Therapeutic Approaches for Parkinson's Disease and Gut Microbiota

Subjects: Biology

Contributor: Angelica Varesi , Lucrezia Irene Maria Campagnoli , Foroogh Fahmideh , Elisa Pierella , Marcello Romeo , Giovanni Ricevuti , Marchesi Nicoletta , Salvatore Chirumbolo , Alessia Pascale

The bidirectional interaction between the gut microbiota (GM) and the Central Nervous System, the so-called gut microbiota brain axis (GMBA), deeply affects brain function and has an important impact on the development of neurodegenerative diseases. In Parkinson's disease (PD), gastrointestinal symptoms often precede the onset of motor and non-motor manifestations, and alterations in the GM composition accompany disease pathogenesis. Several studies have been conducted to unravel the role of dysbiosis and intestinal permeability in PD onset and progression, but the therapeutic and diagnostic applications of GM modifying approaches remain to be fully elucidated.

Parkinson's disease | gut microbiota | dysbiosis | intestinal permeability | diagnosis | probiotics

1. Gut Microbiota-Based PD Interventions: Antibiotics

Antibiotics are chemical compounds able to kill or arrest the growth of certain microorganisms. Although they are mainly used to counteract or prevent bacterial infections, their additional anti-inflammatory, immunomodulator, neuroprotective, antiamyloidogenic and antioxidant properties are becoming of increasing interest in the context of neurological disorders, including neurodegeneration [1][2][3][4][5]. Indeed, beside counteracting dysbiosis and constipation [6], it has been demonstrated that certain antibiotics can inhibit the activity of matrix metalloproteinases and prevent mitochondria dysfunction, microglia activation, protein misfolding and α-synuclein aggregation [7][8][9][10][11]. For example, treating mice where Parkinson's disease (PD) has been induced by MPTP with a cocktail of broad-spectrum antibiotics (ampicillin, metronidazole, and neomycin sulfate) was found to preserve TH and dopamine transporter immunoreactivities, which are generally lost upon MPTP administration [12]. This beneficial effect is mediated by an increase in *Proteobacteria*, as well as by a decrease in *Deferribacteres* and *Saccharibacteria* (*TM7)* abundance, which reflect an altered gut microbiota (GM) composition characterized by diversity loss [12]. Similar results were obtained in 6-OHDA-induced PD rats upon chronic treatment with an antibiotic mixture containing neomycin, pimaricin, bacitracin and vancomycin, which prevented dopaminergic neuronal death, relieved inflammation, ameliorated neurotoxicity and reduced motor impairments as measured by cylinder, rotation and stepping tests [13]. Recently, Cui et al. reported that vancomycin pretreatment of MPTP-induced PD mice improved motor symptoms by reducing SN astrocytes and microglia activation [14]. Notably, the authors proposed that neuroinflammation is indirectly inhibited by *Akkermansia* and *Blautia*, which increase in

abundance upon vancomycin treatment and interfere with the toll like receptor 4 (TLR-4)/NF-κB pathway in the gut and in the brain [14]. Although *Akkermansia* is generally reported as harmful in PD patients, its dual negative and positive role may lean towards the latter when mucin conversion into SCFAs prevails over gut-barrier degradation, thus explaining this apparent discrepancy. In humans, an intestinal decontamination therapy consisting of sodium phosphate enema, oral rifaximin and polyethylene glycol resulted effective in reducing dyskinesia and motor fluctuations related to PD, but more studies are required [15]. Other approaches focused on the use of certain specific antibiotics instead of cocktails have also been proposed to maximize the therapeutic benefit without impacting beneficial bacteria.

Rifaximin is a broad spectrum antibiotic with poor systemic absorption indicated to treat SIBO [6][16][17]. In this respect, rifaximin-mediated SIBO eradication in PD patients resulted in reduced motor fluctuations without impacting on L-dopa treatment [18]. This benefit should be ascribed to rifaximin-mediated modulation of the brain thyrotropin releasing hormone (THR) and THR-like peptides, which have caloric-restriction-like, anti-aging, neuroprotective properties and are known to be involved in the gut-brain axis [19]. However, no improvement in GI symptoms in 8 PD patients treated with rifaximin poses controversy over the actual efficacy of this antibiotic as PD treatment, calling for new studies [20].

