

SYSTEMATIC REVIEW

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Efficacy and safety of fecal microbiota transplantation in the management of parkinson's disease: a systematic review

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Abstract

Background Parkinson's disease (PD) involves progressive neurodegeneration with motor and non-motor symptoms. Gut microbiota alterations are implicated in PD pathogenesis, leading to interest in fecal microbiota transplantation (FMT) as a therapeutic option. This systematic review assesses the efficacy and safety of FMT in managing PD symptoms.

Methods We conducted a comprehensive search across PubMed, Scopus, Web of Science, and Cochrane Central Controlled trials databases. Studies were screened based on predetermined inclusion criteria, focusing on randomized controlled trials (RCTs) involving FMT in PD patients. Two reviewers independently performed the data extraction and quality assessment. Key outcomes included improvements in motor and non-motor symptoms, quality of life, and adverse effects.

Results Five RCTs involving 157 patients met the inclusion criteria. Some studies reported improvements in motor and non-motor symptoms, particularly with colonic FMT, while others found no significant benefit. One trial observed motor function worsening. FMT was generally well-tolerated, with mild and transient gastrointestinal side effects.

Conclusion FMT may relieve PD symptoms, but findings are inconsistent. Larger trials with standardized protocols are needed to determine its long-term efficacy and safety.

Keywords Parkinson's disease, Fecal microbiota transplantation, Motor symptoms, Non-motor symptoms, Gut microbiota, Clinical trials, Systematic review

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Introduction

The idea of continuous, bidirectional communication between the brain and gut dates back to Ancient Greece, where philosophers like Hippocrates, Plato, and Aristotle proposed an intrinsic connection between the brain and the rest of the body [29]. These studies were constrained by basic techniques and a failure to examine how changes in gut physiology affect mental function [16]. Changes in gastrointestinal (GI) function and symptoms have been linked to many central nervous system (CNS) disorders. In conditions like Parkinson's disease, GI dysfunction may precede the onset of central neurological symptoms [5].

The human body is heavily colonized by microbes, with most residing in the gastrointestinal (GI) tract [26]. Recent research has highlighted the substantial role gut microbiota play in regulating central nervous system (CNS) function and neurodevelopment [46]. Gut microbiota (GMB) modulate immune responses in the intestine, periphery, and brain [18, 31, 41]. Interestingly, intestinal inflammation is often observed in PD patients [14], and gastrointestinal abnormalities like constipation frequently precede motor symptoms by several years [6, 51]. Braak's hypothesis proposes that abnormal accumulation of α -synuclein (α Syn) begins in the gut and then progresses to the brain via the vagus nerve [50]. However, the evidence linking gut microbiota to PD remains limited, and the mechanism by which α Syn aggregation originates in the enteric nervous system (ENS) and spreads to the CNS is still unclear [8].

Gut dysfunction is a common premotor symptom of PD and is associated with quicker disease progression [9, 25, 48]. GMB are thought to contribute to PD pathology, influencing both motor and non-motor symptoms and accelerating disease progression [1, 4, 12, 36, 43, 48, 49].

Studies on the gut microbiome have highlighted its significant role in regulating and influencing neurodegenerative diseases like PD. Specifically, they reveal that abnormalities in the gut microbiome of PD patients can trigger systemic inflammation, worsening gastrointestinal symptoms [33, 40]. Additionally, changes in gut microbiota are linked to PD symptoms and its underlying causes, suggesting that treatments targeting the gut microbiota could be effective for managing PD [40, 57].

Dysbiosis refers to an imbalanced microbiome, marked by a deficiency of certain beneficial and harmful bacteria and the metabolites and antigens they generate [3]. Despite the biological distinction between the brain and the gut, gut bacteria can interact with the central nervous system (CNS) through various mechanisms. These interactions involve the production of hormones, metabolites, and neuroactive substances that influence multiple systems, including the parasympathetic vagus nerve,

immune system, endocrine system, gastrointestinal system, and circulatory system [35].

Fecal microbiota transplantation (FMT), an intervention targeting GMB, demonstrated promising effects in animal models of PD, and potentially offering neuroprotective benefits [28, 42]. Zhao et al. demonstrated that FTM improved intestinal and motor dysfunctions in rotenone-treated mice while significantly reducing lipopolysaccharide levels in serum, colon, and CNS tissues. Their findings highlight how reshaping the gut microbiota can enhance IEB integrity and reduce immune and inflammatory processes [56].

