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LEADING ARTICLE

The Gut Microbiota in Parkinson Disease: Interactions with Drugs and Potential for Therapeutic Applications

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Abstract

The concept of a 'microbiota-gut-brain axis' has recently emerged as an important player in the pathophysiology of Parkinson disease (PD), not least because of the reciprocal interaction between gut bacteria and medications. The gut microbiota can influence levodopa kinetics, and conversely, drugs administered for PD can influence gut microbiota composition. Through a two-step enzymatic pathway, gut microbes can decarboxylate levodopa to dopamine in the small intestine and then dehydroxylate it to *m*-tyramine, thus reducing availability. Inhibition of bacterial decarboxylation pathways could therefore represent a strategy to increase levodopa absorption. Other bacterial perturbations common in PD, such as small intestinal bacterial overgrowth and *Helicobacter pylori* infection, can also modulate levodopa metabolism, and eradication therapies may improve levodopa absorption. Interventions targeting the gut microbiota offer a novel opportunity to manage disabling motor complications and dopa-unresponsive symptoms. Mediterranean diet-induced changes in gut microbiota composition might improve a range of non-motor symptoms. Prebiotics can increase levels of short-chain fatty acid-producing bacteria and decrease pro-inflammatory species, with positive effects on clinical symptoms and levodopa kinetics. Different formulations of probiotics showed beneficial outcomes on constipation, with some of them improving dopamine levels; however, the most effective dosage and duration and long-term effects of these treatments remain unknown. Data from faecal microbiota transplantation studies are preliminary, but show encouraging trends towards improvement in both motor and non-motor outcomes. This article summarises the most up-to-date knowledge in pharmacomicrobiomics in PD, and discusses how the manipulation of gut microbiota represents a potential new therapeutic avenue for PD.

1 Introduction

The discovery of a bidirectional communication between the brain and the gut, the so-called gut-brain axis, has revolutionized our current understanding of the physiology of the central nervous system (CNS) and the pathophysiology of several neurological conditions, including Parkinson disease (PD) [1]. Patients with PD are severely affected by gastrointestinal (GI) disorders throughout their lifetime and can present with GI symptoms (e.g., constipation) up to two decades before the onset of motor disturbances [2]. Pathological hallmarks of PD such as accumulation of

Key Points

Gut microbiota pathways influence levodopa absorption and contribute to side effects of dopaminergic medications used to treat Parkinson disease patients.

Dopaminergic medications can alter the composition of the gut microbiota.

Therapeutic interventions that target the gut microbiota have the potential to ameliorate levodopa pharmacokinetic parameters.

Several gut microbiota-targeted strategies are under evaluation as both symptomatic and disease-modifying therapies in Parkinson disease.

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abnormal α-synuclein [3] are detected in the enteric nervous system of PD patients before disease development and in individuals at high risk of developing PD such as those suffering from idiopathic REM (rapid eye movement) sleep behaviour disorder (iRBD) [4–7]. Recent multimodal imaging studies confirmed that some individuals with PD develop peripheral (cardiac and colonic) disease features prior to loss of dopaminergic putaminal uptake, reflecting a bottom-up ascension of α-synuclein pathology from the periphery to the CNS—the so-called 'body-first' subtype [8]. This in contrast to the 'brain-first' subtype characterised by initial pathological changes in the brain with subsequent spread to the brainstem and the periphery [8]. One of the most important routes connecting the gut and the brain, the vagus nerve, has been postulated to play a role in caudo-rostral spread of PD pathology, with truncal vagotomy appearing to protect against development of PD in both some epidemiological [9, 10] and in vivo [11] studies.

In the last two decades, increasing evidence has highlighted the crucial role played by the gut microbiota (GM) as regulator of the gut-brain axis, incorporating its contribution in the novel concept of 'microbiota-gut-brain axis' [1]. Multiple lines of evidence suggest that the microbiota-gut-brain axis can contribute to PD development and influence its progression, thus providing the rationale for GM manipulation as a therapeutic strategy in PD [12]. For instance, individuals with PD display increased colonic barrier permeability and intestinal inflammation [13–17], thus potentially allowing bacterial factors to enter the GI wall and trigger pathological changes implicated in PD. Several case-control studies demonstrated that dysbiosis characterises individuals with PD compared to healthy individuals, thus resulting in a pro-inflammatory milieu (reviewed in [18]). In vivo models showed that GM changes are sufficient to trigger PD-like pathological, neuroinflammatory and behavioural changes in mice, which can be reversed by restoring a 'healthy' GM [19–21]. In vitro studies suggested that bacterial components can trigger abnormal α-synuclein pathology in intestinal cells directly connected with the vagus nerve [22], supporting the hypothesis of α-synuclein accumulation triggered by GM changes.

In this article, we present an overview of the current knowledge regarding the interactions between GM and PD. In particular, we focus on the reciprocal effects of medications used to treat PD and GM composition, which is the research focus of the novel, cutting-edge subfield of pharmacogenomics called 'pharmacomicrobiomics' [23]. We then discuss possible therapeutic strategies to optimise drug absorption by modulating GM as well as the state-of-the-art evidence on therapeutic interventions targeting GM in PD.

2 Literature Search

We performed a literature search on 15 October 2023 for English-written articles published up to that date using the National Center for Biotechnology Information's PubMed database (https://www.ncbi.nlm.nih.gov/pubmed) with the following search terms: 'gut microbiota' AND 'Parkinson' AND 'therapies' OR 'levodopa' OR 'faecal microbiota transplantation' OR 'diet intervention' OR 'prebiotics' OR 'probiotics', for the latter four using filters for clinical trial and randomised controlled trial (RCT). We selected the articles relevant to our article and included additional articles from their reference lists.

3 The Reciprocal Interaction Between Gut Microbiota (GM) and Pharmacological Therapies in Parkinson Disease (PD)

The initial symptomatic treatments of early motor PD rely on oral pharmacological therapies, such as levodopa, long-acting dopamine agonists, or monoamine oxidase type B inhibitors (MAO-BI). Although any of these options can be considered as first-line treatment, recent evidence-based guidelines published by the American Academy of Neurology recommend the use of levodopa for the treatment of early PD given its higher symptomatic efficacy [24].