Ceftriaxone (CTX) is a β-lactam antibiotic with a strong and safe past record [21][22]. The treatment of several PD animal models with CTX is known to improve neuroinflammatory and oxidative stress markers, stimulate neurogenesis and promote astrocyte viability through the suppression of NF-κB/c-Jun-mediated signaling [21][22][23][24]. Mechanistically, CTX also reduces extracellular glutamate levels by increasing the expression of the glutamate transporter-1 in astrocytes, thus avoiding brain excitotoxicity [22][24][25]. Moreover, it has been observed that CTX binds to α-synuclein with considerable affinity and prevents its polymerization in vitro [22][26][27]. in vivo, there is evidence that CTX treatment modifies the GM composition of MPTP-induced PD mice by disadvantaging the growth of *Proteus* while increasing the relative abundance of *Akkermansia* species, which act as probiotics when their SCFAs-converting activity exceeds that of intestinal barrier degradation [28].

Further studies proved the ability of CTX to reduce the levels of the main pro-inflammatory mediators TLR-4, MyD88 (myeloid differentiation primary response 88), IL-1β, TNF-α and NF-κB in the brain, TLR-4, MyD88, and NF-κB in the colon and IL-1β, TNF-α and IL-6 in the serum [28][29][30]. Similarly, CTX-mediated increase in the main antioxidant modulators glutathione, superoxide dismutase (SOD) and catalase was found to prevent the oxidative damage observed in rats treated with MPTP [29][30]. In line with these data, CTX administration was associated with reduced glial fibrillary acid protein (GFAP) and ionized calcium-binding adapter molecule 1 (IBA-1) expression, two markers of astrogliosis and microglia activation, respectively [28][31][32][33]. At the neuronal level, pre- or post-treatment with CTX prevented the loss of TH-positive neurons, reduced glutamatergic hyperactivity, and promoted neurogenesis at the level of SN and hippocampal dentate gyrus in different rat models of the disease [29][33][34][35][36][37][38]. As a consequence, dyskinesia, motor impairment and memory loss were all reverted upon CTX administration [29][30][33][34][35][36][38][39][40], although conflicting evidence still remains about its ability to improve learning outcomes [41]. Of note, CTX has been shown to interact synergistically with other compounds currently

used or under investigation for the treatment of PD, such as erythropoietin, ropinirole and memantine, but the safety as well as the efficacy of these combinations should be further assessed [29][30][42].

Minocycline is a second-generation semisynthetic tetracycline with anti-microbial, anti-apoptotic, anti-inflammatory and antioxidant properties [43][44][45][46]. Thanks to the ability to efficiently cross the BBB, minocycline is considered neuroprotective for a variety of neurological conditions, including PD [47][48][49][50][51][52][53]. This effect is mainly ascribable to the minocycline-dependent suppression of microglia activation, which has been reported by several in vivo studies [47][54][55][56][57][58][59]. In this respect, microglial inactivation by minocycline correlates with decreased IL-1β formation, as well as reduced NADPH-oxidase and inducible nitric oxide synthase (iNOS) activity, suggesting that both anti-inflammatory and antioxidant pathways are involved [58][60]. In vitro, minocycline addition to 6-OHDA treated PC12 cells suppresses the release of lactate dehydrogenase, reactive oxygen species (ROS) and caspase 3 while supporting the activity of the antioxidant enzymes SOD and catalase [47][61][62][63]. Of note, these molecular changes seem to explain the increased striatal dopamine levels as well as the cognitive and locomotor improvements observed in zebrafish, mouse, and rat models [55][56][60][64][65][66][67]. Another mechanism through which minocycline prevents apoptosis is by limiting mitochondria dysfunction, inhibiting caspase 1 and 3 expression, and preventing the degradation of the antiapoptotic protein ICAD (the inhibitor of the caspase-activated deoxyribonuclease) [47][68][69][70]. However, despite the promising results, controversy remains. Indeed, an enhanced toxicity has been reported upon minocycline administration to MPTP-treated rodents and primates, resulting in disease exacerbation [71][72]. Moreover, results from a phase II clinical trial show no benefit from the use of minocycline and evidence decreased tolerability, although more studies are needed before drawing premature conclusions [73][74].