FMT has been evaluated in various pathological conditions, including *Clostridium difficile* infection and ulcerative colitis, due to its ability to comprehensively regenerate gut microbiota, enhance microbial diversity, and restore abnormal intestinal flora (N. [22, 27]).

Segal et al. observed improvements in six PD patients following four weeks of FMT, with minimal side effects [45]. Another study found that FMT delivered through a nasoduodenal tube led to significant improvements, with mild and transient adverse effects [23]. Although the precise mechanisms behind FMT's effects remain unclear, they may be related to immune modulation and metabolic alterations [2, 53].

Although several randomized clinical trials have shown probiotics to be effective in alleviating constipation in PD, studies on FMT are limited and mostly uncontrolled. However, these studies suggest that FMT is both safe and beneficial for improving symptoms, regardless of the method of administration [32, 34, 44]. This systematic review aims to assess the efficacy and safety of FMT in patients with Parkinson's disease.

Methods

We conducted this systematic review and meta-analysis in accordance with the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [38]. The study protocol was registered in the Open Science Framework (OSF) database under DOI: <https://doi.org/https://doi.org/10.17605/OSF.IO/G72K4>

Search Strategy and Data Sources

We conducted a comprehensive search across four electronic databases: PubMed, Scopus, Web of Science, and Cochrane Central Controlled trials. The search strategy included keywords and synonyms related to FMT and Parkinson's disease. The search covered all records available up to May 2024. The search terms used were: ("Fecal Microbiota Transplant" OR "Intestinal Microbiota Transfer" OR "Fecal Bacteriotherapy" OR "FMT" OR "Stool

Transplantation") AND ("Parkinson's disease" OR "Parkinson disease").

Study Selection and Data Extraction

Two independent reviewers conducted the study selection process by screening the titles and abstracts of all identified studies. Then, we conducted full text review on articles that met the inclusion criteria. Discrepancies between reviewers were resolved by a third reviewer. Rayyan software was used to facilitate the screening process [37]. For data extraction, two reviewers independently extracted relevant information from each included study using Excel sheet, such as participant characteristics, intervention details, comparator treatments, outcomes (motor and non-motor symptoms, quality of life), and adverse effects. Any disagreements were resolved through consensus or consultation with the third reviewer.

Selection Criteria

This review included randomized controlled trials or observational studies of adults diagnosed with Parkinson's disease in which the treatment intervention evaluated was FMT, with comparator treatments that included standard care, placebo (e.g. sham transplantation), or other non-FMT interventions. The primary outcomes examined were improvements in motor symptoms, non-motor symptoms, and overall quality of life, while secondary outcomes focused on the safety and adverse effects of FMT.

Quality Assessment

The Cochrane Risk of Bias tool (RoB 2) [47] was used to evaluate the risk of bias in the included RCT studies across its seven domains, and the Newcastle–Ottawa Scale (NOS) was used for observational studies. Two independent reviewers assessed each study's quality and resolved conflicts through mutual agreement, with a third reviewer providing the final decision when necessary.

Results

Study Selection and Characteristics

The initial literature search yielded 710 records from four databases: PubMed (158), Scopus (372), Web of Science (148), and Cochrane Central Controlled Trials (32). After removing 361 duplicates using Rayyan software, 349 unique records remained for title and abstract screening. Of these, 328 articles were excluded for not meeting the relevance criteria, leaving 21 reports for full-text retrieval. Five of these reports could not be accessed, resulting in 16 articles being assessed for eligibility. Ultimately, five studies met the inclusion criteria for the

systematic review, all of which were RCTs involving a total of 157 patients. The PRISMA flow diagram illustrating the study selection process is shown in Fig. 1.

Aiming to provide a comprehensive review of the literature, we screened the entire body of publications to date regarding this topic. Only five studies could not be retrieved despite passing the initial screening criteria for our study. These five studies could not be retrieved as they were locked behind pay walls with no way to obtain them. Contacting the authors directly also yielded no results.

The five included studies on FMT in PD varied in sample size, duration, and outcome measures. Each study evaluated FMT's effects on both motor and non-motor symptoms of PD, investigating factors such as gut motility, alterations in gut microbiota, and dopaminergic medication use. The studies were conducted across different geographical locations and aimed to assess FMT's efficacy in improving PD-related symptoms.

