiota. Bifidobacterium also supports an adequate immune system. This study demonstrated that the great amount of SCFAs, butyrate, propionate and acetate, is influenced by the consumption of this prebiotic [65].

The aim of the following randomized, double-blind, placebo-controlled, cross-over trial was to examine the impact of chicory-derived inulin on bowel activity in healthy subjects with constipation. In two 4-week intervention periods, 12 g of inulin or maltodextrin (placebo control) were given daily for 2 weeks. Before each intervention, the subjects were given placebo control. The washout period followed the first intervention period. This study observed a modest impact on microbiota constitution and specific changes after inulin supplementation in relative abundances of Bifidobacterium, Bilophila and Anaerostipes. The decrease in Bilophila abundances led to softer stools and amelioration of constipation. The reduction of Bilophila, a genus containing pathobionts, is associated with host good health [55].

Table 1. Summary results of prebiotics effects on human microbiome.

Study Type	Study Sample/Duration	Participants	Protocol	Summary of Results	Study Reference
Randomized, double-blind, placebo-controlled, 3-period, crossover trial.	29 healthy adults / 21 days.	29 healthy adults of 20–40 years old.	Participants received 0, 5.0, or 7.5 g agave inulin/day for 21 days and fecal samples were collected and analyzed by 16S Illumina sequencing.	Fecal *Actinobacteria* and *Bifidobacterium* were increased.	[57]
Open-label, non-randomized study.	20 PD participants.	20 PD patients were newly diagnosed, 10 treated PD patients and 10 non-	Participants consumed prebiotics in the form of a bar for 10 days daily during the	This intervention diminished the pro-inflammatory phylum *Proteobacteria*	[63]

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		medicated PD patients.	first three days, and then one bar twice a day for an additional seven days.	and *Escherichia coli* and increased SCFA-producing species and reduced plasma zonulin a marker of intestinal barrier integrity and calprotectin a marker of neutrophils in the intestinal mucosa.	
Randomised, double-blind, placebo-controlled cross-over study.	34 healthy participants / 3 weeks.	34 participants 19-65 years old.	Participants were divided into 2 groups, LDF and HDF and received 16 g/d of inulin-type fructan prebiotic in two doses for 3 weeks or 16 g/d of placebo maltodextrin in two doses for 3 weeks.	In the LDF group, the prebiotic consumption increased *Bifidobacterium*. In the HDF group, prebiotic consumption increased *Bifidobacterium* and *Faecalibacterium* and diminished *Ruminococcus*, *Dorea* and *Coprococcus*.	[59]
Double-blind placebo control clinical trial.	35 adults / 30 days.	35 sedentary constipated adults, 25-62 years old.	17 subjects into an experimental group and 18 subjects into the control group were given 10 g	GOS consumption ameliorated SCFA profile, increased *Lactobacillus, Bifidobacterium* and *Bacteroides*	[58]

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			GOS and sugar gummies, respectively for 30 days.	and considerably diminished the phyla *Bacteroidetes*, *Firmicutes* and the genus *Clostridium*. *Firmicutes* to *Bacteroidetes* (F/B) ratio also ameliorated in the GOS group.	
Cross-sectional study.	41 adult patients / 12 days.	25 males, 16 females.	25 Patients consumed FOS/fibre-enriched formulas and 16 patients consumed standard formula. Standard formulas included no fibre or FOS and the FOS/fibre-enriched formulas included six dietary sources of non-digestible carbohydrate.	Faecal butyrate concentrations were higher in patients consuming the FOS/fibre-enriched formula in comparison to standard formula.	[64]
24-h in vitro culturing method.	18 adults.	3 age groups, young adult (25–35 years old), adult (36–50 years old), and older adult (51–70 years	Fecal samples were collected, after 24 h of incubation with FOS. Gut microbial communities	After 24 h of incubation, there was an increment of *Bifidobacterium* in all groups, the genus *Odoribacter*	[65]

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		old) with 6 subjects for each group.	were cultured to investigate whether FOS can change the microbial communities.	diminished and the genus *Bilophila*, decreased significantly. SCFA levels were increased.	
Randomised, double-blind, placebo-controlled, cross-over trial.	Healthy adults / 4-weeks.	Healthy subjects with constipation to assess the effect of inulin consumption.	In two 4-week intervention periods, 12 g of inulin or maltodextrin (placebo control) were given daily for 2 weeks.	Modest impact on microbiota constitution and specific alterations after inulin consumption in relative abundances of *Bifidobacterium*, *Bilophila* and *Anaerostipes*. The decrease in *Bilophila* abundances led to softer stools and amelioration of constipation.	[55]