Doxycycline (DOX) is another broad-spectrum antibiotic belonging to tetracyclines that has been considered as PD treatment [75]. In vitro, DOX has shown anti-inflammatory properties by interfering with p38 MAP kinase and NF-κB pathways, reducing the expression of the activated microglia marker IBA-1 and inhibiting the production of the pro-oxidant and pro-inflammatory factors ROS, nitric oxide, iNOS, cyclooxygenase-2 (COX-2), IL-1β and TNF-α [76][77][78]. Concerning neuroprotection, DOX exerts an anti-apoptotic activity by repressing the matrix metallopeptidase-3 (MMP-3) in dopaminergic neurons and microglia both in vitro and in vivo [77]. In addition, DOX stimulates neurite growth through the activation of PI3K/Akt and MAPK/ERK pathways, independently from nerve growth factor activity [79]. Of note, recent studies demonstrated that DOX reduces the size and load of α-synuclein oligomers by converting them into high-molecular weight species that are not able to form fibrils, thus increasing cell viability [78][80]. When tested in vivo, DOX confirmed its neuroprotective activity by limiting dopaminergic neuronal loss in SN while increasing striatal dopamine levels [81][82]. This beneficial function is achieved by contrasting glial reactivity and by reducing the major histocompatibility complex-II expression in microglial cells [81][82]. In 6-OHDA-treated rats, both DOX and its derivative COL-3 showed an anti-dyskinetic potential when administered in combination with L-dopa [83]. According to the authors, the reduced levels of MMP-2/-9, MMP-3, ROS and of the dyskinesia-linked immunoreactivity markers FOSB, COX-2, GFAP and OX-42 would explain these benefits [83]. Nevertheless, despite promising in vivo data, clinical evidence is still lacking.

Rifampicin is a macrocyclic antibiotic with cytoprotective functions that have been considered for PD treatment [84][85]. Indeed, there is evidence that rifampicin prevents α-synuclein fibrillation by promoting SUMOylation, which increases fibril solubility preventing neuronal death [86][87][88]. Other studies reported a reduction in IL-1β, TNF-α, IL-6 and ROS released by cells double treated with rotenone and rifampicin, thus indicating a promotion of neuroprotection [89][90][91]. Although not completely defined, rifampicin appears to sustain cell viability through different mechanisms: (i) by enhancing autophagy [89][91]; (ii) via PI3K/Akt/GSK-3β/CREB pathway modulation [92]; (iii) by upregulating the unfolded protein response marker GRP78 through the PERK/eIF2α/ATF4 pathway [93]. In vivo, MPTP-induced PD mice treated with rifampicin showed increased striatal and SN TH immunoreactivity, attenuated levels of oxidative stress and re-established dopaminergic signaling in the striatum [94]. More recently, rotenone-induced PD in zebrafish has shown benefit from rifampicin administration due to the decrease in neuroinflammation [95].

Generally, although promising, two main concerns remain about the use of antibiotics in PD treatment: (i) antibiotics can kill some specific microbial populations leading to intestinal dysbiosis and neurological dysfunction and (ii) their prolonged and widespread intake would favor antibiotic resistance [9][96][97]. There is evidence that ceftriaxone (a third-generation cephalosporin)-induced dysbiosis worsens motor symptoms in 6-OHDA treated mice and correlates with dopaminergic neuron toxicity as well as intestinal and systemic inflammation [98]. Moreover, quinolones and β-lactams are known to trigger neurotoxicity through their interference with gamma-aminobutyric acid and benzodiazepine receptors signaling [9]. Mechanistically, it has been hypothesized that antibiotic-induced dysbiosis may favor the growth of *Enterobacteria* producing the bacterial α-synuclein curli, which promotes neurodegeneration [99][100]. In addition, leaky gut-mediated systemic inflammation might result from dysbiosis and mediate the BBB damage, allowing circulating neurotoxins to enter the brain [101]. In humans, a Finnish study conducted on 13,976 PD and 40,697 healthy individuals showed that taking certain antibiotics years earlier, especially macrolides and lincosamides, correlates with an increased risk of developing PD [102]. However, results from another prospective study involving 59,637 women did not report any correlation between antibiotic intake and PD incidence [103]. Overall, contrasting results and scarce long-term safety data remain a concern. Innovative drug delivery systems based on nanoparticles are now being tested to improve the clinical benefit of these antibiotics [75]. At the same time, synthetic tailoring to potentiate the neuroprotective chemical functions over the antimicrobial ones is another promising approach for the risk-benefit optimization [97].

2. Gut Microbiota-Based PD Interventions: Probiotics

Probiotics are defined as "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host" [104]. It is widely reported that the most common bacteria used as probiotics (Lactobacilli, Bifidobacteria, and Enterococci) [105] have potential benefits in restoring the GM, reducing intestinal permeability, inflammation, and oxidative stress, improving immune homeostasis and GI symptoms (constipation, diarrhoea, bloating, and abdominal pain), as well as preventing or counteracting several conditions, including GI, liver, and cardiovascular diseases, obesity, diabetes, cancer, and H. pylori and urogenital infections [11][106][107][108][109]. Moreover, it is now evident that GM dysbiosis is a factor that takes part in the development of several neurological

