Review

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A nutritional approach to microbiota in Parkinson's disease

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Parkinson's disease (PD) is a neurodegenerative disease characterized by motor impairment and the accumulation of alpha-synucleinopathy (α-syn), which can affect different levels of the brain-gut axis. There is a two-way communication between the gastrointestinal tract, and brain that includes the gut microbiota. This bidirectional communication between the gut microbiota and the brain includes many pathways, such as immune mechanisms, the vagus nerve, and microbial neurometabolite production. The common cause of constipation in PD is thought to be the accumulation of α-syn proteins in the enteric nervous system. Recent studies have focused on changes in microbial metabolites and gut microbiota dysbiosis. Microbiota dysbiosis is associated with increased intestinal permeability, intestinal inflammation, and neuroinflammation. Many factors, such as unbalanced nutrition, antibiotic use, age, and infection, result in alteration of microbial metabolites, triggering α-syn accumulation in the intestinal mucosa cells. Increased evidence indicates that the amount, type, and balance of dietary macronutrients (carbohydrates, proteins, and fats); high consumption of vegetables, fruits, and omega-3 fatty acids; and healthy diet patterns such as the Mediterranean diet may have a great protective impact on PD. This review focuses on the potential benefits of prebiotics, probiotics, and synbiotics to regulate microbiota dysbiosis along with the effect of diet on the gut microbiota in PD.

Key words: Parkinson's disease, alpha-synuclein, microbiota, nutrition, probiotics, gut-brain axis

INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disorder, and it affects 0.5–1% of the population aged 65–69 years and 1–3% of the population above 80 years of age [1]. It is characterized by the aggregation and accumulation of alpha-synucleinopathy (α-syn) proteins in the central nervous system (CNS) and other neural structures. The classical motor symptoms like bradykinesia, resting tremor, rigidity, and late postural instability result from the death of dopamine-producing cells in the substantia nigra. In addition, PD patients frequently exhibit non-motor symptoms including symptoms affecting the olfactory (relating to loss of smell), gastrointestinal, cardiovascular, and urogenital systems [2]. The most common gastrointestinal system (GIS) symptoms are constipation, loss of appetite, dysphagia, drooling, and gastroesophageal reflux. Moreover, gastrointestinal function is further exacerbated following progression of the disease [3, 4]. Constipation is the most common autonomic symptom in PD [2, 5] and is reported to be seen in approximately 80% of PD patients [5]. The accumulation of α-syn protein in the enteric nervous system leads to increased intestinal permeability, oxidative stress, and local inflammation. This causes neurodegenerative changes in the enteric nervous system (ENS) and may result in prolonged intestinal permeability [6], and constipation [7, 8]. Lewy bodies, formed as a result of misfolding α-syn proteins, are found in CNS structures, peripheral autonomous systems, and the ENS [9, 10]. The ENS is a network of neurons in the GIS wall. It plays a major role in bidirectional communication between GIS and CNS [11, 12]. Lewy body pathology in ENS may represent the pathohistological correlate of gastrointestinal symptoms in PD. Current hypotheses suggest that ENS might be one of the first sites where Lewy body pathology appears in PD [9, 10]. Lewy bodies and α-syn proteins may appear in the gut before they appear in the brain, and these observations reveal the hypothesis that PD starts in the gut and spreads to the brain. Increased intestinal permeability in conjunction with the presence of α-syn in the gut at early stages of the disease may cause the spreading of the disease [13].

The role of nutrition in the development and prevention of diseases has always been remarkable. New evidence suggests that the effect of diet on brain health is not because of a diet-induced inflammatory response but is because of the effect of the composition of the diet on the gut microbiome [14]. The gut microbiota is essential for human health and the immune system. It also plays a major role in the bidirectional communication between the gut and the brain [15–17]. Recent research has shown that changes in gut microbiota can influence the physiological, behavioral, and cognitive functions of the brain [12, 18]. Gut microbiota affects brain activity via the microbiota-gut-brain axis under both physiological and pathological disease conditions [6]. Combinations of specific nutrients, which include neuronal precursors and cofactors, can prevent synaptic loss and may

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reduce membrane-related pathology in the CNS and ENS [19]. In recent studies, fecal short chain fatty acid (SCFA) concentrations were significantly reduced in PD patients [7, 9, 20] and *Prevotellaceae* were reduced in the feces of PD patients was reduced as compared with that of control [7]. The formation of the gut microbiota is influenced by many dietary factors. Dietary components plays an important role in the control of gut microbial populations and, thus, in the prevention, management, and treatment of certain diseases. Some dietary factors considered to be effective in patients with PD include vegetables, fruits, fish, protein, fat [21], carbohydrates, fiber [9, 20], polyphenols [22], the Mediterranean-type diet [23, 24], and the Western-type diet [25]. Therefore, this review focuses on the effects of dietary factors on the microbiota composition of PD patients and therapeutic treatment approaches.