7.2. Effects of Probiotics

In a 12-week multicenter, parallel, randomized, double-blind, and placebo-controlled clinical trial there was investigated the impact of probiotic supplementation on the cognitive situation of 90 older adults, aged 50–90 years, suffering by AD. The participants were divided into three groups. The first group was given Lactobacillus rhamnosus HA-114, the second group was given Bifidobacterium longum R0175, and the third group was given a placebo. The cognitive function was estimated using the Mini-Mental State Examination (MMSE) and the categorical verbal fluency test (CFT), at the baseline and after the 12-weeks. Mini-Mental State Examination is used for estimating cognitive disorders. It consists of 11 domains like orientation, language, calculation, with higher score meaning better cognitive ability. The CFT is used for evaluating executive features of cognition, used to estimate people with neurodegenerative disorders and aphasia. It consists of two exercises, the category fluency and the letter fluency. In the category fluency, patients have to name as more fruits and animals as they can in 1 min. In the letter fluency, patients are asked to say as more words beginning from the letter F as they can in 1 min. The number of exact responses is the patient's score in each exercise.

Performance in Activities of Daily Living (ADL) is estimated using the Barthel Index (BI). BI evaluates the grade of independence in performing daily jobs in the elderly via 10 variables such as feeding, dressing, toilet use etc. Instrumental Activities of Daily Living (IADL) scale was used to study the complex ADLs that are very crucial for living in a society. It consists of 8 questions so to evaluate capability in preparing food, being able to handle own medications, taking a bath etc. IADL

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performance usually deteriorates before ADL function. The Generalized Anxiety Disorder (GAD-7) scale contains seven items so to evaluate anxiety with higher scores indicating more anxiety in the elderly. In this study, MMSE total score identified improvement in the B. longum intervention group in comparison to the placebo and L. rhamnosus intervention groups. CFT score was higher in the L. rhamnosus intervention group compared to the placebo. The IADL scale was ameliorated in the intervention groups in comparison to the placebo group. In comparison to the placebo group, L. rhamnosus and B. longum increased IADL significantly. The GAD-7 scale significantly improved after supplementation with probiotics compared with the placebo [66].

In another randomized double-blind, placebo-controlled clinical trial the aim was to examine the impact of the consumption of probiotics and Vitamin D on the inflammatory features of PD and complications. 46 patients, 18 to 80 years old, were randomly separated into two groups A and B, 23 participants per group. Group A was the probiotic/vitamin D group and B was the placebo group. Patients received one capsule per day, either probiotic or placebo capsules, for 12 weeks. Probiotic + vitamin D supplements contained Bifidobacterium longum, Lactobacillus reuteri, Lactobacillus acidophilus, Lactobacillus paracasei, Lactobacillus rhamnosus, Bacillus coagulans (2×10^9 CFU), and 400 IU vitamin D, per capsule. Placebo and probiotic capsules were indistinguishable named capsule A or capsule B. In this trial IFN-γ, IL- 1β, IL-6, IL-10, TNF-α, total antioxidant capacity (TAC) in serum were evaluated. The Gastrointestinal Symptom Rating Scale (GSRS), Beck Anxiety Inventory (BAI) and Unified Parkinson's Disease Rating Scale (UPDRS), were estimated at the beginning and the end of the trial. The BAI was used to calculate the intensity of anxiety. This test includes 21 questions, each question rated from 0 to 3, scored in relation to the severity of anxiety. Another questionnaire used was the GSRS questionnaire. This one is used to estimate the frequency and the intensity of GI symptoms such as constipation, abdominal pain and diarrhea. Another test used was the UPDRS, to determine the severity and symptoms of PD. The supplementation of probiotic and vitamin D induced the reduction of inflammatory cytokines TNF-α, IFN-γ, and IL-1β and increased anti-inflammatory cytokines such as IL-10. BAI, GSRS, and UPDRS determined that the supplementation of probiotic and vitamin D significantly diminished the variables compared to the placebo group [67].

