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Microbiota-metabolite dysregulation in depressive and non-depressive Parkinson's disease: mechanistic and therapeutic implications

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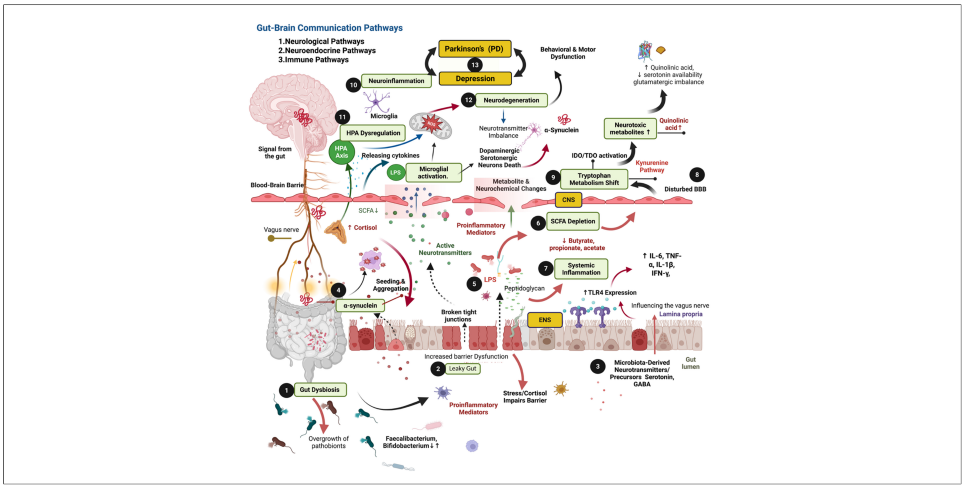

Abstract

Parkinson's disease (PD) is a progressive neurodegenerative disorder frequently accompanied by non-motor symptoms, among which depression is one of the most prevalent and disabling manifestations, affecting approximately 35%-50% of patients. Emerging evidence implicates gut microbiota dysbiosis and associated metabolic alterations in PD pathophysiology through the microbiota-gut-brain axis. This narrative review distinguishes between non-depressive Parkinson's disease (NDPD) and depressive Parkinson's disease (DPD) as clinically relevant phenotypes and synthesizes current evidence describing how microbiota-derived metabolites may contribute to their overlapping yet partially distinct neurobiological features. We focus on alterations in short-chain fatty acids (SCFAs), trimethylamine N-oxide (TMAO), and tryptophan-kynurenine pathway metabolites, which have been shown to influence immune activation,

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neuroinflammation, and monoaminergic signaling. Rather than functioning as independent disease drivers, these microbial and metabolic alterations are discussed as upstream modulators converging on shared molecular pathways, including Toll-like receptor 4 (TLR4)/nuclear factor kappa B (NF-κB) signaling, serotonergic dysfunction, and stress-associated neuroendocrine regulation. These mechanisms are implicated in both α-synuclein pathology and depressive symptomatology, providing a potential mechanistic basis for the coexistence of motor and depressive symptoms in PD. We further propose a gut-brain axis-centered framework in which microbiota-derived signals act as common upstream regulators of neurodegenerative and neuropsychiatric processes. Key microbial taxa, including *Faecalibacterium prausnitzii*, *Bifidobacterium*, and *Lactobacillus*, are highlighted as potential modulators of neuroimmune and neurochemical homeostasis. Collectively, current evidence supports the gut microbiota as a convergent biological interface linking neurodegeneration and depression in PD, with implications for biomarker discovery and microbiota-targeted therapeutic strategies.

INTRODUCTION

Parkinson's disease (PD) is a highly prevalent progressive neurodegenerative disorder whose global burden is rising rapidly alongside population aging; it is projected to affect over 17 million people by 2040[1,2]. Clinically, PD is characterized by motor dysfunction, including tremor, rigidity, bradykinesia, and gait impairment[3-5]. However, non-motor symptoms (NMS), particularly neuropsychiatric complications, are increasingly recognized as major contributors to disease burden and reduced quality of life[6]. Among these, depressive symptoms are particularly prevalent and debilitating, affecting approximately 35%-50% of patients[7], depending on diagnostic criteria and disease stage, substantially worsening motor function, cognition, and quality of life[8,9]. Importantly, depressive symptoms may precede motor dysfunction by several years, suggesting that they reflect early pathogenic processes rather than solely a psychological response to disability[10]. Depression in PD is further associated with accelerated motor progression[11], cognitive decline and poorer clinical outcomes[12,13].

Accumulating evidence implicates the microbiota-gut-brain axis in PD pathogenesis. Braak's staging hypothesis[14,15] proposes that pathological α-synuclein aggregation may originate within the enteric nervous system (ENS) before propagating centrally through the vagus nerve[16,17]. Consistent with this concept, experimental studies demonstrate that germ-free or microbiota-depleted α-synuclein-overexpressing mice exhibit attenuated motor deficits, whereas transplantation of microbiota derived from patients with PD exacerbates motor dysfunction relative to microbiota from healthy donors[18]. Clinical studies similarly report reproducible alterations in gut microbial composition and function in patients with PD[19]. These alterations have been linked to impaired intestinal barrier integrity, systemic inflammation, altered microbial metabolite production, and disrupted gut-brain signaling[20,21]. Neuroinflammation mediated by activated microglia and astrocytes is increasingly recognized as a central driver of PD progression and may also contribute to depressive symptomatology through disruption of monoaminergic pathways involved in mood regulation[22].