diseases, including PD, AD, multiple sclerosis, autism spectrum disorders (ASD), anxiety, depression, schizophrenia, and other mental illnesses [110][111]. Concerning PD, as previously mentioned, altered GM could contribute to the onset of some PD-related complications, such as constipation, the most common non-motor symptom [112]. Therefore, modulation of the microbiota-gut-brain axis using probiotics could be a promising complementary approach to traditional methods to prevent or counteract these disorders, including PD, as widely reported in literature [111][113][114][115][116]. For instance, Bacteroides fragilis has been documented to improve ASD symptoms and gut barrier integrity, and reduce intestinal permeability [117]; further, the probiotic SLAB51, a formulation of nine live bacterial strains (Streptococcus thermophilus, *B. longum*, *B. breve*, *B. infantis*, *L. acidophilus*, *L. plantarum*, *L. paracasei*, *L. delbrueckii* subsp. *bulgaricus*, and *L. brevis*) improves cognition and reduces the accumulation of amyloid plaques, brain injury, and inflammatory cytokines plasma levels in AD mice [118], while the assumption of a probiotic fermented milk drink containing *L. acidophilus*, *L. casei*, *B. bifidum*, and *L. fermentum* improves cognitive function in AD patients [119]. Concerning PD, many studies showed that probiotic intake can reduce neuroinflammation, inhibit the loss of dopaminergic neurons, and modulate brain functions.

3. Gut Microbiota-Based PD Interventions: Prebiotics

According to the International Scientific Association for Probiotics and Prebiotics (ISAPP), prebiotics are defined as "substrates selectively used by host microorganisms that confer health benefits to the host, while retaining the microflora-mediated health benefits" [120]. Prebiotics are dietary fibres originated from soybeans, raw oats, unrefined wheat and barley, non-digestible carbohydrates and oligosaccharides, including galacto-oligosaccharides (GOS), fructo-oligosaccharides (FOS), inulin, and lactulose [121][122]. Polyphenols (catechin, epicatechin and quercetin) can also act as prebiotics [123]. They can alter GM composition, by favouring the growth and the activity of beneficial bacteria, and by decreasing pathogens in the GI tract; further, they have positive effects on lipid metabolism, decrease the recurrence of Clostridium difficile infections, and alleviate GI and allergic disorders [124][125][126].

In the gut, the beneficial microbes metabolize the prebiotics, resulting in the generation of SCFAs (namely, acetate, propionate, butyrate) that are involved in neuromodulation, in anti-inflammatory processes, in the regulation of both intestinal and blood-brain barriers [127][128].

Like probiotics, prebiotics also play a beneficial role in managing neurological and neurodegenerative diseases [129]. For instance, lactulose and melibiose improve short-term memory and cognitive ability in AD mice [130]; bimuno-GOS ameliorate anti-social behavior in children with ASD [131]; oral administration of *Marinda officinalis*-derived oligosaccharides ameliorates memory and learning ability, decreases plaque formation, oxidative stress, and inflammation in both rats and mice AD models [132][133].

Concerning PD, to date, few studies have been conducted to evaluate the effects of prebiotics on PD animal models and patients (**Table 1**) [112][134][135][136][137][138]. In a mouse model of PD, Perez–Pardo et al. found that prebiotic fibers (FOS, GOS and nutriose, a soluble corn fibre) can normalize motor symptoms, reduce α-synuclein levels, and restore GI dysfunction, inflammation and dopamine transporter expression [135]; further, it has been

shown that the prebiotic polymannuronic acid can prevent dopaminergic neuronal loss via SCFAs-mediated anti-inflammatory and anti-apoptotic mechanisms [136]. In addition, another study, performed by using 6-OHDA PD rat model, reported that the supplementation with the medium obtained from the probiotic *L. salivarius* subsp. *salicinium* AP-32 culture can reduce dopaminergic neuronal loss, motor dysfunctions, muscle atrophy, oxidative stress (increased SOD and GPx) and inflammation [134][139]. Interestingly, another study highlighted a raise in BDNF levels in the hippocampus of rats after the administration of FOS and GOS [140]. Since BDNF is involved in neuronal protection, survival, growth, and in synaptic plasticity [141], this finding suggests that prebiotics supplementation might have a role on brain neuroprotection. Finally, some studies performed in PD animal models report the beneficial effects of sodium butyrate in improving PD symptoms [142][143]; therefore, butyrogenic prebiotics could be used to increase butyrate concentration in the colon and help to manage PD [127].

Table 1. The effects of prebiotics treatment regarding in vivo experimental studies.