In Scheperjans' 2024 study, an RCT comparing FMT to placebo that examined around 45 subjects (30 assigned to FMT and 15 to placebo), FMT caused transient GI events with no significant clinical improvements. The placebo group had a faster medication increase and minor gains. FMT led to stronger donor-dependent microbiota changes. Statistically, the Wexner constipation score showed no significant changes at 6 months ($P=0.33$) and 12 months ($P=0.08$). The TUG test (off medication) improved significantly at 6 months ($P=0.04$) but not at 12 months ($P=0.51$). The MoCA score did not show significant changes at 6 months ($P=0.07$). Total colon counts ($P=0.33$) and permeability ($P=0.88$) showed no significant changes. These results suggest limited overall efficacy, with only the TUG test showing significance at 6 months.

On the other hand, Bruggeman's 2024 study, an RCT on 46 subjects (22 assigned to donor FMT and 24 to placebo FMT), single FMT resulted in mild yet long-lasting improvements in motor symptoms in early-stage PD patients. Changes in MDS-UPDRS motor scores in the healthy donor FMT group were statistically significant ($P=0.0235$). However, no significant differences were observed between treatment groups for other assessed scores and scales.

In DuPont's 2023 pilot RCT study involving 12 patients (8 assigned to FMT and 4 to placebo), the study primarily focused on safety and reported transient gastrointestinal symptoms, along with slight improvements in gut function. FMT caused significant differences in beta diversity at 6 weeks ($P=0.008$) and 13 weeks ($P=0.0008$). At 13 weeks, three bacterial families were more abundant in the FMT group: Lactobacillaceae ($P=0.038$), Limnochordaceae ($P=0.014$), and Peptostreptococcaceae

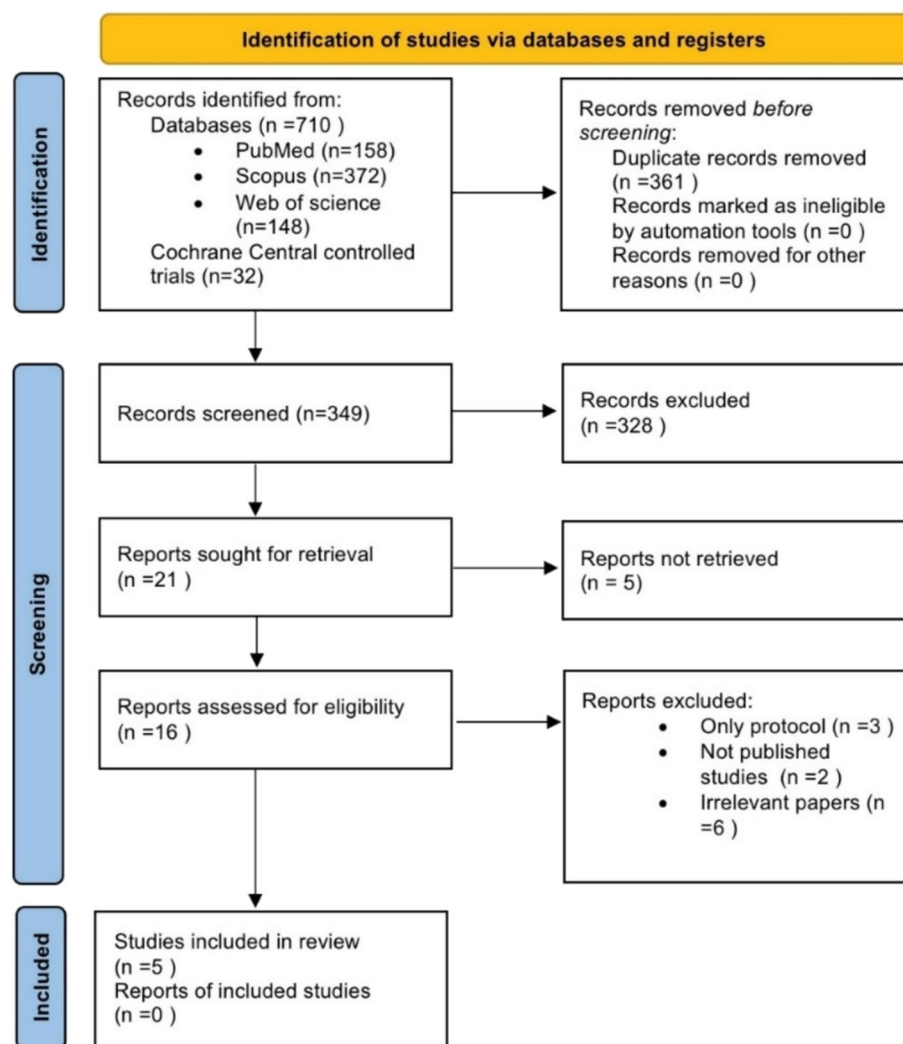


Fig. 1 PRISMA Flow diagram

($P=0.008$). Proteobacteriaceae was more abundant in the placebo group ($P=0.023$). Statistically significant improvements were noted in constipation, falls, sleep disorders, reduced smell, motor deficits, and overall PD symptoms at various time points.