GUT-BRAIN AXIS IN PARKINSON'S DISEASE

Recent research has shown that changes in intestinal microbiota can affect the physiological, behavioral, and cognitive functions of the brain [12, 18]. The gut-brain axis (GBA) is a complex bidirectional communication system between the gut and the brain mediated by hormonal, immunological, and neural signals [15–17]. GBA includes immune mediators such as cytokines, production of bacterial metabolites [26], and signal stimulation to the brain through direct action on the vagus nerve [26, 27]. This axis is also responsible for the modulation of digestive processes under physiological conditions. Dysregulation of the axis, gut dysbiosis, and inflammation are associated with various diseases including mental disorders (anxiety and depression), Alzheimer's, inflammatory bowel disease, and obesity [15, 28–30]. In a study conducted on germ-free (GF) mice, to investigate the role of intestinal microbiota and bacterial metabolites in the pathogenesis of PD, a relationship between intestinal microbiota and behavior-related brain function was found. The microbial colonization process initiates signaling mechanisms that affect neuronal circuits involved in motor control and anxiety behavior. At the same time, GF mice compared with specific pathogen-free (SPF) mice show elevated noradrenaline (NA), dopamine (DA), and serotonin (5-HT) turnover rates in the striatum [31]. Serotonin is a neurotransmitter that plays an important role in the GBA, affecting both ENS and CNS levels. The gut microbiota stimulates the synthesis of various neuroactive molecules such as serotonin, acetylcholine, melatonine, gamma aminobutyric acid (GABA), catecholamine, and histamine [16, 32]. These neurotransmitters affect the regulation and control of blood flow, as well as intestinal motility, absorption of nutrients, the gastrointestinal immune system, and microbiota. Especially in pathological conditions like inflammatory bowel diseases and PD, these neurotransmitters can cause various gastrointestinal symptoms [33]. Although dysbiosis has been reported in PD, it is not yet clear whether changes in the microbiota are a trigger for PD pathology. Fecal microbiota from PD patients or controls were transplanted into individual groups of GF recipient animals. The microbiota derived from individuals with PD promoted increased α-syn-mediated motor dysfunction [34]. Evidence suggests that changes in the microbiota and its metabolites may be an important risk factor for PD through the gut-brain axis. Many factors such as unbalanced nutrition, antibiotics, age, and infection lead to changes in the gut mucosal cells which cause α-syn accumulation. The vagal nerve might provide a path for the spreading of α-syn pathology from the ENS to the brain. The aggregated α-syn spreads towards CNS via the the vagus nerve. Eventually, the aggregated α-syn arrives at the substantia nigra. The accumulation of α-syn in the brain has been linked to neurodegeneration, neuroinflammation, and neuronal death [35, 36]. The microbiota-gut brain axis communication pathway linking gut microbial dysbiosis with brain function in PD is shown in Fig. 1.

INTESTINAL BACTERIAL COMPOSITION AND PARKINSON DISEASE

Alterations in the number as well as composition of gut microbiota and microbial metabolites are found in PD patients. Intestinal dysbiosis in PD has been reported in 12 articles from six countries: one from Finland, Japan and Russia, two from the USA, three from China, and four from Germany.

Scheperjans *et al.* [7] reported that alteration in the composition of gut microbiota in PD has been reported. They compared the fecal microbiomes of 72 PD patients and 72 control subjects by the pyrosequencing of the bacterial 16S ribosomal RNA gene. The abundance of *Prevotellaceae* in feces of PD patients with postural instability and gait difficulties was reduced by 77.6% as compared with controls, and there was a higher abundance of *Enterobacteriaceae* was found among those patients with postural instability along with gait difficulty phenotype compared with those with tremor-dominant PD. Keshavarzian *et al.* [20] found that members of the genus *Faecalibacterium* were significantly more abundant in the mucosa of controls than in PD patients. Putative "proinflammatory" *Proteobacteria* of the genus *Ralstonia* were significantly more abundant, and anti-inflammatory SCFA producers genera *Blautia*, *Coprococcus*, and *Roseburia* were significantly decreased in PD patients. One clinical study reported increased levels of *Akkermansia, Lactobacillus*, *Bifidobacterium,* and decreased levels of *Lachnospiraceae* in PD patients compared with controls [13]. Another study found that the abundance of *Lactobacillus* was higher despite the fact that *Clostridium coccoides, Bacteroides fragilis,* and *Clostridium leptum* were lower in the fecal samples of PD patients [37]. In a recent study, changes in the content of 9 genera and 15 species of microorganisms were revealed in PD patients decreased contents of *Dorea, Bacteroides, Prevotella, Faecalibacterium, Bacteroides massiliensis, Stoquefichus massiliensis, Bacteroides coprocola, Blautia glucerasea, Dorea longicatena, Bacteroides dorei, Bacteroides plebeius,*