Prebiotic	Experimental Model	Treatment Duration	Treatment Effects	Reference
GOS, lcFOS, scFOS, nutriose	Rotenone-induced mice model	10 weeks	Improvement of motor symptoms, gastrointestinal dysfunction, and inflammation (↓GFAP, ↓T-cells infiltration). Restoration of DAT expression. Reduction of α-synuclein levels.	(Perez-Pardo et al., 2017) [135]
Polymannuronic acid	MPTP-induced model mice	5 weeks	Abolition of the apoptotic process (↓Bax, ↓Bax/Bcl-2 ratio). Prevention of dopaminergic neuronal loss (↑TH gene and protein expression in the striatum). Increase of faecal acetate, butyrate, and total SCFAs levels. Inhibition of striatal inflammation (↓TNF-α mRNA levels).	(Liu et al., 2022) [136]
Prebiotic residual medium obtained from *L. salivarius* subsp. *salicinium* AP-32 culture medium	6-OHDA-induced rat model	8 weeks	Reduction of dopaminergic neuronal loss, motor dysfunctions, and muscle atrophy. Increase of GPx and faecal SCFAs (propionate, butyrate). Restoration of mitochondrial function and energy metabolism.	(Nurrahma et al., 2021) [139]
Prebiotic residual medium obtained from *L. salivarius*	6-OHDA-induced rat	8 weeks	Amelioration of motor symptoms.	(Tsao et al., 2021) [134]

Prebiotic	Experimental Model	Treatment Duration	Treatment Effects	Reference
subsp. *salicinium* AP-32 culture medium	model		Reduction of inflammation (↓TNF-α) and OS (↓ROS, ↑SOD, ↑GPx). Increase of SCFAs production (propionate, butyrate). Modulation of GM composition (↑*Ruminococcaceae*, ↑*Bifidobacterium*, ↑*Faecalibacterium*, ↓*Propionibacterium*, ↓*Clostridium*, ↓*Cylindriodes*, ↓*Ruminantium*).	
Dietetic fiber supplements (wheat, pectin, dimethylpolyoxyhexane-900)	19 PD patients	8 weeks	Improvement in constipation and in motor function. Increase of total plasma levodopa levels.	(Astarloa et al., 1992) [137]
Psyllium	7 PD patients	8 weeks	Increase in stool frequency and weight.	(Ashraf et al., 1997) [138]
Resistant starch	57 PD patients	[137][138]weeks	Improvement of non-motor symptoms. Reduction of calprotectin levels. Increase in butyrate concentration.	(Becker et al., 2021) [112]

et al., by found a an oral of SCFAs,

finding an increased butyrate concentration, as well as an improvement in non-motor symptoms [112].

In conclusion, despite few studies on PD, the satisfactory clinical outcomes on patients, especially on constipation, suggest that prebiotics might be a possible adjuvant therapy for PD, although more human clinical trials are mandatory to support this conclusion.

Abbreviations: 6-OHDA: 6-hydroxydopamine; Bax: Bcl-2-associated X; Bcl-2: B-cell lymphoma 2; DAT: dopamine transporter; GFAP: glial fibrillary acid protein; GM: gut microbiota; GOS: galactooligosaccharides; GPx: glutathione peroxidase; lcFOS: long-chain fructooligosaccharide; MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; OS: oxidative stress; PD: Parkinson's disease; ROS: reactive oxygen species; SCFAs: short chain fatty acids; scFOS: short-chain fructooligosaccharides; SOD: superoxide dismutase; TH: tyrosine hydroxylase; TNF-α: tumor necrosis factor alpha; ↑: increase; ↓: decrease.

4. Gut Microbiota-Based PD Interventions: Diet

Although multifactorial interactions are involved in the prevalence and incidence of neurodegenerative diseases, nutrition plays an essential role in the pathogenesis and development of neurodegenerative diseases such as AD and PD [144][145]. Recent findings have revealed that diet, as a non-pharmacological element, plays an important role not only as a risk factor but also as a potential therapeutic approach for treating PD (**Table 2**) [105][146][147][148][149][150][151][152][153][154][155][156][157][158][159][160][161]. The effects of diet intervention on PD development can be attributed to different mechanisms. First, by altering intestinal microbiota composition and consequently affecting the gut-brain axis or by directly interfering with immune cells. As a matter of fact, diet is probably the most influential factor in determining the structure and metabolic function of the intestinal microbiota. Moreover, dietary components might also modulate the chronic inflammatory response that is associated with aging. Intriguingly, diet components can reduce constipation and improve L-dopa uptake, which is the first-line therapy for PD [162][163]. Therefore, consuming a constant diet on a long-term basis can impact the development of PD; however, it is still to

be elucidated as to how a particular diet reduces the risk of this development. Here, the researchers discuss how changes in diet may prevent or modify PD progression, with a special focus on Mediterranean, ketogenic, and omega-3-rich diets.