In most PD patients, the response to dopaminergic medications becomes erratic and variable over time, leading to development of motor fluctuations, unpredictable or sub-optimal levodopa response, and 'delayed on' and 'no on' phenomena [25]. In this complex phase, the use of catechol-O-methyltransferase (COMT) inhibitors or MAO-BI can help. If not effective, non-oral therapies such as levodopa-carbidopa intestinal gel (LCIG) delivered continuously through a percutaneous endoscopic gastro-jejunal (PEG-J) tube, or deep brain stimulation, represent the alternative [24]. Albeit rarer, a sub-optimal clinical response to levodopa might also occur in some patients with PD (labelled as 'primary non-responders') [26].

Among the pathophysiological determinants of these disabling phenomena, the ability for the GM to directly influence drug bioavailability [27, 28] and determine side effects of dopaminergic medications [29], makes it a potential contributor. Unravelling the GM impact on drug metabolism is thus crucial not only for the purpose of optimising drug efficacy, but also for preventing sides effects in PD [29].

3.1 Bacterial Pathways Directly Implicated in Levodopa Metabolism

Levodopa, the mainstream treatment for PD, is a non-proteogenic large neutral amino acid (LNAA) produced by the

hydroxylation at the meta-position of the phenyl ring of tyrosine [30]. Specific amino acid transporters transport levodopa at the GI level and blood-brain barrier (BBB). After passing by the BBB, levodopa is converted in the CNS into dopamine and 3-O-methyldopa (3-OMD) by the aromatic amino acid decarboxylase (AADC)-also known as DOPA decarboxylase (DDC), and the catechol-O-methyltransferase (COMT) enzymes, respectively [30].

Levodopa absorption and oral bioavailability are dependent upon several host-related factors. First, the absorption of levodopa is restricted to the proximal small intestine (duodenum and jejunum), where it is transported from the lumen into the bloodstream using a competitive transport system shared with other LNAAs [31]. Second, dietary proteins, converted into amino acids after digestion, inhibit levodopa absorption [32], and for this reason, low-protein diets can improve levodopa absorption [33]. Third, the enzymes AADC and COMT extensively convert levodopa to dopamine and 3-OMD also in the GI tract and bloodstream. Levodopa is therefore administered with inhibitors of AADC (carbidopa or benserazide) and COMT (tolcapone, entacapone and opicapone) to reduce its peripheral and GI metabolism [30, 34]. However, despite these inhibitors, up to 56% of levodopa fails to reach the brain [35], suggesting that other mechanisms influence levodopa metabolism.

Among these mechanisms, recent advances in pharmacomicrobiomics have shown the influence of the GM in regulating levodopa absorption. The first evidence that GM might influence levodopa bioavailability emerged in the 1970s. Urinary levels of *m*-tyramine, a by-product of dopamine dehydroxylation, were increased upon levodopa administration in six PD patients, but significantly decreased after antibiotic use, suggesting a role of GM in formation of *m*-tyramine from dopamine [36]. A few years later, another study demonstrated that *m*-hydroxyphenylacetic acid and *m*-hydroxyphenylpropionic acid were found in urine only of conventional rats fed with levodopa or dopamine, but not in germ-free rats, suggesting that dehydroxylation reactions were mediated by GM [37].

Despite these intriguing findings, the mechanisms by which GM metabolises levodopa in the small intestine have been clarified only in recent years. In 2019, van Kessel and colleagues showed that gut bacteria expressing tyrosine decarboxylases (TDCs), mainly species of genus *Enterococcus* (*E. faecium* and *E. faecalis*), could effectively decarboxylate levodopa to dopamine in the small intestine of rats [38]. Human AADC inhibitors did not inhibit levodopa decarboxylation activity in *E. faecalis* or *E. faecium*, and bacterial tyrosine decarboxylases (*tdc*) gene levels negatively correlated with plasma and proximal jejunal levels of levodopa/carbidopa in rats fed with levodopa/carbidopa, suggesting that higher abundance of gut bacteria encoding for *tdc* gene in the small intestine reduced levodopa/carbidopa absorption [38]. These conclusions were corroborated by findings in PD patients on levodopa therapy where bacterial *tdc* gene relative abundance positively correlated with the daily dose of levodopa and disease duration [38]. In a recent cross-sectional study conducted on PD patients, it was observed that moderate responders to levodopa had a higher abundance of *tdc* gene and *E. faecalis* than good responders [39]. The abundance of bacterial *tdc* gene rather than *E. faecalis* was independently associated with levodopa responsiveness, possibly because *tdc* gene also exists in other bacterial species such as *E. faecium* and *Lactobacillus brevis*, so bacterial gene abundance might explain drug metabolism better than species abundance [39]. Interestingly, clinical features (disease duration or severity) and PD medication use were not associated with *tdc* gene abundance, supporting the potential use of relative abundance of bacterial *tdc* gene as a biomarker of levodopa responsiveness before treatment initiation [39].

Maini Rekdal and colleagues identified that the bacterium responsible for dehydroxylation of dopamine into *m*-tyramine is a strain of *Eggerthella lenta* [35], which was previously shown to be involved in drug metabolism [40]. The same authors found that the L-tyrosine analogue (S)-α-fluoromethyltyrosine (AFMT), a nontoxic selective inhibitor of TDC (but not AADC), inhibited gut microbial levodopa decarboxylation in vitro. Combined administration of AFMT with levodopa/carbidopa to mice colonized with *E. faecalis* increased the peak serum concentration of levodopa compared to vehicle, opening up the possibility of developing levodopa therapies targeting both host and gut microbial decarboxylation [35].

Other than in levodopa absorption, the GM may play an important role in determining side-effect profiles in levodopa-treated PD patients. Deamination of levodopa by *Clostridium sporogens* can produce the metabolite 3-(3,4-dihydroxyphenyl)propionic acid (DHPPA), which inhibited muscle contraction in the ileum in an ex vivo model [29]. This metabolite (DHPPA) was significantly higher in faecal samples from PD patients on levodopa than age-matched healthy controls, and was actively produced by the GM in PD patients' faecal suspensions, supporting a possible implication of GM in levodopa-induced side effects [29].