In Cheng's 2023 RCT on 54 subjects (27 assigned to FMT and 27 to placebo) to compare FMT to placebo reported that FMT significantly improved PD symptoms through gut microbiota alterations. MDS-UPDRS total scores improved significantly at week 12 ($P<0.05$). Improvements were also noted in MDS-UPDRS Part 1 at weeks 4 and 12 ($P<0.05$), MMSE at week 4 ($P<0.01$), and MoCA at week 12 ($P<0.01$). IBS-SSS and GSRS scores improved significantly at weeks 4, 8, and 12 ($P<0.01$ and $P<0.001$, respectively). IBS-QOL and stool frequency also improved significantly at the same time points ($P<0.001$).

In Xue 2020 was a preliminary observational clinical trial on 15 patients (10 assigned to colonic FMT and 5 to nasointestinal FMT), nasointestinal FMT showed only slight UPDRS improvements. The PSQI, HAMD, HAMA, PDQ-39, NMSQ, and UPDRS-III scores decreased significantly after FMT (all $P<0.05$). The colonic FMT group showed significant improvement and longer maintenance of efficacy compared to nasointestinal FMT ($P=0.002$). The nasointestinal FMT group had no significant therapeutic effect, though the UPDRS-III score slightly reduced.

Overall, while FMT was generally well-tolerated, with most side effects being mild and transient, the efficacy results were mixed. Some studies showed modest improvements, while others reported minimal benefit, highlighting the need for further investigation into the long-term effects and potential of FMT in

treating Parkinson's disease. A summary of the included study characteristics is provided in Table 1, and the population characteristics of the included studies are presented in Table 2.

Risk of Bias of Included Studies

The risk of bias for the included studies was evaluated using two distinct tools based on study design: the RoB 2 for RCTs and the NOS for observational studies. In the randomized studies, the RoB 2 tool indicated that most studies had a low to moderate risk of bias, particularly in the selection and detection domains. However, potential weaknesses were observed in performance and attrition bias due to incomplete blinding and unexplained dropout rates. These issues were highlighted in Fig. 2.

The study by Xue et al. [54] received a score of 4 out of 9, indicating poor quality. In the Selection domain, it earned 2 out of 4 stars for clear patient selection criteria and a well-defined intervention, but its lack of a control group reduced representativeness. No stars were awarded in the Comparability domain due to the absence of a control group and lack of adjustments for confounding factors. In the Outcome domain, the study earned 2 out of 3 stars for utilizing standardized scales (UPDRS-III, HAMA, HAM-D, PSQI) and having an adequate follow-up period. Overall, while the RCTs demonstrated generally acceptable quality, the observational studies exhibited limitations that warrant caution in interpreting their findings.

Discussion

PD patients exhibit a less diverse gut microbiota with greater strain clustering compared to healthy individuals, who tend to have a more diverse microbiota. This observation has led to the exploration of FMT as a potential therapeutic intervention for PD (C. [27]). Alterations in the gut microbiome, such as a reduction in Firmicutes, have been associated with PD-related symptoms like constipation [55]. Although the exact mechanisms of FMT in PD remain unclear, gut microbiota and its metabolites may play a role in regulating neuroinflammation, potentially alleviating non-motor symptoms of PD [24, 39].

FMT has shown potential benefits, including improved gut motility and mood regulation [30], enhanced gut barrier function [13], lowered colonic luminal pH [52], increased production of short-chain fatty acids that promote gut contractions [11], and reduced levels of pro-inflammatory Proteobacteria [21].