Table 2. The effects of dietary interventions in PD clinical trials.

Reference	Type of Study	Type of Dietary Intervention	Aim	Outcomes
Metcalfe-Roach et al., 2021 [146]	CrS	MIND or Medi	MIND/Medi vs. PD onset	Both diets delay PD onset; MIND slightly superior in the female subgroup.
Paknahad et al., 2020 [147]	CT	Medi	Medi vs. cognitive function	Improvement in executive function, language, attention, concentration, active memory and in the total score of cognitive assessment.
Rusch et al., 2021 [148]	CT	Medi	Medi vs. GI function	Correlation with weight loss, improved constipation, and modified gut microbiota in PD patients.
Cassani et al., 2017 [149]		Medi	Medi vs. PD progression	No significant correlation.
Maraki et al., 2019 [150]	CS	Medi	Medi vs. PD onset	Correlation with lower probability of prodromal PD in older people.
Zamzam Paknahad et al., 2022 [151]	CT	Medi	Medi vs. total antioxidant capacity (TAC) and PD severity	Improvements in TAC and PD severity.
Alcalay et al., 2012 [152]	CCS	Medi	Medi vs. PD status	Medi adherence is associated with PD age at onset.
Strikwerda et al., 2021 [153]	CS	Medi, Dutch diets	Medi, Dutch diets vs. PD risk	Protective effect.
Yin et al., 2021 [154]	CS	Medi	Medi vs. PD risk	Protective effect.
Agarwal et al., 2018 [155]	LS	MIND	MIND vs. PD development and progression	Decreased risk and slower progression of PD in older adults.
Lawrie et al., 2022 [156]	CrS	MIND	MIND vs. PD severity	Decreased fatigue and depression.

Reference	Type of Study	Type of Dietary Intervention	Aim	Outcomes
Koyuncu et al., 2021 [157]		KD	KD vs. PD patients voice quality	VHI * score improvement
VanItallie et al., 2005 [158]	Feasibility study	KD	KD vs. PD progression	UPDRS scores improvement.
Phillips et al., 2018 [159]	CT	KD vs a low-fat, high-carbohydrate diet	KD vs. PD progression	Motor and nonmotor symptoms improvement.
Tidman et al., 2022 [160]	CT	KD	KD vs. PD progression	UPDRS scores improvement.

Abbreviations: CCS: case-control study; CrS: cross-sectional study; CT: controlled trial; KD: ketogenic diet; LS: longitudinal study; Medi: Mediterranean diet; MIND: Mediterranean-DASH diet intervention for neurodegenerative delay; PUFAs: polyunsaturated fatty acids; UPDRS: Unified Parkinson's Disease Rating Scale; VHI score: voice handicap index; * VHI is patient-rated scale developed to assess the level of disability experienced by patients affected by various voice disorders.

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Fecal microbiota transplantation (FMT) consists in the transfer of resuspended and filtered stool material from a healthy donor to a patient's gut. The aim of this approach is to counteract dysbiosis while favoring the establishment of a beneficial and balanced microbiota [164][165]. Although colonoscopy is the preferred method of transplantation, delivery through nasogastric or nasojejunal tube, enema, or orally administered capsules have also been tested [164][166]. Following the successful use of FMT in the treatment of refractory or recurrent *Clostridium difficile* infection, several studies have been conducted to explore FMT as a therapeutic strategy for a wide range of neurological disorders, including multiple sclerosis, epilepsy, ASD, Tourette syndrome, diabetic neuropathy, AD and PD, with promising preclinical and clinical data [167][168][169][170][171]. Concerning PD, consistent preclinical studies and a handful of human case reports have shown that FMT might be exploited to reduce motor and non-motor symptoms, as well as constipation, at least in the short term [168][172][173][174][175][176][177][178][179][180][181] (**Table 3**). Early evidence came in 2016 from the work of Sampson et al., who first reported that the transfer of fecal matter from human PD patients to α-synuclein overexpressing mice substantially worsened their physical symptoms in comparison with mice receiving feces from healthy human donors [172]. These results were then confirmed in 2018, when Sun et al. showed that fecal microbiota transfer from PD mice to their healthy counterpart increases motor deficits while reducing the striatal levels of the neurotransmitters dopamine, serotonin and their metabolites, thus reproducing the typical features of the disease [173]. Conversely, fecal matter transplantation from healthy mice to PD recipient mice improved physical performance, ameliorated motor symptoms and reduced dysbiosis in several independent studies [173][174][175][176]. Looking at the GM composition, there is evidence that FMT re-establishes eubiosis by disadvantaging the growth of *Desulfovibrio*, *Akkermansia* and *Proteobacteria* (orders *Enterobacteriales* and *Turicibacteriales*), while simultaneously favoring the proliferation of beneficial bacteria such as *Bacteroidetes* and *Actinobacteria* phyla, with a particular effect on *Blautia* and *Prevotella* species [173][174][176]. Moreover, FMT appears to protect from gut inflammation by promoting intestinal barrier integrity and reducing the levels of LPS in the colon, serum, and SN, therefore preventing leaky gut and systemic inflammation [174]. At the brain level, FMT contrasts cognitive damage by decreasing α-synuclein expression and restoring the optimal levels of the striatal neurotransmitters dopamine and serotonin, thus supporting neuroprotection [173][175][177]. Notably, decreased neuroinflammation following FMT has been reported by numerous preclinical studies [173][174][175][176]. This beneficial effect should be ascribed to the ability of GM to modulate microglia and astrocyte activation in SN by regulating the TLR4/NF-κB pro-inflammatory pathway and reducing the expression of GSK3β, iNOS and IL-1β, which are implicated in PD pathogenesis and progression [173][174][175][176][182][183][184].