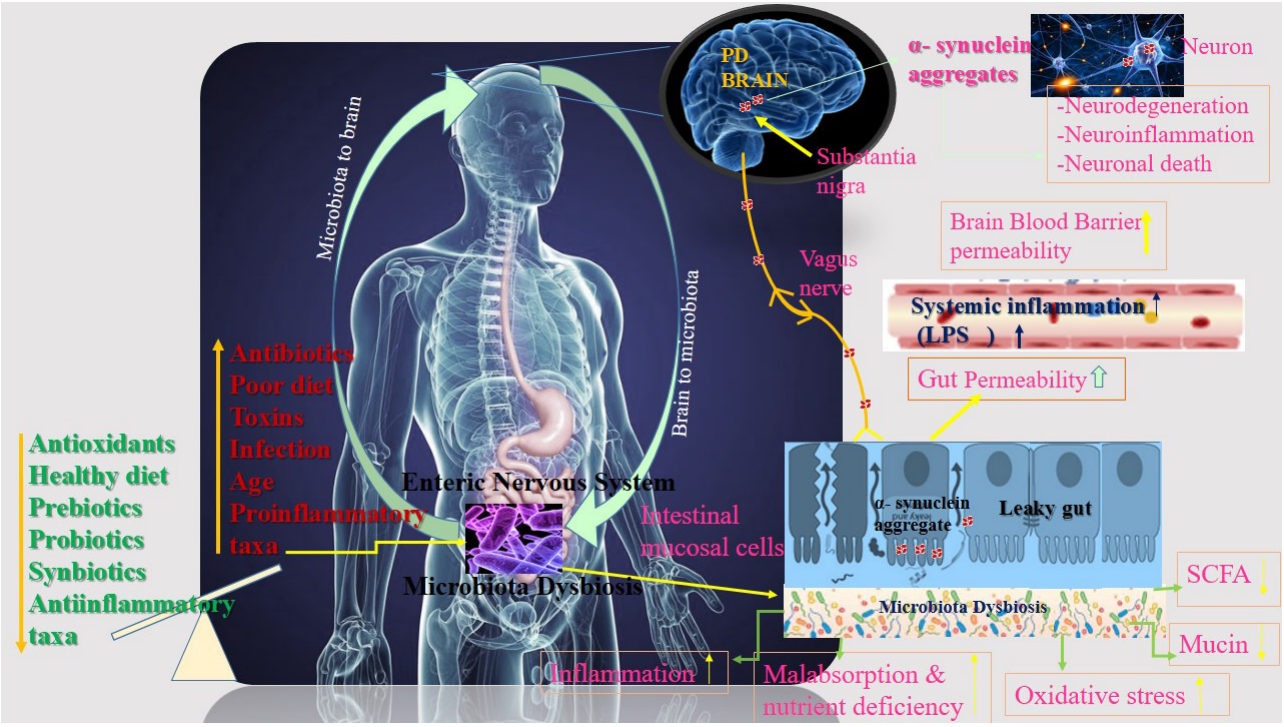

Fig. 1. Microbiota-gut brain axis communication in the pathogenesis of Parkinson's disease. Multiple factors affecting the composition of gut microbiota.

Prevotella copri, Coprococcus eutactus, and Ruminococcus callidus, and increased contents of *Christensenella, Catabacter, Lactobacillus, Oscillospira, Bifidobacterium, Christensenella minuta, Catabacter hongkongensis, Lactobacillus mucosae, Ruminococcus bromii,* and *Papillibacter cinnamivorans* [38]. In a study conducted in southern China, the abundance of *Lachnospiraceae* was decreased by 42.9% in patients with PD, whereas *Bifidobacteriaceae* were increased enriched in patients with PD compared with age-matched controls [39]. Another study conducted in China showed that *genera Clostridium* IV, *Aquabacterium, Holdemania, Sphingomonas, Clostridium* XVIII, *Butyricicoccus*, and *Anaerotruncus* are enriched in the feces of PD patients after adjustment according to age, gender, body mass index (BMI), and constipation. Furthermore, genera *Escherichia* and *Shigella* are negatively associated with disease duration [40]. A study reported that the putative cellulose-degrading bacteria from the genera *Blautia, Faecalibacterium,* and *Ruminococcus* are significantly decreased in PD patients compared with healthy controls. The putative pathobionts from the genera *Escherichia-Shigella*, *Streptococcus*, *Proteus,* and *Enterococcus* were significantly increased in PD subjects [41].

In a northern German cohort study, it was shown that elevated levels of *Lactobacillaceae, Barnesiellaceae,* and *Enterococcacea* occur in fecal samples of PD patients [42]. Another study showed that genera *Akkermansia* and *Prevotella* are significantly more abundant in PD patients compared with healthy controls [43]. Another study found that the bacterial phylum *Bacteroidetes* and the bacterial family *Prevotellaceae* were decreased and that *Enterobacteriaceae* were more abundant in fecal samples from PD patients compared with matched controls [9]. Bedarf *et al.* [44] compared the fecal microbiomes of 31 early-stage, L-DOPA-naïve PD patients with those of 28 age-matched controls. They found increased numbers of *Verrucomicrobiaceae (Akkermansia muciniphila)* and unclassified *Firmicutes*, whereas *Prevotellaceae (Prevotella copri)* and *Erysipelotrichaceae (Eubacterium biforme)* were markedly decreased in PD patients. A summary of the changes observed in the gut microbiota in patients with PD is given in Table 1. This table is revised from Sun and Shen [36].

Recent studies have suggested that *Helicobacter pylori* infections are associated with negative interaction with the gut microbiota. *H. pylori* infections produce dramatic changes in the gastric microenvironment, simultaneously influence the gastric microbiota, and also impacts the intestinal commensal communities [45, 46]. *H. pylori* infection was reported years ago in PD patients [40], and there are also several studies suggesting that the potential relationship between *H. pylori* and Parkinson's disease is controversial [9, 40–43]. *H. pylori* infection was associated with an increased risk of Parkinson's disease. A recent retrospective study involving 2,105 *H. pylori* infected subjects and 9,105 matched uninfected controls found that those who were infected were 2- to 3-fold

Table 1. A summary of the changes observed in the gut microbiota in patients with Parkinson's disease (Revised from Sun and Shen [36])