In the following animal study, the aim was to observe the anti-Alzheimer impact of acetylcholine-producing L. plantarum MTCC1325 against D-Galactose provoked AD in albino rats via its antioxidant features and GBA. L. plantarum MTCC1325 has the capacity to produce acetylcholine neurotransmitters. In this study 48 healthy male wister rats, 3 months old and weight 180g, were separated into 4 groups of 6 animals each group. Control group was given normal saline (1 ml/kg body weight). AD-Model group received intraperitoneal injection of D-Galactose (120 mg/kg body weight). Protective group was given both D-Galactose and L. plantarum (10 ml/kg body weight; 12×10^8 CFU/ml) for 60 days. L.P group was given L. Plantarum for 60 days. Animal attitute was examined on the 30th and 60th day in all groups. When compared with the control group, AD-model rats' hair, skin elasticity became stiff and saggy. In addition, during the AD induction period, the body weight of rats progressively diminished when compared to the control group. The protective group exhibited elevated body weight, when compared with the AD-model group. As a result, protective group rats that received L. plantarum MTCC 1325 for 30 and 60 days showed elevated body weight. AD-model rats exhibited significant diminished activity in comparison to the control group. L. plantarum MTCC 1325 treated groups showed amelioration in the activity of rats. The ACh load diminished in the cortex and hippocampus of AD-model group rat brain. Treatment with L. plantarum MTCC 1325 exhibited an important augmentation of ACh in both cerebral cortex and hippocampus [68].

In another animal study a genetic MitoPark PD mouse model was used. 16 male MitoPark PD mice, 8-week-old were randomly separated into two groups. The probiotic-treated group (n = 10) and sham probiotic-treated group (n = 10). The MitoPark PD mouse has the characteristics of PD, such as degeneration in dopaminergic neurons in older age and evolving impairment of motor activity, GI impairment and gut microbiome modification. The aim of this study was to examine whether the daily consumption of probiotics can reduce motor impairment on a PD mouse model. In the

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probiotic-treated group, each PD mouse was given the probiotics (10^{10} CFU/mouse/day) for 16 weeks. The sham groups received the regular liquid diet only without probiotics. The probiotics contained Bifidobacterium longum, Lactococcus lactis, Bifidobacterium bifidum, Lactobacillus rhamnosis, Lactobacillus plantarum LP28 and Lactobacillus rhamnosus GG. A test used was the beam balance test so to evaluate the performance of motor skill and balance in the experimental rodent Rotarod Testing. A rotarod test is used to estimate motor coordination and balance function. This study showed that the daily consumption of probiotics for 16 weeks has neuroprotective impact and mitigates the progressing impairment of motor activity in the MitoPark PD mice. In addition, the immunohistochemical staining demonstrated more intact dopamine neurons in the probiotic-treated group than in the sham probiotic-treated group, indicating a neuroprotective impact of probiotics. These results together indicate that probiotic supplementation may not only delay the decline of motor dysfunction but also have a neuroprotective impact against the progressing degeneration of dopaminergic cells [69].

A randomized, double-blind, placebo-controlled, multicenter clinical trial investigated the impact of probiotics on brain and intestinal health in 63 individuals over the age of 65. There was a 2-week wash out period and a 12-week treatment period. Participants were randomly divided into two groups, probiotics or placebo group and received their products twice a day for 12 weeks. Probiotic group received two capsules in the morning and evening, for a total of four capsules (1×10^{9} colony-forming unit of Bifidobacterium bifidum BGN4 and Bifidobacterium longum BORI in soybean oil). In the placebo group, each capsule included 500 mg of soybean oil only. Blood and fecal samples were collected at week 0, week 4, week 8, and week 12 and participants executed neuropsychological test at baseline, week 4 and week 12. The Consortium to Establish a Registry for AD (CERAD-K) was used to estimate cognitive function which is a validated test for the screening of AD. Geriatric Depression Scale (GDS-K) was used to estimate the level of depression. Probiotic supplementation ameliorated cognitive function and mental stress. BDNF, a neurotrophic factor very important for learning, memory and stress, in contrast to the placebo group, was elevated at week 12 in the probiotics group. To estimate the impact of probiotics on intestinal health, patients filled in a questionnaire, asking if there was amelioration in bowel behaviour in the last 4 weeks. Frequency of abdominal distention and gas passage exhibited improvements in the probiotics group in comparison to the placebo group. Lastly, at the genus level, the study found important alterations in the gut microbiota diversity in the probiotics group and no changes in the control group [70].