Although depression is highly prevalent in PD, depressive Parkinson's disease (DPD) and non-depressive Parkinson's disease (NDPD) are increasingly recognized as clinically relevant phenotypes with potentially distinct biological characteristics. Neuroimaging studies have demonstrated reduced serotonin transporter binding, diminished mesolimbic dopamine transporter availability, and greater prefrontal metabolic disruption in DPD relative to NDPD[23,24]. Cerebrospinal fluid (CSF) studies similarly report selective serotonergic abnormalities in DPD without equivalent alterations in dopaminergic or noradrenergic metabolites[25,26]. Nevertheless, depression in PD is biologically heterogeneous[9,27], and current studies are limited by inconsistent diagnostic criteria and inadequate phenotypic stratification. Furthermore, DPD should be distinguished from primary major depressive disorder (MDD), as depressive symptoms in PD occur within the context of ongoing nigrostriatal degeneration, α-synuclein pathology, and progressive

monoaminergic dysfunction[28,29]. Unlike MDD, in which serotonergic dysfunction predominates[30]. DPD involves concurrent (dopaminergic, serotonergic, and noradrenergic deficits alongside neuroinflammatory processes driven by Lewy body pathology[9].These distinct metabolic patterns may help in the early differentiation of DPD from MDD in patients with depression, suggesting a distinct neurobiological substrate that may respond differently to both conventional antidepressant therapies and microbiota-targeted interventions.

Emerging evidence suggests that microbiota-derived metabolites may represent a mechanistic interface linking neurodegenerative and neuropsychiatric processes in PD. Alterations in short-chain fatty acids (SCFAs), trimethylamine N-oxide (TMAO), bile acids (BAs), and tryptophan-kynurenine pathway metabolites have been associated with neuroinflammation, intestinal permeability, immune activation, and altered serotonergic signaling[31]. Rather than acting as isolated disease drivers, these microbial and metabolic alterations may converge on shared molecular pathways, including Toll-like receptor 4 (TLR4)/nuclear factor kappa B (NF-κB) signaling, microglial activation, and stress-associated neuroendocrine dysregulation, thereby influencing both α-synuclein pathology and depressive symptomatology. However, whether distinct microbiota-metabolite signatures consistently differentiate DPD from NDPD remains unclear because of limited and heterogeneous evidence.

This review examines current evidence linking microbiota-metabolite dysregulation with depressive and non-depressive phenotypes in PD. We synthesize findings from microbiome, metabolomic, and experimental studies to evaluate how gut microbial metabolites may influence neuroinflammation, monoaminergic dysfunction, α-synuclein pathology, and gut-brain communication. We further discuss the mechanistic and therapeutic implications of microbiota-targeted interventions, including probiotics, prebiotics, dietary modulation, and metabolite-based strategies, while highlighting current limitations and key directions for future translational research.

GUT MICROBIOTA IN NEUROINFLAMMATION: FROM DYSBIOSIS TO PARKINSON'S PATHOGENESIS

The gut microbiota is a complex and dynamic microbial community shaped by host genetics, diet, aging, and environmental exposures[32]. In recent years, its role as a key modulator of the gut-brain axis (GBA), a bidirectional network of neural, immune, and endocrine pathways, has become a focal point in understanding neurological disorders, including PD[33]. A balanced gut microbiome supports intestinal barrier integrity, regulates immune function, and produces bioactive metabolites essential for systemic homeostasis[34]. Conversely, gut dysbiosis characterized by overgrowth of harmful species and reduction of beneficial ones disrupts this equilibrium. These disruptions can compromise the gut barrier, resulting in a "leaky gut", which allows microbial products such as lipopolysaccharides (LPS) to translocate into systemic circulation[35,36]. Once in the bloodstream, LPS can trigger systemic inflammation and, crucially, promote neuroinflammation by activating microglia and astrocytes. This effect is amplified when the blood-brain barrier is compromised[37]. This cascade of events positions gut dysbiosis as a critical upstream factor in the neuroinflammatory processes central to PD pathogenesis.

Microbial signatures in NDPD

Studies specifically stratifying DPD and NDPD remain limited, and further heterogeneity arises from the fact that most available studies do not stratify patients according to disease stage or motor subtype. Early-stage PD is characterized predominantly by nigrostriatal dopaminergic dysfunction with relatively preserved gut microbiome diversity, whereas advanced disease is associated with more pronounced dysbiosis, greater intestinal barrier disruption, and broader monoaminergic involvement including serotonergic and noradrenergic systems, which may differentially influence vulnerability to depressive symptoms[38]. The tremor-dominant subtype has generally been associated with a more benign disease course and slower

progression compared with the PIGD subtype, which exhibits greater cognitive impairment, autonomic dysfunction, and potentially greater neuroimmune dysregulation[39]. These differences suggest that microbial signatures and their functional consequences may vary substantially across disease stages and subtypes, further complicating efforts to define reproducible DPD-specific microbiota alterations. Consequently, much of the current understanding of microbial signatures in NDPD is derived from broader PD cohorts in which depressive status was either not assessed or not reported. Although this represents an important limitation of the existing literature, these studies provide an essential reference framework for evaluating microbiota alterations potentially associated with depressive phenotypes in PD.