İncreased	Decreased	Country	Reference
Enterobacteriaceae	*Prevotellaceae*	Finland	[7]
Akkermansia, *Lactobacillus* *Bifidobacterium* *Ruminococcaceae*	*Lachnospiraceae*	USA	[13]
*Proteobacteria (*Genus *Ralstonia)*	*Faecalibacterium* *Blautia*, *Coprococcus* *Roseburia*	USA	[20]
Lactobacillus	*Clostridium coccoides* *Bacteroides fragilis* *Clostridium leptum*	Japan	[37]
Christensenella *Catabacter* *Lactobacillus* *Oscillospira* *Bifidobacterium* *Christensenella minuta* *Catabacter hongkongensis* *Lactobacillus mucosae,* *Ruminococcus bromii,* *Papillibacter cinnamivorans*	*Dorea* *Bacteroides* *Prevotella* *Faecalibacterium* *Bacteroides massiliensis* *Stoquefichus massiliensis* *Bacteroides coprocola* *Blautia glucerasea* *Dorea longicatena* *Bacteroides dorei* *Bacteroides plebeus* *Prevotella copri* *Coprococcus eutactus* *Ruminococcus callidus*	Russia	[38]
Bifidobacteriaceae	*Lachnospiraceae*	China	[39]
Cluster IV *Aquabacterium* *Holdemania* *Sphingomonas* Cluster XVIII *Butyricicoccus* *Anaerotruncus*	*Lactobacillus* *Sediminibacterium*	China	[40]
Escherichia-Shigella *Streptococcus* *Proteus* *Enterococcus*	*Blautia* *Faecalibacterium* *Ruminococcus*	China	[41]
Enterobacteriaceae *Bifidobacterium*	*Bacteroidetes* *Prevotellaceae* *Faecalibacterium prausnitzii* *Lactobacillaceae* *Enterococcaceae*	Germany	[9]
Lactobacillaceae *Barnesiellaceae* *Enterococcacea*	-	Germany	[42]
Akkermansia *(Akkermansia* parent taxa *Verrucomicrobiaceae, Verrucomicrobiales, Verrucomicrobia)*	-	Germany	[43]
Prevotella			
Verrucomicrobiaceae (Akkermansia muciniphila) Unclassified *Firmicutes*	*Prevotellaceae (Prevotella copri)* *Erysipelotrichaceae (Eubacterium biforme)*	Germany	[44]

more likely to be PD patients than those who were uninfected [9]. In another study, *H. pylori* was reported in 32% of PD patients [43]. Therefore, the presence of *H. pylori* infections should not be ignored when evaluating the gut microbiota in PD patients.

A pro-inflammatory microbiota profile in the PD patient's intestinal tract might increase gut permeability, allowing leakage of bacterial products and inflammatory mediators from the intestines [11]. A dysregulated microbiota-gut-brain axis in PD might underlie gastrointestinal dysfunctions which predominantly emerge many years prior to the PD diagnosis, corroborating the theory that the pathological process spreads from the gut to the brain [2, 4]. Changes in the gut microbiota also affect GIS epithelial cells, the immune system, and the ENS (both neurons and glial cells) [47]. Taken together, these results may suggest that changes in the intestinal microbiota may have a direct effect on the CNS through the GBA via chronic mild systemic inflammation [48]. For this reason, an adequete and balanced antioxidant-rich diet may play a potential role in preventing proinflammatory conditions.

Nowadays, based on the current understanding of gut microbial dysbiosis, fecal microbiota transplantation is used to regulate immunological mechanisms though the microbiota-gut-brain axis for the treatment of autism, multiple sclerosis, and other CNS diseases [49]. A previous study reported that the fecal microbiota transplantation in mice with PD reduced the activation of microglia in addition to astrocytes in the substantia nigra and reduced expression of TLR4/TNF-α signaling pathway components in the gut and the brain [50]. However, there are still concerns regarding safety that remain to be addressed. As far as we know, there have been no randomised controlled studies. So, further studies on a new therapeutic approach are needed in relation to the gut microbiota and fecal microbiota transplantation.

EFFECT OF DIETARY THERAPY APPROACHES ON MICROBIOTA IN PD

Dietary fiber, antioxidants, healthy diet patterns, prebiotics, probiotics, synbiotics, etc., may impact the gut microbiota composition, enhance intestinal epithelial integrity, and reduce the proinflammatory response, impacting the initiation of PD. For example, antibiotics, poor diet, toxins, etc., may lead to a pathological process in the enteric cell plexus causing mucosal inflammation, oxidative stress, and decreased mucin and SCFA, thereby initiating α-synuclein accumulation.

Fiber, carbohydrates and microbiota

Dietary fiber means carbohydrate polymers with ten or more monomeric units according to the CODEX Alimentarius Commission [51]. It is categorized into two groups: as soluble and insoluble. There are two basic types of food fiber—insoluble fiber, which does not dissolve in water and is not fermented by the gut's bacteria, in addition to soluble fiber, which does dissolve in water and is fermented by the colon's microorganisms or bacteria. The polysaccharides pectin, and mucilage are examples of soluble fiber, whereas cellulose, hemicellulose, and lignin are all insoluble forms [52, 53]. SCFAs (non-digestible carbohydrates) are produced by fermentation of intestinal microbiota bacteria in the large intestine and provide up to 10% of the daily caloric requirements in humans [54, 55].

SCFAs may have a beneficial effect on PD as they increase the motility of the gastrointestinal tract by modulating ENS activity [9]. In recent studies, it has been pointed out that there are low levels of SCFAs in the stool samples of PD patients and that the chance in SCFAs indicate a change in the intestinal microbiota composition [9, 20]. Unger *et al.* [9], analyzed SCFA concentrations (using gas chromatography) and microbiota composition (using quantitative PCR) in the fecal samples of 34 PD patients in addition to 34 age-matched controls who were analyzed. Fecal SCFA concentrations were significantly reduced in PD patients, their levels of the the bacterial phylum *Bacteroidetes* and the bacterial family *Prevotellaceae* were reduced, and *Enterobacteriaceae* were more abundant in fecal samples from PD patients compared with those of matched controls [9]. It should be noted that especially, *Prevotellaceae* has various functional role which promotes a healthy intestinal environment. This enterotype is related to higher levels of health-promoting neuroactive short chain fatty acids and a high capacity for biosynthesis of thiamine as well as folate [7]. On the other hand, the decreased abundance of the *Prevotellaceae* bacteria family might be related to reduced mucin synthesis and increased intestinal permeability [56, 57]. Increased intestinal permeability may provoke local and systemic exposure to bacterial endotoxins, which may lead to increased α-syn expression in the large intestine [57, 58].

Since the reduction of beneficial bacteria leads to a decrease in the production of SCFAs [56], supporting adequate fiber intake in PD patients could slow down the progression of the disease by affecting the bacterial composition positively, and possibly solve many problems including gastrointestinal dysmotility.