3.2 Other Bacterial Mechanisms Influencing Levodopa Bioavailability

Small intestinal bacterial overgrowth (SIBO), a condition characterised by an increased concentration of bacteria above 10^5 colony-forming units/ml and/or presence of colonic-type bacteria in the small intestine [41, 42], is reported in up to 54% of PD patients, and associates with development of motor complications and variability in motor

response [43–45]. SIBO could influence levodopa metabolism because it can select gut bacteria expressing *tdc* gene in PD patients [30], or alternatively increase small intestine permeability and inflammation [43]. Regardless of the mechanisms, if SIBO directly interferes with levodopa absorption, eradication of SIBO should improve levodopa bioavailability and motor symptoms. In an open-label trial, 400 mg rifaximin administered three times a day for 1 week was tested in a group of 18 SIBO-positive PD patients [43]. One month after initiation of antibiotic treatment, nearly 80% of patients were SIBO-negative, with improvement in motor fluctuations (both OFF time and delayed-ON), but there were no significant differences in levodopa pharmacokinetic parameters. Unfortunately, the study reported a high percentage of relapse after 6 months from SIBO eradication (42.9%) [43]. Another single-centre, double-blind, RCT was designed to evaluate the effect of rifaximin on OFF symptoms in SIBO-positive PD patients with at least 4 h/day of 'OFF' time (ClinicalTrials.gov ID: NCT02470780, SIBO-PD). The study failed because of difficulties in patient recruitment and unexplained spontaneous conversion to SIBO negativity in patients in the placebo arm [46]. Taken together, these results pose some questions about the role played by SIBO in levodopa metabolism.

Another bacterium that could interfere with levodopa absorption is *Helicobacter pylori* (HP). HP infection is associated with increased PD risk [47], and progressive deterioration of motor symptoms [48, 49]. In initial studies, HP-positive PD patients displayed more severe motor fluctuations compared to HP-negative patients, and eradication of HP by antibiotic treatment (amoxicillin+clarithromycin) improved motor fluctuations and significantly increased the area under the curve (AUC) of levodopa plasma concentration by about 20% in these individuals [50, 51]. The benefits on motor fluctuations following HP eradication were confirmed by follow-up studies [52–54]. However, a small double-blind RCT (N = 67) showed no improvement in motor function tested in the ON phase, at either short-term (12-week) or longer-term (52-week) follow-up [55]. Moreover, no significant differences in pharmacokinetic parameters of levodopa and 3-OMD were found between HP-positive and -negative PD patients in another study [56]. Although the small sample size of the more recent studies could have reduced their statistical power, current data regarding benefits of HP eradication remain controversial. Prior to the design of larger clinical trials evaluating the potential benefit of HP eradication in PD, further research aiming to disentangle the mechanisms behind levodopa absorption modulation by HP infection is needed. Only a few mechanisms have been proposed so far. Reduced gastric acidity (hypochlorhydria), which is linked to HP infection, can favour the development of SIBO, whose potential role as modulator of levodopa metabolism has been discussed above [57]. The existence of a direct interaction between levodopa and the outer membrane proteins of HP was suggested by one in vitro study where levodopa concentration was reduced in a time- and HP density-dependent manner when exposed to HP, and pre-incubation of levodopa with HP showed significantly reduced bacterial adhesion to gastric epithelial cells [58]. Further studies are therefore needed to clarify whether the benefits achieved by HP are exclusively secondary to HP eradication or can be due to elimination of other bacterial species that might interfere with levodopa absorption in the small intestine [30].

Indirect evidence of GM influence on levodopa absorption comes from other examples of effective use of antibiotics at reducing motor fluctuations and dyskinesias in PD (beyond SIBO or HP eradication) [59]. Treatment with sodium phosphate enema followed by oral rifaximin and polyethylene glycol for 7 and 10 days improved duration and severity of dyskinesia in 57% of cases, and functional impact and complexity of motor fluctuations [59]. Levodopa plasma levels were not measured pre- and post-intervention, so more research is needed to clarify the effects of such treatment on levodopa pharmacokinetics.

To conclude, a variety of bacterial pathways are implicated in the metabolism of levodopa, expanding the range of potential pharmacological targets to improve levodopa absorption. These might include, among others, the use of bacterial TDC inhibitors and the selective eradication of HP. A summary of possible GM-focused strategies to screen response to treatment in drug-naïve PD patients and optimise levodopa absorption in treated patients is presented in Fig. 1. Further studies are needed to better understand this complex interaction between GM, host and medications in PD. Although this goes beyond the scope of this review, it is worth mentioning that other factors can contribute to limit levodopa absorption in PD patients. These include transport barriers, such as dysphagia, delayed gastric emptying, and slow transit constipation. Therapeutic strategies aimed to address these disturbances can therefore improve levodopa bioavailability [25].

3.3 PD Medications Influence GM Composition

The interaction between GM and medications is bidirectional, with a direct effect of pharmacological treatments used in PD on GM composition. This observation is important to identify disease-related changes in GM of PD patients, not secondary to drugs, and for the potential interference of these changes on bioavailability of concomitant medications and overall gastrointestinal health. Although this is beyond the primary scope of this article, we will briefly summarise the evidence on GM changes induced by use of PD medications. For a comprehensive review on the effect of non-pharmacological therapies, such as deep brain stimulation, on GM, the reader is referred elsewhere [27].

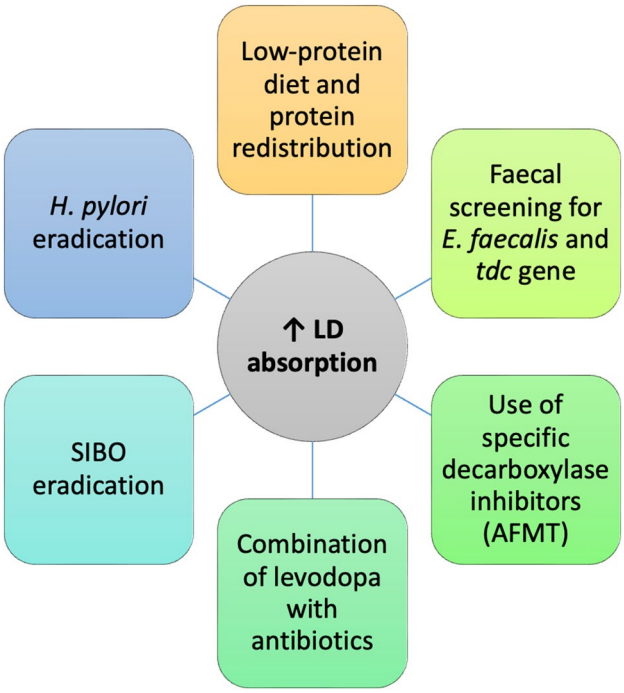

Fig. 1 Possible gut microbiota (GM)-based strategies to optimise levodopa absorption. *AFMT* (S)-α-fluoromethyltyrosine, *LD* levodopa, *SIBO* small intestinal bacterial overgrowth, *tdc* tyrosine decarboxylase