Clinical studies have identified relatively reproducible alterations in the gut microbiota of patients with PD without comorbid depression, although considerable variability remains across cohorts and analytical approaches[40,41]. At the family level, a meta-analysis by Shen *et al.* reported decreased abundance of Prevotellaceae, Lachnospiraceae, and Ruminococcaceae, alongside increased Bifidobacteriaceae, Lactobacillaceae, Verrucomicrobiaceae, and Christensenellaceae in PD cohorts[42]. Genus-level alterations in *Prevotella*, *Bacteroides*, and *Faecalibacterium* have been described in individual case-control studies but did not reach significance in this meta-analytic synthesis[42,43]. In parallel, several cohort studies have observed enrichment of *Akkermansia*, *Lactobacillus*, and *Bifidobacterium* in PD[44]. The relative abundance of Enterobacteriaceae was positively associated with the severity of postural instability and gait difficulty (PIGD)[45]. In contrast, Barichella *et al.* reported that decreased Lachnospiraceae and increased Lactobacillaceae and Christensenellaceae were linked to worse clinical profiles including cognitive impairment and gait disturbances[46].

Constipated PD patients additionally exhibit increased relative abundances of Bifidobacteriales and Lactobacillales[47,48]. The reduction in SCFA-producing taxa, including *Roseburia* and *Faecalibacterium,* is of particular mechanistic relevance, as it may reduce butyrate production, a metabolite that supports intestinal barrier integrity and exerts anti-inflammatory effects[49,50]. Animal models of PD display analogous microbial alterations, and microbiota-targeted interventions can partially ameliorate motor dysfunctions[51]. Notably, Bifidobacteriaceae abundance at the family level is reported as elevated in PD relative to healthy controls.

Distinct dysbiosis in DPD

Depression, affecting a substantial subset of patients with PD, is associated with gut microbial alterations that partially overlap with, yet remain distinct from, those observed in non-depressive PD[13,52]. Although both phenotypes share core features of dysbiosis, DPD appears to exhibit more pronounced alterations in microbial communities implicated in gut-brain and neuroimmune signaling pathways. Several studies have reported reductions in commensal and short-chain fatty acid-producing genera, including *Prevotella, Romboutsia,* and *Roseburia*, together with enrichment of pro-inflammatory taxa such as Deltaproteobacteria in DPD[53]. Importantly, these microbial alterations correlate more strongly with depressive symptom severity than with overall motor or non-motor disease burden, indicating that these microbial alterations are associated with depressive symptoms rather than general PD progression [Figure 1].

Experimental evidence further supports the association between depressive phenotypes and gut dysbiosis in PD. In a rotenone-induced PD model with depression-like behavior, dysbiosis was characterized by increased Firmicutes and Proteobacteria together with decreased *Bacteroidetes*, *Actinobacteria*, *Bacteroides*, *Alistipes*, and *Lactobacillus reuteri*. Notably, these microbial alterations were partially reversed following prebiotic intervention[54]. Direct comparative studies involving PD, DPD, and MDD further suggest that DPD may possess partially distinct microbial characteristics. One recent study reported higher relative abundance of Megamonas in MDD compared with PD and DPD, whereas *Prevotella* abundance was lower in MDD. In contrast, *Escherichia-Shigella* was more abundant in PD than in DPD and MDD. Within the