The following study included 20 patients (9 females, 11 males, aged 76,7 ± 9.6 years old) with AD. Probiotic consumption was received daily in the morning for 28 days, including Lactobacillus acidophilus W22, Lactobacillus plantarum W62, Lactococcus lactis W19, Bifidobacterium lactis W52, Bifidobacterium bifidum W23, Lactobacillus casei W56, Lactobacillus paracasei W20, Bifidobacterium lactis W51 and Lactobacillus salivarius W24. Gut inflammation markers, microbiota constitution in fecal samples and biomarkers of immune activation (serum neopterin and tryptophan breakdown) were examined at baseline and after probiotic supplementation for 4 weeks. High production of neopterin and increased breakdown of tryptophan are implicated in cognitive decline in patients affected by AD and other forms of dementia. Fecal inflammation markers, calprotectin, α1-antitrypsin and zonulin were measured using the enzyme-linked immunoassorbent assays (EIAs). Neopterin, vitamin D and BDNF were measured using ELISA. The kynurenine to tryptophan ratio (Kyn/Trp) was measured as an indicator of tryptophan breakdown. The elevation of kynurenine was found after probiotic consumption. Faecalibacterium prausnitzii increased. Zonulin concentrations declined after 4 weeks of supplementation with the probiotic [71].

Table 2. Summary results of probiotic effects.

Study Type	Study Sample/Duration	Participants	Protocol	Summary of Results	Study Reference
Randomized double-blind and placebo-controlled clinical trial.	90 older adults with mild and moderate AD/12 weeks.	Aged 50–90 years old.	The participants were randomly divided into three groups, placebo (n = 30), *L. rhamnosus* (n = 30), and *B. longum* (n = 30). The cognitive function was evaluated using MMSE and CFT. IADL scale and GAD-7 scale were used to estimate the ability in executing daily jobs and level of anxiety, respectively.	12-week probiotic consumption compared with placebo, had positive impact on the anxiety, cognitive status and instrumental daily functions of patients suffering by AD.	[66]
Randomized double-blind, placebo-controlled clinical trial.	46 patients with PD / 12 weeks.	18 to 80 years old.	Patients were randomly divided into two groups: Group A was given probiotic/vitamin D supplementation (n = 23), and Group B placebo capsules (n = 23) for 12 weeks. GSRS, BAI, UPDRS were used to estimate the intensity of anxiety, the frequency and the intensity of GI problems and the severity and symptoms of PD respectively.	Probiotic consumption and vitamin D diminished inflammatory cytokines, IFN-γ, IL-1β, IL-6 and increased anti-inflammatory cytokines such as IL-10, diminished disease severity, anxiety, and GI symptoms in PD patients.	[67]
Animal study.	48 albino rats (wistar strain) /60 days.	48 albino rats separated into 4 groups of 6 animals each group.	The control group was given normal saline (1 ml/kg body weight). AD-Model group received intraperitoneal injection of D-Galactose (120 mg/kg body weight). Protective group was given both D-Galactose and *L. plantarum* (10 ml/kg body weight; 12×10^8 CFU/ml) for 60 days. L.P group was given *L.*	Supplementation with *L. plantarum MTCC1325* for 60 days, ameliorated cognition problems, treated groups exhibited amelioration in the activity of rats, showed elevated body weight, exhibited an	[68]

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			Plantarum for 60 days. Animal behaviour was evaluated on the 30th and 60th day in all groups.	important augmentation of ACh in both cerebral cortex and hippocampus.	
Animal study.	Transgenic MitoPark PD mouse model / 16 weeks.	16 males MitoPark PD mice, 8-week-old.	8-week-old PD mice were randomly divided into the probiotic-treated group and sham treatment group. After daily oral supplementation with probiotics for 16 weeks, the Beam balance test was used so to estimate the execution of motor skill and balance.	Probiotic consumption delays the decrease of motor dysfunction but also has neuroprotective impact against the progressing degeneration of dopaminergic cells in MitoPark PD mice.	[69]
A randomized, double-blind, placebo-controlled, multicenter clinical trial.	63 participants / 12 weeks.	63 subjects / over 65 years old	31 and 32 subjects in the placebo and probiotics group, respectively. Probiotics or placebo group received their products twice a day for 12 weeks, (1×10^9 CFU of *Bifidobacterium bifidum BGN4* and *Bifidobacterium longum BORI* in soybean oil). In the placebo group, each capsule included 500 mg of soybean oil only.	Probiotic supplementation ameliorated cognitive function and mental stress, elevated BDNF, frequency of abdominal distention and gas passage, exhibited benefits in the probiotics group, and important changes in the gut microbiota diversity in the probiotics group.	[70]
Explorative Intervention Study.	20 patients / 4 weeks.	9 females, 11 males, aged 76.7 ± 9.6 years with AD.	Supplementation of probiotics were consumed daily for 28 days. Gut inflammation markers, microbiota constitution in fecal specimens and biomarkers of immune activation (serum neopterin and tryptophan breakdown) were estimated.	Elevation of kynurenine was found after probiotic consumption, *Faecalibacterium prausnitzii* increased, Zonulin concentrations declined after 4 weeks of supplementation of probiotics.	[71]