Levodopa effects were evaluated in a small group of PD patients ($N = 19$) after 90 days from treatment initiation. Levodopa did not induce any alteration in α-diversity (i.e., diversity within a community sample) or β-diversity (i.e., similarity between two community samples), or relative abundance of bacterial genera; only a marginal lower abundance of bacteria belonging to *Clostridium* group IV was found in those patients who showed a better response to levodopa [60]. Significant alterations in the abundance of family *Bacillaceae* [61], increased relative abundance of genera *Peptoniphilus* and *Finegoldia*, and decreased relative abundance of genus *Faecalibacterium* and *Ruminococcus gauvreauii* were detected in PD patients treated with levodopa versus controls; however, no significant differences at the genus or family levels were found between PD patients on levodopa and levodopa-naïve patients [62]. In another study evaluating 46 patients treated with levodopa, decreased abundance of genera *Faecalibacterium*, *Roseburia* and *Pseudobutyrivibrio*, and species belonging to *Bacteroides*, *Blautia* and *Lachnospira*, and increased abundance of *Colinsella*, were found in comparison to drug-naïve subjects [63].

We mentioned above that LCIG represents an effective strategy to address motor fluctuations in advanced cases of PD [64]. After 4 weeks from LCIG initiation, patients displayed an over-representation of *Pseudoflavonifractor* and *Escherichia/Shigella*, and under-representation of *Gemmiger* [65]. Considering that *Escherichia/Shigella* are bacteria that tolerate acidic conditions [66], the authors suggested that their higher abundance was secondary to the mildly acidic (~ pH 6.0) properties of LCIG [65]. In another study, increased abundance of *Proteobacteria* and *Enterobacteriaceae* and reduction of *Firmicutes*, *Lachnospiraceae* and *Blautia* were detected in LCIG patients compared to drug-naïve PD patients [63]. When patients treated with oral levodopa and LCIG were compared, there was a significant difference in β-diversity between groups and higher abundance of genera *Escherichia* and *Serratia* in LCIG patients [63]. Intestinal bacteria were collected from the tips of the PEG-J tube in six patients receiving LCIG therapy after tube replacement. *E. faecalis* was identified in four out of the six patients, and *tdc* in two patients out of these four. Only the four *E. faecalis* positive samples showed the ability to metabolize levodopa to dopamine *in vitro* [67]. Regardless of the presence of *E. faecalis*, however, no differences in mean blood concentration of levodopa were detected among patients. Despite the limited sample size, these preliminary findings might suggest that the effect of GM in metabolising levodopa in patients receiving LCIG therapy is blunted, possibly due to the shorter time of the drug in the GI tract compared to oral administration of levodopa [67].

Use of COMT inhibitors, especially entacapone, was associated with reduction in abundance of *Firmicutes*, species *Faecalibacterium prausnitzii* [68, 69] and *Lachnospiraceae* [68, 70], and increased abundance of *Actinobacteria*, *Lactobacillaceae*, *Porphyromonadaceae* and *Proteobacteria* [68]. Use of opicapone or tolcapone was not associated with changes in *F. prausnitzii* [71]. Entacapone use was uniquely associated with reduced relative abundance of *Lactobacillus*, *Intestinibacter*, *Dorea* and *Blautia*, and increased abundance of *Christensenellaceae*_R_7_group, *Eubacterium* and *Bifidobacterium* [72], and negatively correlated with relative concentration of butyrate, one of the most abundant short-chain fatty acids (SCFAs) produced by GM [69, 71]. Considering that SCFAs play a physiologically central role in several host functions and serve as essential energy sources for colonocytes [1], the potential implications of entacapone on GI physiology deserve attention.

The impact of dopamine agonists in combination with levodopa-carbidopa on GM was evaluated in rats. Treatment with pramipexole and ropinirole (in combination with levodopa-carbidopa) for 14 days significantly reduced small intestinal motility, increased bacterial overgrowth in the distal small intestine, increased bacterial richness in the jejunum (not the ileum), and had a significant effect on β-diversity in both proximal small intestine and ileum, with *Muribaculaceae* and *Lactobacillus* mostly contributing to the variation [73]. Alterations in the abundance of specific taxa were found (for instance, decreased abundance in

Romboutsia spp. in the proximal small intestine and *Lachnospiraceae* spp. in the ileum in the pramipexole-treated group, and increased *Lactobacillus* spp. in both the pramipexole- and ropinirole-treated groups) [73]. Interestingly, there was a negative correlation between *Lactobacillus* abundance and plasma levodopa levels [73]. Although we acknowledge that there are differences in the composition of the GM between rats and humans and therefore translating findings requires caution, it is interesting to note that the above-mentioned changes in *Lactobacillus* or *Lachnospiraceae* observed in the healthy rats treated with dopamine agonists and levodopa have been previously reported in PD patients when compared to healthy subjects [18]. Increasing doses of levodopa were found to correlate with reduced levels of SCFA-producing bacteria (e.g., *Lachnospiraceae*) and increased levels of *Lactobacillus* or *Bifidobacterium*, supporting the hypothesis that these alterations in the GM composition could be a consequence of PD medications, rather than of the disease itself [74]. Deciphering the exact role played by single medications (levodopa-carbidopa vs. dopamine agonists) on the GM composition and their effect on gastrointestinal motility remains an open but crucial area to address.

To date, a few longitudinal studies have investigated the impact of medications on GM composition over time. Entacapone and dopamine agonists positively contributed to an increase in *tdc* gene abundance over 2-year follow-up, whereas the opposite effect was achieved by MAO-BI [75]. When PD patients were separated into slow- and rapid-progressing clinical sub-categories, specific medications contributed to changes in *tdc* abundance, such as entacapone in rapid-progressing PD [75]. Regarding LCIG, the same authors who evaluated the short-term effect of LCIG also investigated long-term effects. After 12 months from LCIG initiation, inconsistent results compared to short-term changes were found, with relative increased abundance of family *Prevotellaceae* and genera *Prevotella* and *Bacillus*, and relative reduced abundance of genera *Hespellia*, *Eggerthella*, *Holdemania*, *Gordonibacter* and *Acetanaerobacterium* [76].

Overall, the current results might suggest that the GM composition in PD patients is not static, and specific drugs and treatment duration might differentially shape the GM composition. The small sample size of most studies and the use of low-taxonomical sequencing techniques, for example, 16S rRNA amplicon sequencing, currently limit our ability to draw definite conclusions. Large, prospective studies on human cohorts, in combination with in vivo models, are needed to elucidate which changes occur as a consequence of the disease itself and which are caused by medications. Moreover, future studies will need to evaluate the effect of such changes on other drugs pharmacokinetics and disease progression.