Dietary fatty acids (Omega-3) and microbiota

Fatty acids (FAs) are major components in neuronal cell membranes and synapses and are essential for maintaining their structure and function. FAs have also been found to have anti-inflammatory, antioxidative, and neuroprotective properties. The FA composition of the cell membranes is affected by diet [59]. There remains much to be learned about the effects of dietary factors on the development of PD [60]. Evidence from animal models suggests that dietary fatty acids, especially docosahexaenoic acids (DHA), regulate oxidative stress in the brain [61, 62]. A case-control study has investigated the association between dietary fatty acid intake of individuals and the risk of PD in Japan. Cholesterol and arachidonic acid intake were significantly positively associated with the risk of PD. However, intake of total fat, saturated fatty acids, monounsaturated fatty acids, n-3 polyunsaturated fatty acids, α-linolenic acid, eicosapentaenoic acid, docosahexaenoic

acid, n-6 polyunsaturated fatty acids, linoleic acid, and the ratio of n-3 to n-6 polyunsaturated fatty acid intake were not associated with PD [60].

In recent studies, identification of the relationship between omega-3 fatty acids and the human gut microbiota has provided a new insight into the composition of the microbiota [63–65]. Omega-3 (PUFAs), like DHA, have anti-inflammatory properties which might reduce oxidative stress and therefore reduce alpha-synuclein accumulation [19, 66]. Holmqvist *et al.* [67], demonstrated in an *in vivo* animal model from PD patient brain lysate is taken up and transported retrogradely over a long distance via the vagal nerves from the gut to the brain after injection into the intestinal wall in an in vivo animal model [34]. In another study, colonization of α-syn-overexpressing mice with microbiota from PD patients enhanced physical impairments compared with microbiota transplants from healthy human donors. These findings indicated that gut bacteria regulate movement disorders in mice and suggest that alterations in the human microbiome represent a risk factor for PD [34]. There has only been one study evaluating the effect of fish oil on the brain-gut axis in the mice with PD. When oral or intrastriatal rotenone (neurotoxin) was administered to mice, both oral and intrastriatal rotenone induced similar PD-like motor deficits, dopaminergic cell loss, delayed intestinal transit, inflammation, and α-syn accumulation in the colon. In addition, it was found that GIS and rotetone-induced motor dysfunctions were prevented in these mice following a uridine and DHA-containing dietary intervention. So, a the dietary intervention may provide benefits in the prevention of motor and non-motor symptoms in PD [19]. Another recent study revealed that found that dietary fat intake may modify PD risk directly or by altering the response to environmental neurotoxicants including pesticides. PUFA intake was consistently associated with lower (PD) risk, and dietary fats modified the association of PD risk with pesticide exposure. It was concluded that a diet high in PUFAs and low in saturated fat might reduce the risk of PD [68]. All these results may be related to bidirectional communication between the gut and the brain for the formation of the Parkinson's-like phenotype and pathology. Although the relationship between dietary fatty acids and PD has not been fully clarified in the literature [59, 60], it can be said that dietary interventions may help prevent both motor and non-motor symptoms in PD [19].

Polyphenols and microbiota

Dietary phenolics and polyphenols are natural compounds found in foods such as vegetables, fruit, cereals, tea, coffee, and wine [69]. Phenolics are characterized by having at least one aromatic ring with one or more hydroxyl groups attached. Phenolics occurring naturally can be classified into two large groups: flavonoids and nonflavonoids [70–72]. The rate of total polphenol absorption in the small intestine after deconjugation reactions such as deglycosylation is relatively low (5–10%) in comparison with other macro- or micronutrients [73, 74]. The remaining 90–95% of polyphenols, which are not absorbed, produce various metabolites of physiological importance in the colon [74]. The interaction between the phenolic compounds as dietary components and gut microbiota has gained a lot of attention in the last few years [75, 76]. Some polyphenols, such as flavan-3-ols, proanthocyanidins, and hydrolyzable tannins (ellagitannins) have been demonstrated to exert both selective prebiotic effects and selective antimicrobial effects against pathogenic gut bacteria [77]. First, polyphenols are biotransformed into their metabolites by gut microbiota, which results in the increased bioavailability of polyphenols. Second, they modulate the composition of the gut microbial population, mostly through the inhibition of pathogenic bacteria and the stimulation of beneficial bacteria. In the latter, they may act as prebiotic metabolites and enrich the beneficial bacteria [9]. Therefore, the interaction between dietary polyphenols and gut microbiota may result in an impact on the health of the human host [78].

Polyphenols are deconjugated by bacterial glycosidases, glucuronidases, in addition to sulfatases and further fermented to a wide range of low-molecular-weight phenolic acids. Therefore, the gut microbiota has a critical role in the bioavailability of polyphenols and has been shown to regulate the health-promoting activity through conversion into more active derivatives [79]. In addition to anti-inflammatory, antioxidant, antiproliferative, antidiabetic and antimicrobial effects [80], polyphenols have been reported to exert their neuroprotective actions via the potential to protect neurons against injury induced by neurotoxins, via an ability to suppress neuroinflammation and the potential to promote memory, learning, and cognitive function [81]. Along with all these effects, there are also important roles in the microbiota. The bioactive components of tea rich in polyphenols have been found to inhibit the growth of pathogenic bacteria such as *H. pylori,* [22] *Staphylococcus aureus*, and *E. coli* [82]. It has been found that citrus polyphenols such as hesperidin, naringenin, poncirin, and diosmetin have an inhibitory effect on the growth of *H. pylori* [83]. Queipo-Ortuño *et al.* [84] evaluated the effect of a moderate intake of red wine polyphenols on select gut microbial groups implicated in host health benefits. They found that compared with baseline, daily consumption of red wine polyphenols for 4 weeks significantly increased the numbers of *Enterococcus, Prevotella, Bacteroides, Bifidobacterium, Bacteroides uniformis, Eggerthella lenta*, and *Blautia coccoides-Eubacterium rectale* groups. To the best of our knowledge, the effect of polyphenol intake on the gut microbiota of PD patients has not been examined. However, a study has reported that the influence of the bioavailability of flavonoid metabolites may interfere with the misfolding of alpha (α)-synuclein, a process that plays a central role in Parkinson's disease and other α-synucleinopathies. The study worked on two experimental groups of humanized gnotobiotic mice with compositionally diverse gut bacteria were orally treated with a flavanol-rich preparation (FRP). The study demonstrated that gnotobiotic mice with compositionally diverse human microbiotas generate unique phenolic acid profiles in the cecum after orally consuming FRP flavanols