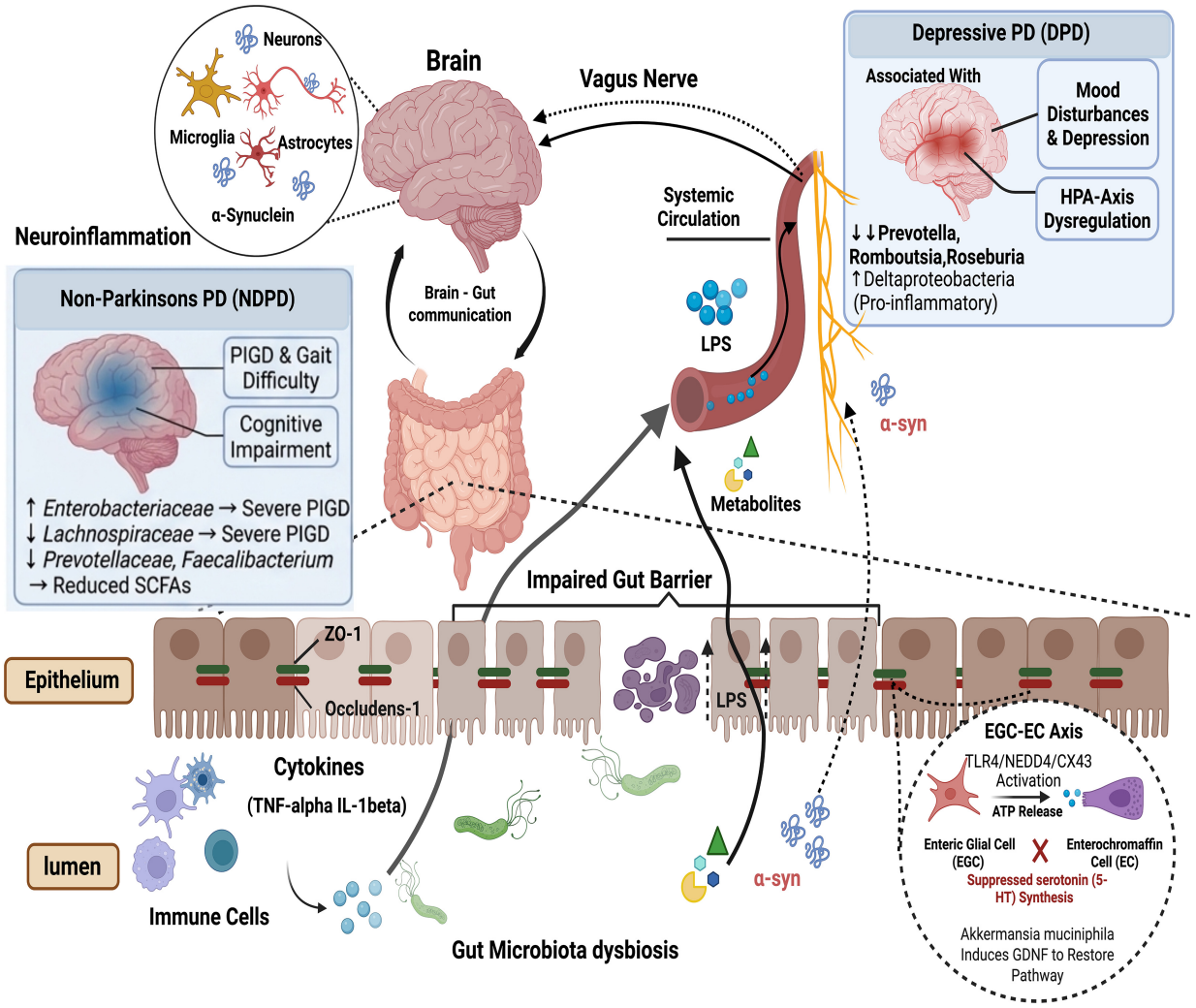

Figure 1. Gut microbial signatures associated with depressive and non-depressive PD. Schematic overview of gut microbiota alterations reported in DPD and NDPD. DPD is characterized by reduced abundances of *Roseburia*, *Romboutsia*, *Butyricicoccus*, *Prevotella*, *Faecalibacterium*, *Bifidobacterium*, *Coprococcus*, *Blautia*, and *Lactobacilli*, together with enrichment of *Bacteroides*, *Escherichia-Shigella*, *unclassified Deltaproteobacteria*, and members of *Ruminococcaceae*. In contrast, NDPD exhibits microbial alterations involving increased *Akkermansia*, *Lactobacillus*, *Enterococcus*, *Bifidobacterium*, *Coprococcus*, and Ruminococcaceae, alongside reduced *Prevotella*. Variability in the reported abundance of *Faecalibacterium* and *Roseburia* across NDPD studies likely reflects differences in cohort characteristics, disease stage, medication exposure, and analytical methodologies. Arrows indicate relative increases (↑) or decreases (↓) in microbial abundance compared with healthy controls. The figure was created with BioRender.com. PD: Parkinson's disease; DPD: depressive Parkinson's disease; NDPD: non-depressive Parkinson's disease; TNF-α: tumour necrosis factor-alpha; IL-1β: interleukin-1 beta; EGC: enteric glial cell; EC: enterochromaffin cell; LPS: lipopolysaccharide; HPA: hypothalamic-pituitary-adrenal.

DPD cohort, resilience scores positively correlated with *Vibrio* and *Shewanella*, whereas rumination scores positively correlated with *Hydrogenophaga* and *Rhodococcus*. These findings indicate that specific microbial taxa may be associated with distinct psychological dimensions of DPD. Collectively, the microbial signatures reported in DPD only partially overlap with those described in MDD, suggesting that while shared dysbiotic features exist, DPD possesses a partially distinct microbiota profile shaped by the concurrent neurodegenerative context of PD[55].

Neurotransmitter modulation by the gut microbiota

Gut microbiota significantly influence the synthesis, metabolism, and signaling of several neurotransmitters involved in gut-brain communication, including dopamine (DA), serotonin (5-HT), γ-aminobutyric acid (GABA), noradrenaline (NA), acetylcholine, and histamine[56]. Increasing evidence suggests that microbial

dysbiosis can alter neurotransmitter homeostasis and contribute to neurological and neuropsychiatric disorders, including PD and depression[57,58]. Certain microbial taxa can directly produce neuroactive compounds or regulate host neurotransmitter precursor availability[56]. For instance, species of *Lactobacilli* and *Bifidobacteria* can produce GABA, while *Escherichia coli* influences 5-HT and DA, and *Lactobacilli* can additionally synthesize acetylcholine[56,59]. Disruption of this microbial neurochemical balance may therefore influence central nervous system (CNS) function through the microbiota-gut-brain axis.