4 GM-Focused Interventions in the Treatment of PD

In the previous section, the evidence supporting the role of GM in influencing levodopa absorption, and some possible therapeutic options to ameliorate levodopa metabolism, were presented. In addition, several GM-focused strategies have been tested in PD with the purpose of ameliorating symptoms and/or slowing down disease progression. These include dietary interventions, prebiotic fibres, probiotics and faecal microbiota transplantation [77].

In the following section, we present the current evidence related to the application of GM-focused strategies in human PD populations. We focus on studies designed in a randomised, controlled fashion that have incorporated evaluation of GM composition pre- and post-intervention.

4.1 Dietary Interventions

Diet modifications can reduce risk of PD development as well as attenuate symptoms, but whether the effects of these interventions are mediated by changes in GM or alterations in chronic inflammatory status is unclear [77]. Aside from a few exceptions, most studies evaluating dietary interventions did not include GM analysis in their study design. An overview of dietary and/or supplement interventions tested in RCT studies is summarised in Table 1 [33, 78–89].

The most studied dietary intervention in PD is the Mediterranean diet. The Mediterranean diet is associated with a 25% risk reduction in PD development, suggesting a neuroprotective effect that might be mediated by GM [90]. A single-arm, 5-week Mediterranean diet intervention study conducted in eight people with PD in the USA resulted in increased adherence to the Mediterranean diet, weight loss and improvement in constipation, with increased abundance of *Roseburia* and decreased abundance of *Bilophila* post-intervention [91]. Following this study, the MEDI-PD study was designed (ClinicalTrials.gov ID: NCT04683900): this was an RCT, double-blind study in which participants were randomised to follow either a Mediterranean diet or their habitual diet for 8 weeks [86]. Primary outcome was change in constipation at 10 weeks compared to baseline [86]. Recruitment status is completed, and results are yet to be published. In two RCT studies, the Mediterranean diet improved cognitive function and global disease severity, and promoted antioxidant benefits in the intervention group [83, 84].

The ketogenic diet, characterised by high-fat, low-carbohydrate and adequate protein intake [92], has been marginally evaluated in PD. An initial open-label study conducted on five patients who adhered to a ketogenic diet for 28 days showed improvement in disease severity as measured by

Table 1 Overview of relevant randomised controlled trials testing dietary and/or supplement interventions in Parkinson disease

Diet or supplement interventions	RCT study design	No. of individuals included in final analyses	Treatment duration	Main outcome	References
Controlled protein diet with consumption of low-protein products vs. balanced diet	Cross-over, single-blind	18	8 weeks	Reduced OFF time	Barichella (2006) [33]
Fish oil containing omega-3 vs. placebo	Double-blind	29	12 weeks	Reduced depressive symptoms and/or remission of depression	da Silva (2008) [81]
Vitamin B supplementation (B6, B12, folic acid) vs exercise vs combined vitamin + exercise vs. no intervention	Not specified	36 divided into 4 groups	6 weeks	Reduced homocysteine levels (vitamin B supplementation group). Increased glutathione levels, strength and aerobic capacity (exercise group). No greater changes in vitamin and exercise group vs. single interventions	DiFrancisco-Donoghue (2012) [82]
Individualised dietetic advice vs. standard care	Not specified	10 (intervention) vs. 9 (standard care)	12 weeks	No changes in quality of life	Sheard (2014) [87]
Amino acid supplementation vs. placebo	Double-blind	7 (intervention) vs. 7 (placebo)	6 months	No changes in symptoms or medications requirement. Improvement in insulin sensitivity and reduction of oxidized glutathione levels in treated arm	Cucca (2015) [80]
Whey protein supplementation vs. soy protein (control)	Double-blind	15 (intervention) vs. 17 (control)	6 months	No changes in motor function. Increased plasma levels of reduced glutathione and ratio of reduced to oxidized glutathione, and reduced homocysteine levels in treated arm. Increased plasma BCAA and EAA in treated arm	Tosukhowong (2016) [89]
1,000 mg omega-3 fatty acids from flaxseed oil plus 400 IU vitamin E supplements vs. placebo	Double-blind	30 (intervention) vs. 30 (placebo)	12 weeks	Improvement in MDS-UPDRS score, decrease in high-sensitivity C-reactive protein and insulin, and increase in total antioxidant capacity in treated arm	Taghizadeh (2017) [88]
Low-fat diet vs. ketogenic diet	Single-blind	20 (low-fat) vs. 18 (ketogenic)	8 weeks	Decreased MDS-UPDRS scores in both groups, with more decreased MDS-UPDRS part I scores in ketogenic group	Philips (2018) [85]
Whey protein-based nutritional supplement + leucine + vitamin D vs. standard hospital diet	Single-blind	75 (intervention) vs. 75 (control)	30 days multidisciplinary intensive rehabilitation treatment	Greater increase in distance walked during 6-min walking test in treated arm	Barichella (2019) [78]
Mediterranean diet vs. normal diet	Single-blind	35 (intervention) vs. 35 (control)	10 weeks	Improvement in mean score of MOCA test and sub-scores (executive function, language, attention, concentration, and working memory) in treated arm	Paknahad (2020) [83]
Mediterranean diet vs. normal diet	Single-blind	36 (intervention) vs. 34 (control)	10 weeks	Improvement in MDS-UPDRS score. Increased serum total antioxidant capacity in treated arm	Paknahad (2022) [84]

Table 1 (continued)

Diet or supplement interventions	RCT study design	No. of individuals included in final analyses	Treatment duration	Main outcome	References
High flavonoid cocoa beverage vs. low (control)	Double-blind	15 (high) vs. 15 (low)	6 days	Small effect on fatigability in treated arm	Coe (2022) [79]
Mediterranean diet vs. standard care	Single-blind	46 (not specified by group)	8 weeks	Changes in constipation at 10 weeks	Rush (2021) [86]

BCAA branched-chain amino acids, *EAA* essential amino acids, *MDS-UPDRS* Movement Disorders Society Unified Parkinson's Disease Rating Scale, *MOCA* Montreal Cognitive Assessment, *RCT* randomised controlled trial

Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) in all subjects (decrease in total scores varied from 21% to 81%) [93]. Only one RCT study has been completed where patients were randomized to either follow a low-fat or ketogenic diet for 8 weeks. Amelioration of disease severity was observed in both groups; however, the ketogenic group showed more significant improvement in non-motor symptoms as measured by MDS-UPDRS part I [85].