Xue et al. [54] reported notable improvements in various scales, including the Pittsburgh Sleep Quality Index (PSQI), PD 39-Items Questionnaire (PDQ-39), Non-Motor Symptoms Questionnaire (NMSQ), Hamilton Anxiety Scale (HAMA), Hamilton Depression Scale

(HAM-D), and the Unified Parkinson's Disease Rating Scale III (UPDRS-III) one and three months after FMT. Despite the small sample size of 15 participants and the lack of a control group, the reported adverse effects were mild, consisting of diarrhea and abdominal discomfort. Colonic FMT was found to be more effective and safer than nasointestinal FMT, likely due to better microbiota colonization in the colon [15, 54]. This study's strengths include identifying key symptomatic improvements, but limitations include the small sample size and lack of a placebo group [54].

DuPont et al. [17] conducted a randomized controlled trial with 12 participants to assess the effects of oral FMT capsules in PD patients. Improvements were observed in the Non-Motor Symptoms Scale (NMS), PDQ-39, Geriatric Depression Scale (GDS), Parkinson's Anxiety Scale (PAS), and UPDRS, though only the UPDRS improvement reached statistical significance. While gastrointestinal side effects were more frequent in the FMT group, none were severe. The study's strength lies in its randomized controlled design and detailed statistical analysis. However, the small sample size limits the generalizability of findings, and the short follow-up duration of one month may not fully capture long-term effects [17].

In contrast, Scheperjans et al. [44] randomized 48 PD patients to receive either FMT or a placebo. They found no significant differences in MDS-UPDRS scores between groups. Interestingly, the FMT group exhibited an increase in Timed Up and Go (TUG) test time at the 6-month follow-up ($P=0.04$), indicating a decline in motor function, though this was not statistically significant at 12 months ($P=0.51$). Non-Motor Symptoms Scale scores also increased in the FMT group. Adverse events in the FMT group were double that of the placebo group, including all severe adverse events. Strengths include the randomized, double-blind design and detailed statistical analysis, such as the constrained longitudinal data analysis model. However, limited statistical significance across outcomes, participant exclusions, and short follow-up duration of 6 months limit the study's reliability. The findings challenge the efficacy of FMT in PD and highlight potential risks [44].

Cheng et al. [10] conducted the largest study on FMT in PD, involving 56 participants with mild to moderate PD. Improvements were observed in Mini-Mental State Examination (MMSE) scores and reductions in MDS-UPDRS total scores at 12 weeks, indicating enhanced cognitive function. However, no significant changes were found in anxiety or depression measures such as GAD-7, GDS-15, or PHQ-9. Strengths of this study include the larger sample size and comprehensive cognitive and motor assessments. Limitations include the absence of

Table 1 Summary of included studies

Study ID	Location	Year	Study Design	Total No. of Participants	Comparator	PD Disease Duration (years)	Outcome	Key Finding
Scheperjans 2024	Finland	2024	RCT	45	Placebo	5.78 (1.59)	MDS-UPDRS	FMT caused transient GI events with no significant clinical improvements. The placebo group had a faster medication increase and minor gains. FMT led to stronger donor-dependent microbiota changes
Bruggeman 2024	Belgium	2020–2021	RCT	46	Placebo	4.2 (0.7) in FMT / 4.4 (0.7) placebo	MDS-UPDRS, LEDD, PDQ-39, NMS	Single FMT resulted in mild yet long-lasting improvements in motor symptoms in early-stage PD patients
DuPont 2023	USA	2019–2020	RCT	12	Placebo	FMT 2 (1.7) placebo 5 (6.7)	GDS, PAS, NMS, PDQ-39	FMT caused mild, transient upper GI symptoms. It improved gut motility index ($p = 0.0374$) and showed non-significant improvement in gut transit times
Cheng 2023	China	2023	RCT	54	Placebo	FMT: 6.74 (4.00) / Placebo: 5.85 (4.35)	MDS-UPDRS	FMT significantly improved PD symptoms, attributed to gut microbiota alterations
Xue 2020	China	2020	Preliminary observational clinical trial	15	Nasointestinal FMT group	4.73 (3.17)	UPDRS-III, PSQI, PDQ-39	The naso-intestinal route showed only slight UPDRS improvements. Mild, self-limiting side effects occurred in 5 patients