Table 3. Preclinical and clinical studies on the use of fecal microbiota transplantation for Parkinson's disease.

Ref.	Study Cohort	Study Groups	Donor	Recipient	Experimental Procedure	Results	Adverse Events
Zhao et al., 2021 [174]	Mice	Controls (*n* = 15), rotenone (*n* = 15) and rotenone + FMT (*n* = 15)	Control mice	Rotenone-induced PD mice	Oral gavage (100 µL bacterial suspension) daily for 2 weeks	↓ Dysbiosis ↓ Motor symptoms ↑ Intestinal barrier and BBB integrity ↓ Systemic inflammation ↓ Neuroinflammation (SN) ↓ LPS (serum, colon and SN) ↓ TLR4/NF-κB pathway (colon and SN)	N.A.
Sun et al., 2018 [173]	Mice	Controls (*n* = 15), MPTP + PBS (*n* = 15) and MPTP + FMT (*n* = 15)	Control mice	MPTP-induced PD mice	Gavage (200 µL bacterial suspension containing 10^8 CFU/mL) daily for 7 days	↓ Dysbiosis ↓ Fecal SCFAs ↓ Motor symptoms ↑ DA and 5-HT (striatum) ↓ Microglia and astrocyte activation (SN) ↓ TLR4/TNF-α pathway (gut and brain)	N.A.
Zhong et al., 2021 [175]	Mice	Controls + PBS (*n* = 10), controls + FMT (*n* = 10), MPTP + PBS (*n* = 10), MPTP + FMT (*n* = 10)	Control mice	Controls or MPTP-induced PD mice	Gavage (200 µL bacterial suspension containing 10^8 CFU/mL) daily for 7 days	↓ Motor symptoms ↓ Fecal SCFAs ↓ α-syn (SN) ↓ Microglia activation (SN) ↓ TLR4/NF-κB pathway (striatum and SN)	N.A.
Zhang et al., 2021 [176]	Mice	Controls (*n* = 3), MPTP (*n* = 3) and MPTP + FMT (*n* = 3)	Control mice	MPTP-induced PD mice	Transplantation with 200 µL bacterial suspension (containing 10^8 CFU/mL) daily for 2 weeks	↓ Neuroinflammation (SN) ↓ Motor symptoms ↑ *Blautia* ↓ *Anaerostipes*, *ASF356*, *Ruminococcus* and *Bifidobacterium* ↓ Microglia and astrocyte activation (SN) ↓ IL-1β, iNOS, GSK3β and p-PTEN (SN)	N.A.
Zhou et al., 2019	Mice	Mice pre-treated with	Control mice or	MPTP-induced PD mice pre-	Gastric gavage (200 µL	↑ DA and 5-HT (striatum) in PD-NF	N.A.