Neurotransmitter dysregulation appears particularly relevant in DPD. According to Braak staging, serotonergic nuclei may become affected during relatively early stages of PD progression. CSF studies have reported reduced concentrations of 5-hydroxyindoleacetic acid (5-HIAA), a major serotonin metabolite, in patients with DPD compared with NDPD[26]. A more recent metabolomic study further demonstrated that dopaminergic and noradrenergic metabolites, including DA, 3,4-dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA), noradrenaline, and 3-methoxy-4-hydroxyphenylglycol (MHPG), did not differ significantly between DPD and NDPD, whereas serotonin-related pathway alterations were more prominent[25,60]. These findings support the hypothesis that depression in PD involves neurochemical disturbances extending beyond classical dopaminergic degeneration.

However, not all studies report consistent serotonergic alterations in DPD. Lian *et al.* (2020) measured CSF dopamine, serotonin, and norepinephrine concentrations in patients with DPD and NDPD and observed significantly lower dopamine levels in DPD, whereas serotonin and norepinephrine did not differ between groups[61,62]. Moreover, depressive symptom severity negatively correlated only with dopamine levels, suggesting that dopaminergic dysfunction may also substantially contribute to depressive manifestations in PD.

Preclinical studies further support a role for the gut microbiota in modulating neurotransmitter pathways relevant to PD. Administration of specific probiotic strains has been shown to increase dopamine concentrations in frontal brain regions in rodent models, while in vitro studies demonstrated that *Enterococcus faecium* can convert levodopa into dopamine under gastrointestinal-like conditions[63]. These findings suggest that microbiota-targeted interventions may influence neurotransmitter balance and potentially modulate both motor and depressive symptoms in PD.

Gut microbial metabolites in PD

Gut microbial metabolites are increasingly recognized as functional mediators linking intestinal dysbiosis with neuroinflammation, neurotransmitter imbalance, and neurodegeneration in PD[64]. Beyond microbial taxonomic composition, microbiota-derived metabolites represent a critical functional layer through which the gut microbiome influences CNS physiology[65]. A substantial proportion of circulating metabolites are either directly produced or extensively modified by the gut microbiota, including SCFAs, TMAO, BAs, and amino acid-derived metabolites, many of which exert important metabolic, immunological, and neuroactive effects[66,67].

These microbiota-derived metabolites function as key mediators linking gut dysbiosis with neuroinflammation and gut-brain signaling in PD, as summarized in Figure 2.

Most currently available metabolomic evidence is derived from general PD cohorts without stratification according to depression status, whereas DPD-specific studies remain limited and methodologically heterogeneous. Nevertheless, emerging evidence suggests that although several metabolic disturbances are shared across PD phenotypes, DPD may involve additional alterations associated with serotonergic dysfunction, inflammatory signaling, and stress-related neuroendocrine pathways[25]. The following sections