The combination of dietary intervention (ovo-lacto vegetarian diet intervention including SCFAs for 14 days) and bowel cleansing (faecal enema for 8 days) was evaluated in a small group (N = 10) of PD patients [94]. At 1-year follow-up, combined treatment improved motor function and reduced medication requirements [94]. No long-term evaluation of the GM was performed in this study [94], so whether the observed clinical benefits can be ascribed to changes in the GM composition remains to be proven.

A number of different supplementation interventions have been tested in RCTs in PD, but no definite conclusions can be drawn from most of these studies (see Table 1). Although some resulted in a positive metabolic effect induced by the intervention, no beneficial clinical effect was detected [80, 89]. The main limitation of these studies might be the small sample size, which is one of the commonest challenges in dietary clinical trials [95]. Moreover, the evaluation of GM composition was absent in their study design.

A small exploratory, open-label pilot study was launched in 2022 to assess the SCFA-prodrug tributyrin as a potential therapy for PD (ClinicalTrials.gov ID: NCT05446168; BUTTER study). Unfortunately, the study was terminated in late 2023 because of funding withdrawal after recruiting only 18 patients.

Convincing results were reported only from a relatively large RCT study recruiting hospitalised patients with PD or other parkinsonian disorders undergoing a 30-day multidisciplinary intensive rehabilitation treatment (MIRT). Patients were randomised 1:1 to receive either a whey protein-based nutritional supplement enriched with leucine and vitamin D or a standard diet (N = 75/group). The muscle-targeted nutritional supplement significantly improved the efficacy of MIRT gait outcomes and helped the recovery of lower body physical function and the preservation of muscle mass compared to standard diet, supporting the use of muscle-targeted nutritional support in addition to intensive rehabilitation programmes in PD patients [78].

4.2 Prebiotics

Prebiotics are currently defined as "substrates that are selectively utilised by host microorganisms conferring a health benefit" [96]. The source of these dietary fibres can vary, from unrefined wheat and barley, soybeans, breast milk

and raw oats, to non-digestible carbohydrates and oligosaccharides, including galacto-oligosaccharides (GOS), fructo-oligosaccharides (FOS), inulin and lactulose [77, 97]. Consumption of prebiotic fibres can favour the growth of bacterial families such as *Ruminococcaceae* and *Bacteroidaceae* that produce SCFA [98, 99]. Recent in vitro fermentation studies demonstrated that when exposed to different prebiotic fibres, faeces from PD patients can produce SCFA at a similar level to controls, indicating the potential of prebiotic fibres to increase SCFA in PD patients [100]. Some studies have investigated the use of prebiotics in PD patients.

Two studies evaluated the effect of 8-week treatment with diet rich in either insoluble fibre (DRIF, composed of wheat, pectin and dimethylpolyoxyhexane-900) [101] or psyllium [102] in a small number of PD patients ($N = 19$, and $N = 7$, respectively). Positive outcomes were reported in both studies, with improvement in motor function and constipation and increase in plasma levodopa levels after DRIF [101], and increase in stool frequency and weight but no effect on colonic transit time after psyllium treatment [102].

More recently, the effect of 8-week dietary supplementation with resistant starch (RS; 5 g RS given twice a day orally) compared to solely dietary instructions (high-fibre diet) was evaluated in a group of 57 PD patients (of whom 32 received RS and 25 dietary instructions only) and 30 control subjects receiving RS (the RESISTA-PD trial, ClinicalTrials.gov ID: NCT02784145) [103]. RS supplementation significantly increased faecal butyrate and reduced faecal calprotectin concentrations in the PD group compared to baseline, whereas no changes were observed in controls supplemented with RS or in PD patients given dietary advice only [103]. Non-motor symptoms and depression, but not bowel habits, improved after RS supplementation in PD patients. At the GM level, the ratio between relative abundances of *Dorea longicatena* and *Blautia wexlerae* to *Ruthenibacterium lactatiformans* was positively associated with relative butyrate concentrations [103].

Another open-label, non-randomized study (ClinicalTrials.gov ID: NCT04512599) was conducted in newly diagnosed, non-medicated ($N = 10$) and treated (N = 10) PD patients to evaluate the effect of a 10-day prebiotic intervention [100]. The intervention was well tolerated and safe, reduced the relative abundance of putative pro-inflammatory bacteria (e.g., phylum Proteobacteria), and increased the abundance of putative SCFA-producing bacteria (e.g., species *Fusicatenibacter saccharivorans*, *Parabacteroides merdae*) in faeces with an increase in plasma levels of SCFA [100]. Moreover, the prebiotics improved markers of intestinal barrier integrity and inflammation (like plasma zonulin levels), and decreased levels of neurofilament light chain as a marker of neurodegeneration [100]. The authors hypothesized that the latter change might be mediated via changes in plasma levels of SCFA [100]. From a clinical perspective, gastrointestinal symptoms improved in treated PD participants, and motor function improved in all patients, but the unblinded nature of the study poses limitations to the interpretation of these findings [100].

4.3 Probiotics

Probiotics are defined as "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host" [104]. The most common bacteria used as probiotics, *Lactobacillus* and *Bifidobacterium*, have potential benefits in the restoration of favourable GM, thus promoting healthy gastrointestinal tract and immune system [104]. Use of probiotics has been successfully applied in several in vitro and in vivo studies (for a reference, the reader is directed elsewhere [77]), and initial studies in human populations showed beneficial effects on constipated PD individuals treated with probiotic *Lactobacillus casei* strain Shirota [105]. Based on these premises, numerous probiotics preparations have been tested in the controlled setting of RCTs. An overview of the study design, outcome and GM changes of the most important RCTs is presented in Table 2 [106–113].

Improvement in constipation symptoms was the primary outcome in most studies, and all the studies reported a significant improvement in the treated arm [106, 109, 110, 112, 113]. Global disease severity measured by MDS-UPDRS significantly improved in one study [111], whereas severity of motor function measured by MDS-UPDRS part III was significantly reduced in the treated arm at 1 and 3 months versus baseline, while only at 3 months in the placebo arm in another study [110]. One study compared probiotics to trimebutine, a prokinetic agent, instead of placebo. Interestingly, both treatments effectively addressed bloating and abdominal pain, whereas only trimebutine ameliorated incomplete defecation [108]. The authors concluded that the association of prokinetics with probiotics could be beneficial in some individuals with PD [108]. In one RCT study, the use of multi-strain probiotics downregulated gene expression of interleukin-1 (IL-1), IL-8 and tumour necrosis factor α (TNF-α), whereas upregulated transforming growth factor beta (TGF-β) and peroxisome proliferator activated receptor gamma (PPAR-γ) in peripheral blood mononuclear cells (PBMC) of PD patients [114].