Table 2 Baseline of the Characteristics of the included studies

Study ID	Groups	Males n (%)	BMI	Age Mean (SD)	LEDD (mg)	MDS-UPDRS Score				
						Total	Part 1	Part 2	Part 3	Part 4
Scheperjans 2024	FMT	16 (53.3%)	26.28 (2.42)	65 (8.17)	702.4 (487.38)	29.66 (12.45)	9.66 (6.32)	10.5 (5.83)	29.66 (12.45)	NA
	Placebo	9 (60%)	25.92 (1.85)	65 (8.58)	686.24 (447.17)	23.28 (10.5)	9 (2.45)	10 (5.72)	23.28 (10.5)	NA
Bruggeman 2024	FMT	15 (68.2%)	24.6 (0.8)	61 (1.1)	383 (53)	63.9 (4.2)	11.0 (1.3)	10.7 (1.3)	40.3 (2.7)	2.2 (0.6)
	Placebo	14 (58.3%)	24.3 (0.8)	60.5 (0.7)	431 (51)	58.2 (4.0)	10.6 (1.3)	8.0 (1.2)	37.1 (2.5)	2.6 (0.5)
DuPont 2023	FMT	5 (62.5%)	NA	68.1 (11.7)	211.3 (-33.5)	25 (10.9)	NA	NA	NA	NA
	Placebo	4 (100%)	NA	66 (15)	648.3 (419.3)	47.3 (36)	NA	NA	NA	NA
Cheng 2023	FMT	15 (55.56%)	22.33 (2.16)	60.52 (8.68)	NA	NA	11.1 (4.42)	12.04 (4.78)	24.74 (10.58)	3.44 (3.26)
	Placebo	17 (62.96%)	22.43 (2.16)	62.63 (8.41)	NA	NA	12.11 (4.89)	14.74 (4.89)	29.59 (13.07)	3.70 (3.20)
Xue 2020	Colonic FMT group	7 (70%)	NA	60.9 (8.16)	474 (219)	NA	NA	NA	45.30 (12.5)	NA
	Nasointestinal FMT group	4 (80%)	NA	60.2 (6.10)	370 (410)	NA	NA	NA	40.20 (19.42)	NA

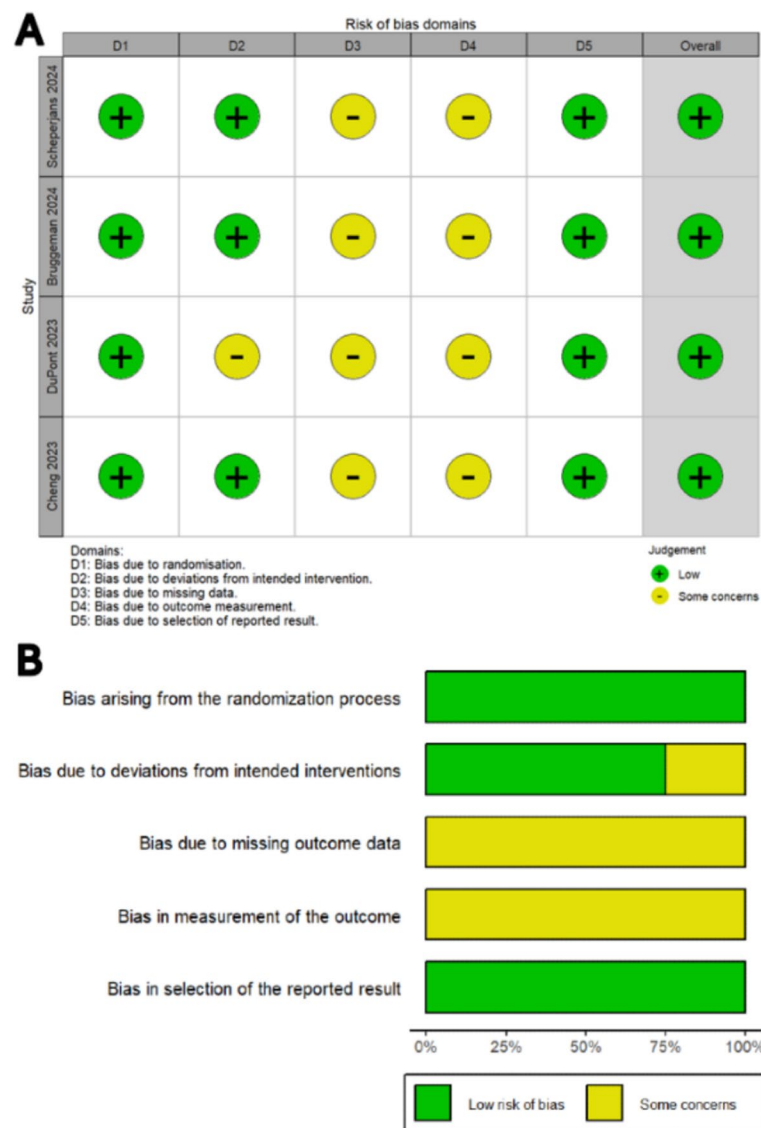


Fig. 2 Assessment of the Methodological Quality of the Included Trials, Evaluated Using the Cochrane Risk-of-Bias Tool (v. 2.0). **A** Risk of bias graph represents the percentage of each bias level for five items. **B** Risk of bias summary represents the level of specific items in each study

long-term follow-up and inconsistent results for non-motor outcomes [10].