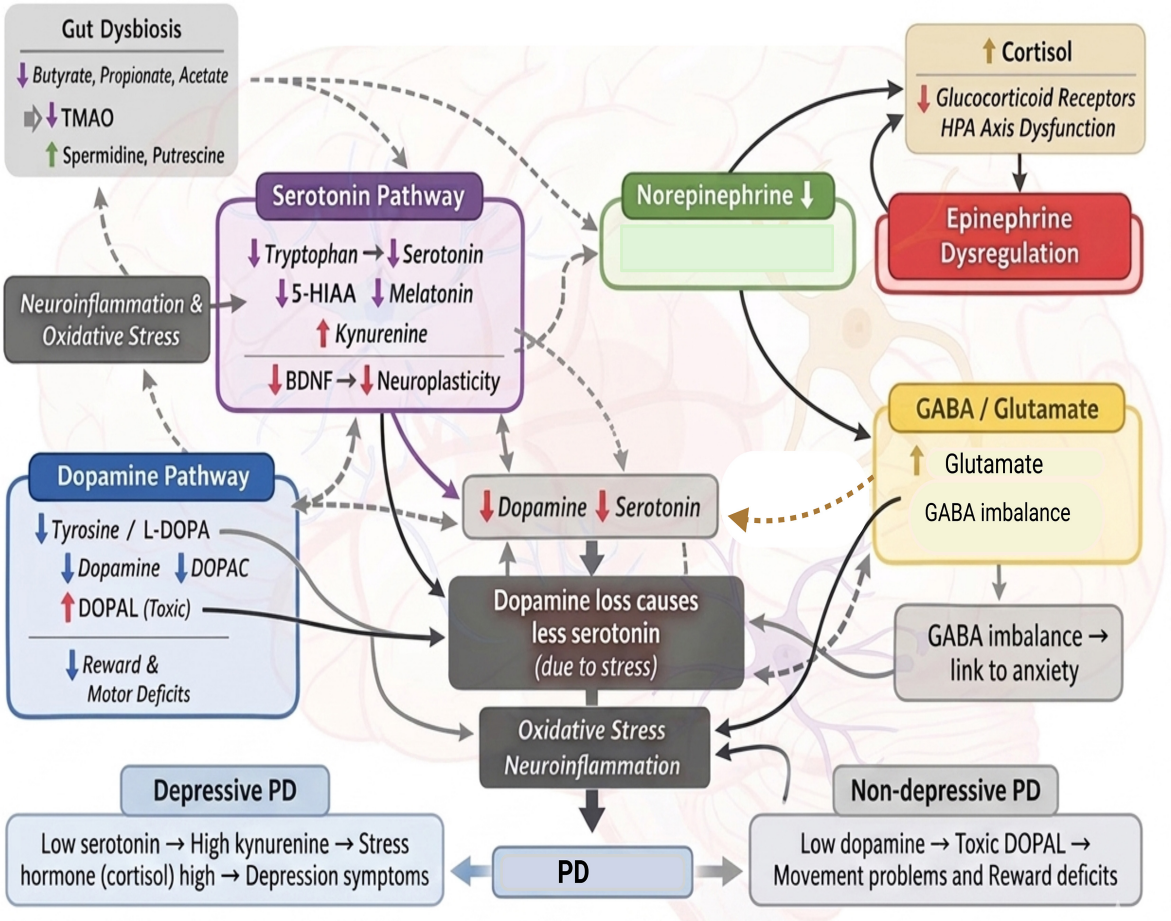

Figure 2. Proposed microbiota-metabolite-neurotransmitter framework underlying depressive and non-depressive Parkinson's disease. The illustration summarizes how gut dysbiosis and altered microbial metabolites may contribute to the pathophysiology of DPD and NDPD through interconnected neuroinflammatory and neurotransmitter-associated pathways. Gut dysbiosis is characterized by reduced SCFAs (butyrate, propionate, and acetate), increased TMAO, and altered polyamine metabolism, promoting oxidative stress and neuroinflammation. These alterations disrupt multiple neurotransmitter pathways, including serotonin, dopamine, norepinephrine, epinephrine, and GABA/glutamate signaling. Dysregulation of the tryptophan-serotonin pathway is associated with reduced serotonin, 5-HIAA, melatonin, BDNF, and neuroplasticity, alongside increased kynurenine pathway activity. Concurrent impairment of dopaminergic metabolism, characterized by reduced tyrosine/L-DOPA availability, decreased dopamine and DOPAC levels, and accumulation of toxic DOPAL, contributes to motor dysfunction and altered reward processing. HPA axis dysfunction, increased cortisol signaling, and GABA/glutamate imbalance further promote excitotoxicity, anxiety, cognitive dysfunction, and depressive symptomatology. Collectively, these interconnected microbiota-metabolite and neurochemical disturbances converge on oxidative stress and neuroinflammatory pathways, contributing to the divergent neuropsychiatric manifestations of DPD and NDPD. Colored arrows in the figure represent distinct mechanistic associations: purple arrows indicate alterations involving serotonin-related pathways and gut microbiota-mediated serotonergic regulation; yellow arrows denote glutamatergic/GABAergic neurotransmitter imbalance and related signaling interactions; red arrows indicate pathological changes, including increased or decreased expression/activity of key molecules or neurotransmitters. Solid arrows represent established mechanistic links, while dashed arrows indicate indirect or emerging associations. The figure was created with BioRender.com. 5-HIAA: 5-hydroxyindoleacetic acid; BDNF: brain-derived neurotrophic factor; DOPAC: 3,4-dihydroxyphenylacetic acid; DHBA: 3,4-dihydroxyphenylacetaldehyde; GABA: gamma-aminobutyric acid; HPA: hypothalamic-pituitary-adrenal; SCFAs: short-chain fatty acids; TMAO: trimethylamine N-oxide.

summarize the principal metabolite-associated mechanisms implicated in PD and highlight pathways that may preferentially contribute to depressive symptomatology.

SCFAs

Patients with PD harbor a significantly reduced abundance of the SCFA-producing colonic bacteria Lachnospiraceae and Ruminococcaceae, with a concomitant reduction in the levels of SCFAs[68], including acetate, propionate, and butyrate, are generated through bacterial fermentation of dietary fiber and play

important roles in intestinal and immune homeostasis[69]. Clinical studies have further demonstrated that reduced SCFA levels and depletion of butyrate-producing bacteria correlate with motor and non-motor symptom severity in PD[70].

Several independent cohorts across different geographic populations have consistently reported reductions in SCFA-producing taxa, including *Roseburia*, *Eubacterium rectale*, *Ruminococcus*, *Blautia*, *Faecalibacterium prausnitzii*, and *Coprococcus* in PD[71,72]. These microbial alterations are associated with impaired colonic motility, increased intestinal permeability, and mucosal inflammation, suggesting sustained low-grade intestinal immune activation[64]. Integrated fecal and plasma metabolomic studies additionally demonstrated significantly lower fecal concentrations of acetate, propionate, and butyrate in patients with PD compared with healthy controls, with fecal SCFA depletion inversely correlating with Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) motor scores after adjustment for anti-PD medication dosage. In contrast, plasma concentrations of propionate and butyrate were elevated in PD, potentially reflecting increased intestinal permeability and systemic translocation of luminal metabolites[69].