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8. Discussion

This review presents evidence on the connection between the GBA and NDDs. This relationship takes place via direct communication between the CNS and ENS through the vagus nerve and via indirect pathways like the immune system and microbial products [11,12]. Several studies suggest that the gut microbiota play a crucial role in the neuropathogenesis of NDDs through modulation of the activity of the GBA [3,4]. Gut dysbiosis describe an imbalance in the gut microbiota, a decrease in microbial diversity and abundance, a decrease in profitable bacteria like Bacteroides and Firmicutes, and an increase in pathogens like Prevotellaceae and Enterobacteriaceae. This imbalance lead to systemic inflammation, metabolic disorders, and reduced metabolites [72]. Dysbiosis can increase intestinal and BBB permeability, can lead to changes in intestinal mucus and translocation of gut microbes and their metabolites. These alterations bring to a state of toxic inflammation [73]. Many factors can bring to dysbiotic microbiomes, like a diet containing refined products, with not abundant fiber incorporation, elevated alcohol consumption, antibiotics, bacterial or viral infections, medical conditions like diabete and NDDs [74].

The correlation between gut dysbiosis and NDDs suggest that dietary interventions having as a target gut dysbiosis, could be an approach for treating symptoms and delaying the neuroinflammatory and degenerative processes in NDDs. Prebiotics are indigestible dietary components in the upper GI tract but are used by profitable gut microbes in the large bowel, ameliorating host health. During their fermentation the production of byproducts helps cross-feeding between microorganisms. Acidic fermentation products offer a favorable milieu for beneficial bacteria, like Lactobacilli and Bifidobacteria, and inhibit pathogenic bacteria [75]. The most valuable by-products produced by prebiotics are SCFAs, that can enter into the blood circulation. Therefore, prebiotics have an impact not only on the GI tract but also on distant organs, including the brain [54]. In a study, the consumption of FOS provoked amelioration in learning and memory abilities, in rats affected by AD. There was also observed a decrease in oxidative stress and inflammation and an augmentation of neurotransmitters, such as 5-HT and dopamine. These effects were ascribed to the capacity of FOS to modulate both gut and brain equilibrium [76].

Probiotics, as previously mentioned, are live nonpathogenic microorganisms that provide health benefits when consumed in adequate quantities. Probiotics mostly used are Bifidobacterium, Lactobacillus, Enterococcus, Streptococcus and Bacillus [77]. Studies have shown that probiotics apply their beneficial effects via different mechanisms: they regulate gut microbiota and diminish pathogens invasion and installation, they promote epithelial cell development in order to fortify intestinal barrier and diminish immunomodulation. Probiotics also produce healthy products like SCFAs, with anti-inflammatory and neuroprotective activity that enter the blood circulation and cross the BBB, regulate CNS immune cell function, inflammatory cytokines, BBB integrity and neurogenesis, thereby inducing brain health [77,78]. They trigger the production and release of neurotransmitters, affecting neuronal activity in NDDs [79].

9. Conclusion

Continuous studies concerning gut microbiome are giving us information about the connection between gut microbiota and their symbiotic correlation with humans. In the future, knowledge about the effects of gut microbiome on NDDs like AD, PD and MS, will provide to their prevention and therapy. Daily dietary interventions could have therapeutic function. The development of functional foods containing prebiotics and probiotics seems to have profound significance. In addition, as our knowledge about gut microbiomes proceeds, predictive biomarkers for various NDDs and their outcomes can be developed. However, extensive studies are still required, based on clinical evidence in humans. Moreover, new studies related to the modification of the human gut microbiome through dietary intervention should be done.

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