[7] performed the GUT-PARFECT trial with 46 participants, which showed improvements in MDS-UPDRS scores in the FMT group compared to the placebo group. The study demonstrated a favorable safety profile, with adverse effects limited to transient abdominal discomfort [7]. This trial used nasojejunal FMT, which Xue et al. [54] had found to be less effective than colonic FMT [54]. The study's strength lies in its rigorous design and the consistency of motor improvements across multiple studies, while its limitation is the use of a delivery method that may affect colonization efficiency [7].

It is worth highlighting that all the studies, regardless of utilizing the old form of the Unified Parkinson's Disease Rating Scale (UPDRS), as in DuPont et al. [17] and Xue et al. [54], or the new MDS-UPDRS, as used in the other three studies, reported improvements on the respective scale, except for Scheperjans et al. [44], which found no significant change [17, 44, 54].

The original UPDRS was a 55-item scale covering four parts: non-motor aspects, motor experiences, motor examination, and motor complications [19]. Despite its widespread use, it lacked clarity in instructions and overlooked some non-motor symptoms. The revised MDS-UPDRS expanded to 65 items, maintained the four-part

structure, and introduced standardized scoring, detailed instructions, and better integration of non-motor aspects [20].

Scheperjans et al. [44] noted no significant improvement, possibly due to gut-brain axis dysregulation linked to fecal microbiota transplantation (FMT). This treatment might have adversely affected neuroinflammation and dopamine regulation, exacerbating motor and non-motor symptoms. Additionally, the higher gastrointestinal side effects in the FMT group may have contributed to the lack of observed benefits [44].

Despite these promising findings, our study is limited by a relatively small sample size of 157 participants, which may affect the generalizability of the results. Additionally, the included studies produced inconsistent outcomes, particularly Scheperjans et al. [44], who reported worsened clinical outcomes in the FMT group compared to the control group [44]. The studies also assessed a wide range of heterogeneous outcomes. To improve the reliability of future findings, we recommend conducting larger studies with standardized outcome reporting. Overall, FMT in PD may possibly alleviate various symptoms and is generally well-tolerated, with no significant adverse effects.

Conclusion

FMT was generally well-tolerated, with mild and transient gastrointestinal side effects being the most common adverse events. Despite these findings, the results remain inconsistent, and the small sample size of 157 patients limits the generalizability of the outcomes. Therefore, larger, well-designed studies with standardized outcome measures are needed to better understand the long-term efficacy and safety of FMT in PD management.

Authors' contributions

Yehia Nabil contributed to revising and organizing the manuscript, reviewing, and overseeing study conceptualization, design, and protocol development. Mohamed Mohsenz and Israa Qutob were responsible for screening and data extraction, with Wadi Sleibi reviewing these processes. Ghaida Majid Manasrah prepared the summary, baseline table, and references. Amr Hassan drafted the discussion, which was reviewed by Esraa Mohammed. Ali Abbas Dawoud handled the results section, outcome table, and reviewed the conclusion, with Roa Haddad assisting in reviewing the results. Salma Allam contributed to drafting the methods and managing the ROB2. Ayhan contributed to creating the PRISMA diagram, writing the abstract, data extraction, and conducting the quality assessment for an observational study by using New-Castle Ottawa Scale (NOS). The Risk of Bias (ROB 2) assessment was handled by Ghaida Majid Manasrah, Salma Allam, Roa Haddad, and Ali Abbas Dawoud, while Mohamed Mohsenz prepared the Risk of Bias graph, conclusion, and introduction.

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N/A.

Data Availability

datasets were generated or analysed during the current study.

Declarations

Ethical approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent was obtained from all individual participants included in the study.

Consent for publication

All authors' consent has been obtained by the corresponding author for publication.

Competing interest

The authors declare no competing interests.

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