Only three studies reported GM data pre- and post-intervention [107, 110, 113]. Interestingly, one study reported increased serum levels of acetate and dopamine after the Probio-M8 (*Bifidobacterium animalis* subsp. *lactis*) supplementation [110]. Another study showed that probiotic *Lactobacillus paracasei* strain Shirota was able to change concentration levels of L-tyrosine in stool (reduction) and plasma (increase), with a negative correlation between

Table 2 Overview of randomised clinical trials investigating probiotics supplementation in Parkinson disease (adapted from [77])

Probiotic type	No. of individuals included in final analyses (probiotics vs. placebo)	Treatment duration	Clinical outcome	Influence on gut microbiota	Other effects	References
Fermented milk, containing multiple probiotic strains and prebiotic fibre	80 vs. 40	4 weeks	Increase in number of complete weekly bowel movements Changes in stool consistency, reduction in laxatives use; no change in dopaminergic therapy	NA	NA	Barichella (2016) [106]
Lactobacillus acidophilus and *Bifidobacterium infantis*	20 (probiotics) vs. 20 (receiving trimebutine)	12 weeks	*Probiotics group*: reduction of abdominal pain and bloating *Trimebutine group*: reduction of abdominal pain, bloating and incomplete defecation	NA	NA	Georgescu (2016) [108]
Lactobacillus acidophilus, *Bifidobacterium bifidum*, *Lactobacillus reuteri*, *Lactobacillus fermentum*	30 vs. 30	12 weeks	Reduction in MDS-UPDRS total score	NA	Reduced high-sensitivity C-reactive protein and malondialdehyde, and increased glutathione levels Reduced insulin levels and insulin resistance, and increased insulin sensitivity Trend towards decrease in triglycerides and VLDL-cholesterol levels	Tamtaji (2019) [111]
Lactobacillus acidophilus, *Lactobacillus casei*, *Lactobacillus lactis*, *Bifidobacterium infantis*, *Bifidobacterium longum* (Hexbio®)	22 vs. 26	8 weeks	Improvement in number of bowel movements and gut transit time. No differences in motor outcomes, non-motor symptoms and quality of life	NA	NA	Ibrahim (2020) [109]
Lactobacillus acidophilus, *Lactobacillus gasseri*, *Lactobacillus reuteri*, *Lactobacillus rhamnosus*, *Bifidobacterium bifidum*, *Bifidobacterium longum*, *Enterococcus faecalis*, *Enterococcus faecium*	34 vs. 38	4 weeks	Improvement of spontaneous bowel movements, stool consistency and quality of life related to constipation	NA	No changes in faecal calprotectin	Tan (2021) [112]
Bacillus licheniformis, *Lactobacillus acidophilus*, *Bifidobacterium longum*, *Enterococcus faecalis*	23 vs. 23	12 weeks	Improvement of complete weekly bowel movements and defecation effort	Increased abundance of *Negativicutes* and decreased abundance of *Prevotellaceae* after treatment	NA	Du (2022) [107]

Table 2 (continued)

Probiotic type	No. of individuals included in final analyses (probiotics vs. placebo)	Treatment duration	Clinical outcome	Influence on gut microbiota	Other effects	References
Bifidobacterium animalis subsp. *lactis* (Probio-M8) (added to benserazide and dopamine agonist)	48 vs. 34	12 weeks	Improvement of sleep quality, anxiety and gastrointestinal symptoms Higher scores for satisfaction of treatment and possibility of continuing medication in probiotic group vs. placebo	Increased abundance of *Bifidobacterium animalis*, *Ruminococcaceae* and *Lachnospira*, and reduced abundance of *Lactobacillus fermentum* and *Klebsiella oxytoca* in treated group vs. placebo	Increased acetate, dopamine and reduced glutamine and tryptophan serum concentration in probiotic group	Sun (2022) [110]
Lacticaseibacillus (formerly *Lactobacillus*) *paracasei* strain Shirota	65 vs. 63	12 weeks	Improvement of constipation, non-motor symptoms and quality of life	No difference in β-diversity between baseline and follow-up Change in relative abundance of genus *Lacticaseibacillus* in probiotic group compared to baseline and placebo group	Decreased faecal concentration and increased plasma concentration of L-tyrosine in probiotic group	Yang (2023) [113]

CFU colony-forming unit, *MDS-UPDRS* Movement Disorders Society Unified Parkinson's Disease Rating Scale, *NA* not available, *RCT* randomized controlled trial, *VLDL* very-low-density lipoproteins

plasma and stool concentrations [113]. Both studies seem to point towards an effect of probiotics supplementation on dopaminergic levels.

Based on the available studies, the latest recommendations by the MDS EBM Committee published in 2019 considered probiotics and prebiotic fibres as efficacious, clinically useful and associated with an acceptable risk profile that does not require specialized monitoring in clinical practice [115]. Nonetheless, numerous questions remain. First, more studies including metagenomics and metabolomics analysis on faecal samples are needed to understand the causal relationship between clinical outcomes and treatments. Second, type and duration of treatment varied across studies, and more research is needed to refine the best regimen, dose and duration. Third, the studies conducted so far evaluated the short-term effect of intervention, so long-term evaluations are needed. Fourth, it is very likely that not all individuals with PD might benefit from these treatments to the same extent, so screening tools based, for instance, on GM profile should be applied to stratify individuals a priori and personalise treatments.

4.4 Faecal Microbiota Transplantation

Faecal microbiota transplantation (FMT) consists of transplantation of filtered faecal material from healthy donors into the recipient's gut [77]. The beneficial effects of FMT from healthy donors have been clearly shown in several PD animal models where behavioural, motor, pathological and GM features were rescued by the treatment [20, 21, 116]. These promising results together with the already broad application of FMT in humans to treat recurrent *Clostridium difficile* infection [117] have prompted various groups of researchers to test the efficacy of FMT in PD populations.