[85]. So, polyphenols might influence the microbiota through their effects on the high levels of *H. pylori* [86] and low levels of *Prevotella* [9] in PD. In addition, polyphenols could be used in therapies for PD with respect to the impact of inflammation and α-syn misfolding. Epidemiologic studies have found an inverse relationship between the consumption of high amounts of vegetables and fruits in PD [87, 88]. For this reason, increasing the consumption of vegetables and fruits in the prevention of PD could have positive effects on the intestinal microbiota composition by increasing the intake of antioxidant vitamins and polyphenols.

The Mediterranean diet and western diets

The Mediterranean diet (MD) is regarded as one of the healthiest eating patterns [25]. It is characterized by high amounts of vegetables, fruits, grains, fish, and polyunsaturated fatty acids, and is especially based on olive oil and moderate wine consumption [25, 89]. Many components of MD have positive effects on health and can lead to a reduction in the incidence of many diseases, such as cancer, obesity, metabolic syndrome, cardiovascular diseases, neurodegenerative diseases, diabetes, and inflammatory bowel disease [90]. The possible biological mechanisms of MD that prevent chronic diseases are attributed to the consumption of components such as antioxidants, polyphenols, and monounsaturated-polyunsaturated fatty acids [91, 92]. MD are the main determinants of intestinal microbial diversity, and dietary components affect both the microbial population and their metabolic activities in the early stages of life [25]. There are some contradictory results regarding compliance with MD in PD. In a case-control study, there was no difference in adherence to the Mediterranean diet in patients with PD [93], whereas in another study, adherence to MD in patients with PD was found to be lower than that in the control group [23]. In addition, little is known about the effects of diet patterns, dietary components, and nutrients on the gut microbiota. A higher ratio of *Firmicutes–Bacteroidetes* was related to lower adherence to MD, and greater presence of *Bacteroidetes* was associated with lower animal protein intake [24]. High-level consumption of plant-derived foods consistent with (MD) is associated with beneficial microbiome-related metabolomic profiles [94]. *Prevotella* concentrations were significantly reduced in PD patients [7, 9]. *Prevotella* is associated with plant-rich diets (high levels of complex carbohydrates and fruit/vegetable intake) [24, 95] along with fiber intake [96, 97]. For this reason, the impact of a Mediterranean diet pattern on microbiota may be very important in patients with PD.

The Western diet is characterized by high intake of protein (animal and processed meat products), saturated fat, refined grain, sugar, alcohol, salt, and high fructose corn syrup and low intake of fruits and vegetables [98, 99]. It promotes inflammation that arises from both structural and behavioral changes in the resident microbiome [100]. The Western diet can lead to increased levels of endotoxin-producing bacteria in the intestinal tracts of both humans and mice, resulting in metabolic endotoxemia [101, 102]. Lipopolysaccharides (LPS), commonly referred to as endotoxins, are components of the cell wall of gram-negative bacteria found in the gut microbiota [103]. It has been found that the Western diet induces changes in the barrier function mechanism associated with metabolic endotoxemia in rats [104]. Pro-inflammatory stimulants of Toll-like receptor-2 and Toll-like receptor-4 (pathogen-associated molecular patterns, PAMPs), are abundant in some processed foods [105]. Diet-induced inflammation could be mediated partly by the PAMPs produced by microbes in processed foods. PAMPs (such as LPS and other Toll like receptor stimulants) arise from bacterial growth during the process between food preparation and heat treatment, which are likely to be extended in industrial processing compared with home cooking [100].

There are some contradictory results regarding compliance with the Western diet in PD. In an epidemiological study utilizing the Health Professionals Follow-Up Study (1986–2002) and Nurses' Health Study (1984–2000), 49,692 men and 81,676 women free of (PD) at baseline were included, and 508 of them were diagnosed with PD after 16 years of follow up. In the study, the prudent dietary pattern, characterized by high intake of fruit, vegetables, and fish, was inversely associated with PD risk, but the Western pattern was not [88]. Although there have not been any studies in the literature that have assessed the relationship between intestinal microbiota and the Western diet in PD, the effect of the Western diet on microbiota, has been evaluated in various studies [106, 107]. The gut microbiota diversity and composition were remarkably changed in apolipoprotein E (apoE) knockout (KO) mice compared with wild-type (WT) mice, especially on a Western diet. *Firmicutes* and *Clostridia* (from class to family) were found to be enriched in apoE KO mice on a Western diet [106]. The relative abundance of Firmicutes could result in an increased amount of metabolic endotoxins such as lipopolysaccharides [108]. A Western diet could aggravate the inflammatory process and endotoxin-production, so these mechanisms may explain the impact on disease onset or prognosis of PD.