Metabolic modeling studies further predicted that reduced abundances of *Faecalibacterium prausnitzii* and *Roseburia intestinalis* contribute to diminished butyrate and leucine production in PD-associated metabolomic profiles, identifying these taxa as potential targets for microbiota-based interventions[73]. Supporting this concept, oral administration of Faecalibacterium prausnitzii in α-synuclein-overexpressing mice improved motor and gastrointestinal dysfunction, reduced α-synuclein aggregation, and promoted anti-inflammatory immune responses[74]. These findings further support the potential contribution of SCFA-producing bacteria to neuroimmune regulation and disease modulation in PD.

In DPD, SCFA depletion may have additional relevance to depressive symptomatology. Fecal butyrate levels inversely correlate with depressive symptom severity measured by the Geriatric Depression Scale (GDS-15), while reduced abundances of *Prevotella*, *Romboutsia*, and *Roseburia* are associated with higher depression scores. Genome-wide DNA methylation analyses further revealed that butyrate-associated epigenetic alterations in leukocytes and neurons overlapped with genes dysregulated in the PD prefrontal cortex and converged on PD-related immune pathways, particularly neutrophil degranulation and innate immune signaling[53]. Another clinical study similarly reported that lower serum propionate concentrations were associated with worse motor performance, cognitive impairment, and higher Hamilton Depression Rating Scale (HAMD) scores in PD[75]. Although direct comparisons between depressive and non-depressive PD remain limited, current evidence suggests that DPD may involve more pronounced disruption of SCFA-associated microbial and metabolic pathways. Preclinical studies additionally support a broader role for SCFAs in non-motor manifestations of PD. Butyrate supplementation improved abnormal sleep architecture and behavioral deficits in PD mouse models[76]. Together, these observations highlight the potential relevance of SCFA dysregulation to both motor and non-motor manifestations of PD.

TMAO

TMAO is a gut microbial metabolite generated from dietary precursors including choline, phosphatidylcholine/lecithin, L-carnitine, betaine, and γ-butyrobetaine. Gut bacteria convert these substrates into trimethylamine (TMA) through enzymes such as CutC/D and CntA/B, after which TMA is absorbed and primarily oxidized in the liver by flavin-containing monooxygenase 3 (FMO3), with a smaller contribution from FMO1, to produce circulating TMAO[77].

TMAO has emerged as an important metabolite at the intersection of gut-brain signaling and systemic inflammation[78,79]. Experimental studies demonstrate that TMAO activates the NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) inflammasome through the SIRT3-SOD2 mitochondrial reactive

oxygen species signaling pathway, promoting release of caspase-1, interleukin-1β, and downstream pro-inflammatory mediators[80,81]. At the cerebrovascular level, TMAO disrupts tight junction integrity in brain microvascular endothelial cells by reducing expression of occludin, claudin-1, and ZO-1, thereby increasing blood-brain barrier permeability and facilitating neuroinflammatory signaling[82]. In 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced PD mouse models, TMAO increased activation of astrocytes and microglia in the striatum, substantia nigra, and hippocampus while elevating tumour necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL-1β) levels, findings consistent with glial-driven neuroinflammation[83]. Given that PD pathology is strongly associated with α-synuclein misfolding and aggregation, the interaction between TMAO and α-synuclein has attracted increasing attention. In vitro studies demonstrated that TMAO promotes conformational changes in α-synuclein toward a more compact structural state, suggesting a potential role in protein aggregation dynamics[84].

Clinical evidence regarding TMAO in PD remains inconsistent. While several studies associate elevated circulating TMAO levels with worse motor symptoms and cognitive decline, others report opposite or non-significant associations, indicating a potentially context-dependent and non-linear relationship with disease progression[85]. In a cross-sectional study comparing patients with PD and healthy controls, increased abundances of TMAO-producing bacteria, including Lachnospiraceae and Enterobacteriaceae, were accompanied by elevated plasma and urinary TMAO concentrations in PD. TMAO levels positively correlated with MDS-UPDRS III motor scores and non-motor symptom severity, while functional analyses demonstrated enrichment of microbial TMAO biosynthesis pathways[86]. These findings suggest that gut-derived TMAO may contribute to PD progression and could represent a potential biomarker or therapeutic target.

In the context of DPD, microbial depletion of choline, an essential methyl donor involved in S-adenosylmethionine (SAM)-dependent DNA methylation, has been linked to depressive-like phenotypes in experimental models[87,88]. This observation raises the possibility that TMAO-associated microbial choline metabolism may influence epigenetic regulation and mood-related pathways in DPD. However, direct evidence linking TMAO dysregulation with depressive phenotypes in PD remains limited, and further studies using clinically stratified DPD and NDPD cohorts are required.

Amino acid and tryptophan kynurenine metabolism

The gut microbiota plays a central role in regulating host amino acid availability and metabolism[89], with important consequences for neurotransmitter synthesis and immune homeostasis[56]. In PD, fecal and serum metabolomic studies consistently report reduced concentrations of branched-chain amino acids (BCAAs) and aromatic amino acids (AAAs) compared with healthy controls[90], alterations associated with gut microbial dysbiosis[89]. Because tyrosine and phenylalanine serve as essential precursors for dopamine synthesis, disruption of amino acid availability may contribute to impaired dopaminergic homeostasis in PD. Preclinical studies further demonstrate that BCAA-enriched dietary interventions attenuate pro-inflammatory responses, restore intestinal barrier integrity, and protect dopaminergic neurons, resulting in improved motor performance[91]. Metabolic modeling additionally predicts that reduced abundance of Roseburia intestinalis contributes to decreased L-leucine production in PD-associated metabolomic profiles, providing a mechanistic link between microbial dysbiosis and BCAA depletion in PD[73].