Two preliminary studies conducted on a small group of PD patients evaluated the effect of FMT in humans [118, 119]. In one study conducted on 11 PD patients with constipation, 12 weeks after FMT administered via nasoduodenal tube, both motor and non-motor symptoms, especially constipation, improved. Moreover, FMT increased the relative abundance of *Blautia* and *Prevotella*, reduced the relative abundance of *Bacteroidetes*, and corrected SIBO [118]. In the other study, 15 patients with PD received FMT (ten via coloscopy and five via nasal-jejunal tube) with improvement in sleep, mood, non-motor and motor symptoms at 1 and 3 months after treatment [119]. In the group receiving FMT via colonoscopy, two patients reported prolonged satisfactory response up to 2 years after treatment [119].

Currently, seven clinical trials, mostly RCT studies, evaluating the effectiveness of FMT in PD are ongoing or have been completed. An overview of these studies is given in Table 3 [120–122]. Results from two studies are already

Table 3 Current clinical trials evaluating FMT in Parkinson disease patients

Clinical trial ID	Location	Study design	No. of participants (enrolled or expected if study not completed)	Methods of transplantation	Primary outcomes	Recruitment status (reference if available)
NL9438	Netherlands	RCT, double-blinded	16	Duodenal administration through gastroscopy	Safety and feasibility	Active [122]
NCT04837313	China	Open label	30	NA	Changes in constipation (measured by Gastrointestinal Symptom Rating Scale and Wexner Constipation Scoring system) at 6 months	Active
NCT05204641	Poland	RCT, double-blinded	60	Colonoscopy	Changes in MDS-UPDRS part III in OFF state at 12 months	Active, not recruiting
NCT03808389	Ghent	RCT, quadruple-blinded	49	Nasojejunal administration	Changes in MDS-UPDRS and NMSS score at 3, 6, 12 months	Completed
NCT04854291	Helsinki	RCT, quadruple-blinded	51	Intracaecal infusion	Changes in sum of MDS-UPDRS I-III at 6 months	Completed
NCT03876327	Israel	Open label	6	Colonoscopy	Changes in MDS-UPDRS part III and constipation at 6 months	Completed [121]
NCT03671785	United States	RCT, single-blinded (participant)	12	Lyophilized and encapsulated in enteric-coated capsules	GM diversity and richness at weeks 6 and 13, and months 4, 6 and 9	Completed [120]

FMT faecal microbiota transplantation, *GM* gut microbiota, *MDS-UPDRS* Movement Disorders Society Unified Parkinson's Disease Rating Scale, *NMSS* non-motor symptoms scale for Parkinson's disease, *RCT* randomised clinical trial

available. The first study was an open-label study conducted on six patients with FMT administered via colonoscopy, showing positive effects on motor, non-motor and constipation symptoms in five out of six patients after 4 weeks [121]. The second RCT study evaluated 12 patients with constipation receiving oral multi-dose FMT for 12 weeks. After 9 months from treatment, FMT improved constipation and gut motility, and increased β-diversity and bacteria belonging to families *Lactobacillaceae* and *Peptostreptococcaceae* [120], which are known to protect the gut wall [123]. Overall, FMT was generally well tolerated and adverse events were mostly transient and self-limiting [118–121]. Recently, the protocol for a single-centre, prospective, self-controlled, interventional, safety and feasibility donor-FMT pilot study with randomisation and double-blinded allocation of donor faeces has been published by the FMT4PD study group in the Netherlands [122]. Sixteen PD patients with motor complications will receive FMT into the duodenum through a gastroscope and be followed up over 12 months. Primary outcomes will be feasibility and safety of FMT, while secondary outcomes will include changes in motor and non-motor symptoms, as well as alterations in GM composition [122].

4.5 GM-Based Interventions: Potential Use as Disease-Modifying and Preventive Treatments

To date, studies testing GM-based interventions have been conducted in groups of patients with manifest PD, with the main goal to treat symptoms. Emerging evidence suggests, though, that the same interventions (e.g., prebiotics, probiotics, FMT) might be suitable as disease-modifying and preventive therapies.

On the one hand, longitudinal studies suggest that GM composition might predict PD progression. Lower abundance of genera *Bifidobacterium*, *Barnesiella* or *Roseburia*,

or predominance of the *Firmicutes*-dominated enterotype were associated with faster progression in PD [76, 124–126], whereas abundance of genus *Prevotella* was protective towards deterioration [125]. Lower abundance of *Ruminococcaceae* and *Actinobacteria* was also associated with faster deterioration in global cognitive function [126].

On the other hand, groups at risk of future PD development, such as iRBD subjects, display similar changes in GM observed in manifest PD patients. When compared to controls, both iRBD and early PD patients showed depletion in butyrate-producing bacteria (e.g., *Roseburia*), and increased abundance of proinflammatory *Collinsella* and mucin-degrading *Akkermansia* [127]. A progressive gradient in GM changes was also observed between healthy, constipated, prodromal PD (characterised by constipation, hyposmia and probable RBD) and PD individuals, showing a gradual decrease in total abundance of strict anaerobes with anti-inflammatory properties (including *Roseburia inulinivorans*, *Roseburia intestinalis* and *Faecalibacterium prausnitzii*) [128]. These studies complete the existing in vivo and in vitro studies supporting a causative role of GM in PD presented in the *Introduction* [19–22].

5 Conclusions

Pharmacomicrobiomics is an emerging discipline that investigates how medications interact with gut bacteria [23]. Being involved in medication biotransformation, the GM can modify the bioavailability of medications [28], including levodopa. By improving levodopa absorption, the modulation of the GM potentially offers a wide range of benefits in PD, from optimal medication management to treatment of disabling motor symptoms secondary to peripheral levodopa resistance. In this scenario, the development of levodopa formulations combined with inhibitors of both host AADC and gut microbial TDC represent one of the most exciting areas of future research.

Next to pharmacological interventions, dietary interventions and use of pre/probiotics intended to change the GM composition represent a future avenue in the PD symptomatic therapeutic pipeline. Moreover, GM-focused interventions, in particular FMT, are now under evaluation as disease-modifying therapies in PD. The research in this field is at an early stage but must face many important challenges. How can we distinguish 'responders' and 'non-responders' to GM-oriented interventions? Which clinical measure outcomes, microbial features, or combination thereof, can define the success of an intervention? Would acute/short-term interventions have long-term effects? Beyond individual personal preferences and intervention adherence that might influence the outcome, would these interventions benefit all patients, or only certain subtypes of PD? Addressing these and several other challenges is of paramount importance for the success of GM-based interventions in PD.

Declarations

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