Ref.	Study Cohort	Study Groups	Donor	Recipient	Experimental Procedure	Results	Adverse Events
[177]		MPTP and antibiotics, divided in PD-PBS (*n* = 8), PD-NA (*n* = 8), PD-NF (*n* = 8) and PD-NF/HK (*n* = 8)	control mice undergoing FMT	treated with antibiotics	bacterial suspension containing 10^8 CFU/mL) daily for 7 days	mice ↑ Neuroprotection in PD-NF mice	
Sampson et al., 2016 [172]	Mice	GF + FMT from SPF control mice, GF + FMT from PD patients, GF + FMT from healthy patients	Human PD patients (*n* = 6), human healthy controls (*n* = 6) or SPF control mice (*n* = 3)	α-syn-overexpressing mice	Oral gavage	In GF + PD-FMT mice: ↑ Physical impairment ↑ *Proteus*, *Bilophila* and *Roseburia* ↓ *Lachnospiraceae*, *Rikenellaceae*, *Peptostreptococcaceae* and *Butyricicoccus* ↓ Acetate ↑ Proprionate and butyrate	N.A.
Huang et al., 2019 [178]	Human (case report)	PD patient presenting tremor for 7 years and constipation (>3 years)	26 y.o. healthy male	71 y.o. male PD patients	Colonoscopy (200 mL of fecal microbiota suspension) daily for 3 days	↓ Tremor (no tremor for 2 months) ↓ Constipation ↑ α-diversity ↓ UPDRS score 1 week after FMT	No
Kuai et al., 2021 [179]	Humans (prospective single study)	PD patients	Frozen fecal microbiota from the China fmtBank	PD patients (*n* = 11)	Intra-intestine transplantation of 40–50 mL of frozen fecal microbiota resuspended in 200 mL saline solution	↑ *Blautia* and *Prevotella* ↓ *Bacteroidetes* ↓ H-Y, UPDRS and NMSS scores ↓ Wexner constipation and PAC-QOL scores	No
Xue et al., 2020 [180]	Humans	PD patients + FMT (via colonoscopy, *n* = 10; nasointestinally, *n* = 5)	5 Healthy donors (mean 22 y.o., 3 males and 2 females)	PD patients	Colonoscopy or nasointestinal administration	↓ PSQI, HAMA, PDQ-39, HAMD, UPDRS-III and NMSQ	5 cases: diarrhea (*n* = 2), abdominal pain (*n* = 2) and flatulence (*n* = 1)
Segal et al., 2021 [181]	Humans (uncontrolled case series)	6 PD patients with symptoms for 5 years (mean).	2 healthy donors (males, 38 and 50 y.o.)	6 PD patients with constipation (mean 52 y.o.), 3 males and 3 females	Colonoscopy (300 mL of fecal suspension)	↓ Motor and non-motor symptoms ↓ Constipation	1 case requiring hospitalization for observation

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compared to nasointestinal delivery [180]. In line with preclinical data, PD patients undergoing FMT showed an increased presence of *Blautia* and *Prevotella* and a diminished overall abundance of *Bacteroidetes*, thus confirming the efficacy of this approach in modifying the GM composition [179].

Despite the therapeutic potential of FMT for the treatment of PD, several limitations still exist and need to be addressed. Standard clinical protocols, delivery methods, periodicity, donor's selection criteria, patient's inclusion criteria, long-term benefits and potential risks remain an issue [165][170][185][186][187][188][189]. Within this context, 6 cases of adverse events occurred in human studies: flatulence (1), diarrhea (2), hospitalization under observation (1) and GI pain (2) [180][181]. Therefore, although not life-threatening, the nature of these complications should be better investigated.

Abbreviations: RCT: randomized controlled trial; BBB: blood brain barrier; CFU: colony forming units; DA: dopamine; FMD: fasting mimicking diet; FMT: fecal microbiota transplantation; GF: germ-free; GSK-3β: glycogen synthase kinase-3 beta; H-Y: Hoehn and Yahr scale; HAMA: Hamilton anxiety scale; HAMD: Hamilton depression rating scale; 5-HT: serotonin;IL-1β: interleukin 1 beta; iNOS: inducible nitric oxide synthase; LPS: lipopolysaccharide; MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; NMSQ: non-motor symptoms questionnaire; NMSS: non-motor symptoms scale; p-PTEN: phosphorylated PTEN; PAC-QOL: patient assessment of constipation quality of life questionnaire; PBS: phosphate buffered saline; PD-NA: MPTP induced PD mice treated receiving FMT from control mice; PD-NF: MPTP induced PD mice treated receiving FMT from control mice undergoing FMD; PD-NF/HK: MPTP induced PD mice treated receiving heat inactivated FMT from control mice undergoing FMD; PD-PBS: MPTP-induced PD mice treated receiving PBS; PD: Parkinson's disease; PDQ-39: Parkinson's Disease Questionnaire; PSQI: Pittsburgh sleep quality index; SCFAs: short chain fatty acids; SN: substantia nigra; SPF: specific pathogen free; TLR4: toll like receptor 4; TNF-α: tumor necrosis factor α; UPDRS: Unified Parkinson's Disease Rating Scale; yr: years; ↓: decrease; ↑: increase.

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