COMPLEMENTARY THERAPEUTIC APPROACHES

Probiotics

Probiotics that have essential beneficial effects on human health are defined as live microorganisms. In the early 20th century, Metchnikoff discovered "healthy bacteria", and the interest in probiotics in food markets has increased [109]. The requirements that a probiotic organism should meet are as follows: resistance to gastric acidity, resistance to bile and pancreatic enzymes, adherence to intestinal mucosa cells, colonization capacity, remain alive for long periods during transportation and storage so they can effectively colonize a host, production of antimicrobial substances against pathogenic bacteria, and absence of translocation [110]. Probiotics are one of the treatment modalities that can be involved in the modulation of intestinal microbiota

[111]. The most commonly used probiotic microorganisms are lactobacilli, enterococci, bifidobacteria, and a mixture of different beneficial bacteria [112]. The findings of gut microbiota in constipation are inconsistent [113, 114] and currently no consensus exists. In one study, *Bifidobacterium* and *Lactobacillus* were shown to be significantly less abundant in adult patients with constipation [113]. However, in a cross-sectional pilot study, the conventional probiotic genera *Lactobacillus* and bifidobacteria were not decreased in the microbiomes of constipated patients, and a significantly decreased abundance of *Prevotella* and increased presence of several genera of *Firmicutes* were observed in constipated patients compared with controls [114]. In a systematic review and meta-analysis including 14 randomized controlled trials, various *Lactobacillus* and *Bifidobacterium* strains were found to have the potential to have a positive effect on functional constipation by improving gut transit time, stool frequency, and stool consistency [115]. Regarding the use of probiotics for the treatment of patients with PD, the studies to date are inadequate. Cassani *et al.* [116] assessed the effects of milk fermented with the probiotic strain *Lactobacillus casei* Shirota in PD patients with constipation according to the Rome III criteria. After probiotic intake, there was a statistically significant increase in the frequency of stool and normal consistency and significant reduction the number of patients who felt bloating, abdominal pain, and experienced a sensations of incomplete emptying. On the other hand, probiotics play an important role in providing normal microbial balance. It has been reported that they have a potential role in the treatment along with the prevention of anxiety and depression via the brain-gut axis [28]. In addition, gut microbiota can affect various neurological outcomes, such as cognition, learning, and memory [117]. In a double-blind, placebo-controlled clinical trial that included 40 patients with a diagnosis of major depressive disorder (MDD) based on the (DSM-IV) and whose ages ranged between 20 and 55 year, the suplementation group received *Lactobacillus acidophilus* (2×10^9 CFU/g), *Lactobacillus casei* (2×10^9 CFU/g), and *Bifidobacterium bifidum* (2×10^9 CFU/g) in a capsule for 8 weeks. Probiotic administration in patients with MDD for 8 weeks had beneficial effects on the Beck's Depression Inventory and some metabolic markers [118]. Bifidobacteria treatment also resulted in a reduced 5-hyroxyindoleacetic acid concentration in the frontal cortex and a decrease in dihydroxyphenylacetic acid in the amygdaloid cortex. The attenuation of pro-inflammatory immune responses and the elevation of the serotonergic precursor tryptophan by bifidobacteria treatment provides encouraging evidence in support of the proposition that this probiotic might have acquire antidepressant properties [119]. The effects of probiotics on severe cognitive disorders and metabolic disorders in Alzheimer's patients have also been investigated. In a randomized, double-blinded, and controlled clinical trial, patients were administered either milk (control group) or a mixture of probiotics (probiotic group). The probiotic supplemented group took 200 mL/day probiotic milk containing *Lactobacillus acidophilus, Lactobacillus casei, Bifidobacterium bifidum*, and *Lactobacillus fermentum* (2×10^9 CFU/g for each) for 12 weeks. The Mini-Mental State Examination (MMSE) score was recorded for all subjects before and after the treatment. After 12 a week of the intervention, the probiotic-treated patients showed a significant improvement score compared with the control group in the MMSE score [120]. In a randomized, double-blind, placebo-controlled clinical trial was conducted on 50 patients with PD, participants were randomly allocated into two groups to take either 8×10^9 CFU/day of a probiotics containing, *Lactobacillus acidophilus, Bifidobacterium bifidum, L. reuteri,* and *Lactobacillus fermentum* or a placebo (n=25 each group, one capsule daily) for 12 weeks. Probiotic supplementation for 12 weeks in PD patients significantly downregulated gene expression of proinflammatory IL-1, IL-8, TNF-α; and upregulated TGF-β along with peroxisome proliferator-activated receptor gamma (PPAR-γ). However, probiotic supplementation did not affect the gene expression of Vascular endothelial growth factor (VEGF) and low-density lipoprotein receptor (LDLR) [121]. Another randomized, double-blind, placebo-controlled clinical trial, the impact of probiotic supplementation (8×10^9 CFU/day probiotic or placebo) for 12 weeks on the movement and the metabolic parameters were evaluated in 60 people with PD. Compared with the placebo, consuming the probiotics decreased the Movement Disorders Society-Unified the Parkinson's Disease Rating Scale (MDS-UPDRS) scores; reduced high-sensitivity C-reactive protein, malondialdehyde, and insulin levels, insulin resistance, enhanced glutathione levels, and insulin sensitivity [122]. Therefore, it is not possible to give a clear recommendation for probiotic supplementation in patients with PD, due to insufficiency of the randomized controlled trials to date, lack of knowledge about the effect on levodopa, and insufficient knowledge of the recommended dose amount, optimal duration of treatment, and reliability.

Prebiotics

Prebiotics are dietary substances (mostly consisting of nonstarch polysaccharides and oligosaccharides poorly digested by human enzymes) which nurture a selected group of microorganisms living in the gut. They favor the growth of beneficial bacteria over that of harmful ones [123]. An ideal prebiotic should 1) be resistant to the action of acids in the stomach, bile salts, and other hydrolyzing enzymes in the intestines, 2) not be absorbed in the upper gastrointestinal tract, 3) be easily fermentable by the beneficial intestinal microflora [124, 125]. Prebiotics are nondigestible nutrients. Short-chain nondigestible carbohydrates, inulin-type fructans, fructooligosaccharides (FOS), and galactooligosaccharides (GOS) are the most important prebiotics. They target bacterial groups which are generally *Bifidobacterium* and *Lactobacillus.* Fructans such as inulin and FOS are naturally present in different foods [126, 127]. Prebiotic forms a group of diverse carbohydrate ingredients. These include vegetables, fruits, cereals, and other edibles of plant origins. Some of the

Table 2. Examples of synbiotics used in human nutrition (Adapted [128, 135, 136])

Synbiotics	
Prebiotics +	Probiotics
Inulin	*Lactobacillus* and *Bifidobacterium* [128] *Lactobacillus*, *Streptococcus,* and *Bifidobacterium* [136]
FOS	*Lactobacillus*, *Bifidobacterium* [137,138] *Lactobacillus*, *Streptococcus,* and *Bifidobacterium* [139]
Oligofructose	*Lactobacillus* and *Bifidobacterium* [140]
FOS and GOS	*Bifidobacterium breve* M-16V [141]
GOS	*Lactobacillus*, *Bifidobacterium,* and *Propionibacterium* [142]

FOS: fructooligosaccharides; GOS: galactooligosaccharides.

sources of prebiotics include tomatoes, artichokes, bananas, asparagus, berries, garlic, onions, chicory, green vegetables, and cereals such as oats, flax seeds, and barley [128].

Prebiotics have beneficial effects on cardiovascular diseases, type 2 diabetes/glycemic control, appetite control, obesity, cancer, immune function, and inflammation [129]. Inulin-like fructan consumption can also be beneficial because it stimulate intestinal movements by affecting microflora [130] in PD patients with constipation. Very recently, it has been demonstrated that treatment with microbial-produced SCFAs could rescue impaired microglial function impaired in GF animals [131]. It has been suggested that SCFAs resulting from fermentation of dietary fiber could have epigenetic and neuromodulatory effects through histone acetylation and improve cognitive functions for neurodevelopmental and neurodegenerative diseases [132]. In a study by Savignac and colleagues [133], healthy rats were gavaged with FOS, GOS, or water for five weeks. After prebiotic intake, it was found that the increase of hippocampal brain-derived neurotrophic factor (BDNF) and increased N-methyl-d-aspartate receptor (NMDAR) subunits translate to improved cognitive performance. This study demonstrates that prebiotics may play a role in the neurological preservation of the CNS. There are no studies that have evaluated the effects of prebiotics in PD alone. However, prebiotics could be considered an effective treatment for both constipation and gastrointestinal disturbance.

Synbiotics

The word 'synbiotics' alludes to synergism, and this term should be reserved for products in which prebiotic compound(s) selectively favors the probiotic organism(s) [134]. Synbiotics have both probiotic and prebiotic properties. They were also created to overcome some possible difficulties in the survival of probiotics in the gastrointestinal tract. The principal purpose of this type of combination is the improvement of the survival of probiotic microorganisms in the gastrointestinal tract [127]. Polysaccharides such as inulin, reflux starch, cellulose, hemicellulose, and pectin may potentially be prebiotics. Examples of prebiotics and probiotics most commonly used together as synbiotics are are indicated in Table 2 (Adapted [128, 135, 136]). Synbiotic intake may efficiently restore the balance of gut microbiota and improve gastrointestinal functions. A randomized, placebo-controlled trial suggested that dietary supplementation with a synbiotic (the synbiotic [BIFICOPEC]containing 0.63 g of bifid triple viable capsules [BIFICO] and 8 g of soluble dietary fiber) improved evacuation-parameters-associated symptoms and colonic motility in patients with slow transit constipation [137]. GIS-related problems in particular are of great importance for patients with PD. For example, in a randomized, double-blind, placebo-controlled trial, on PD patients with Rome III-confirmed constipation based on 2-week stool diary data at baseline, patients were randomly assigned (80 in the experimental group, 40 placebo group) to either fermented milk containing multiple probiotic strains and prebiotic fiber, or placebo once daily for 4 weeks. Consumption of the fermented milk containing probiotics and prebiotics resulted in a higher increase in the number of bowel movements and relieved constipation [138]. The coexistence of prebiotics and probiotic microorganisms may be a therapeutic approach to the prevention and treatment of many diseases, including PD, in terms of the ability to regulate the microbiota composition.

CONCLUSION

Little is known about the role of the molecular causes of altered homeostasis in PD. However, in recent evidence, some motor and non-motor symptoms observed in PD may be attributed to intestinal microbiota dysbiosis. PD patients are characterized by an altered gut microbiota composition and impairment of the intestinal barrier and enteric neuroimmune system that result in enteric inflammation which contributes to neuroinflammation and neurodegeneration in CNS.

Recent advances have highlighted in the understanding of probiotic modulation of neurological and neuropsychiatric disorders via the gut-brain axis. The intestinal microbiota can directly or indirectly alter the neurochemistry of the brain by influencing different physiological and behavioral outcomes

through modulation of neuroendocrine pathways. The diversity and amount of microorganisms in the gut may affect both the ENS and CNS. Therefore, a better understanding of the gut-brain axis may prevent the pathogenesis of the disease. In this context, dietary approaches, probiotics, prebiotics, and synbiotics will play an important role. However, the studies conducted on the microbiota-gut-brain axis in patients with PD to date are inadequate, and randomized controlled trials are needed to evaluate nutritional or probiotic supplementation for gut microbiota dysbiosis.

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