Tryptophan metabolism represents another major pathway linking gut microbial activity with neurodegeneration and depressive symptomatology in PD[92,93]. Within the gastrointestinal tract, tryptophan is metabolized through three principal pathways: the serotonin pathway, the kynurenine pathway (KP), and the indole pathway, all of which are directly or indirectly influenced by the gut microbiota[94]. Among these, KP dysregulation has emerged as a prominent metabolic feature of PD. Clinical studies report reduced

concentrations of the neuroprotective metabolite kynurenic acid (KA) together with elevated levels of the neurotoxic metabolites 3-hydroxykynurenine (3-HK) and quinolinic acid (QA) in plasma and CSF of patients with PD[95]. In a cohort study including 177 patients with PD and 158 healthy controls, the neuroexcitatory QA/KA ratio was significantly elevated in both plasma and CSF and was associated with inflammation and vitamin B6 deficiency. Increased QA concentrations additionally correlated with greater motor and non-motor symptom severity as well as elevated CSF tau and sTREM2 levels[95]. These findings position the KP as an important metabolic interface linking inflammation, microbial dysbiosis, and neurodegeneration in PD.

Gut microbial dysbiosis may further amplify KP-associated neurotoxicity. Depletion of SCFA-producing taxa, including Faecalibacterium and Prevotellaceae, may contribute to loss of SCFA-mediated epigenetic regulation of kynurenine monooxygenase (KMO), thereby promoting accumulation of 3-HK and QA, although this mechanism remains to be experimentally validated[92]. In contrast, indole pathway metabolites such as indole-3-propionic acid (IPA), indole-3-acetic acid (IAA), and indole-3-lactic acid (ILA), generated by *Lactobacillus*, *Bifidobacterium*, and *Clostridium* species, exhibit neuroprotective and anti-inflammatory properties. These metabolites reduce intestinal permeability, attenuate peripheral inflammation, and modulate glial cell activity through activation of the aryl hydrocarbon receptor (AHR)[92,93].

Emerging evidence suggests that DPD may exhibit more pronounced disturbances in tryptophan-related metabolic pathways than NDPD. Untargeted metabolomic analysis in a large population-based cohort identified 6-hydroxy-1H-indole-3-acetamide as a depression-associated metabolite; however, supplementary analyses showed that its levels were strongly associated with current selective serotonin reuptake inhibitor (SSRI)/serotonin-norepinephrine reuptake inhibitor (SNRI) use, suggesting that it may primarily reflect recent antidepressant treatment rather than the underlying pathophysiology of depression in PD[25]. Additionally, Lin *et al.* identified dysregulation of 14 metabolic pathways in PD patients with depression, with glycerophospholipid metabolism associated with both depression history and current depressive symptoms, while tryptophan, tyrosine, folate, and biopterin metabolism were primarily associated with higher Geriatric Depression Scale (GDS) scores[25]. Alterations in GABA-associated microbial pathways may also contribute to depressive symptomatology in PD. *Lactobacillus* and *Bifidobacterium* species[58], participate in microbial GABA production, and reduced abundance of these taxa in DPD may influence gut-brain signaling through vagal, inflammatory, and hypothalamic-pituitary-adrenal-axis associated mechanisms[96].

Taken together, current evidence suggests that gut microbiota-associated amino acid and tryptophan metabolism contribute to both neurodegenerative and depressive manifestations of PD through interconnected inflammatory, serotonergic, and microbial metabolic pathways.

BAs and vitamins

BAs are increasingly recognized as important signaling molecules within the GBA, and their dysregulation has been implicated in both PD and depressive disorders. Patients with PD exhibit altered BA profiles characterized by reduced levels of secondary BAs, particularly deoxycholic acid (DCA) and lithocholic acid (LCA), consistent with decreased abundance of BA-metabolizing bacterial taxa including *Clostridium* clusters[97]. Disruption of BA signaling may contribute to PD pathophysiology through multiple mechanisms. Reduced activation of the BA receptor Takeda G protein-coupled receptor 5 (TGR5) impairs glucagon-like peptide-1 (GLP-1) release, a pathway with established neuroprotective effects on dopaminergic neurons[98]. In addition, specific BAs, particularly LCA, act as ligands for the pregnane X receptor (PXR) and vitamin D receptor (VDR)[99], pathways capable of modulating hypothalamic-pituitary-adrenal (HPA) activity and stress-associated signaling[100].

Microbiota-modified BAs also exhibit direct neuroprotective and anti-inflammatory properties. Tauroursodeoxycholic acid (TUDCA) suppresses NLRP3 inflammasome activation, attenuates oxidative stress, and restores monoaminergic balance in experimental models[101]. In chronic PD mouse models, TUDCA protected dopaminergic neurons against MPTP-induced degeneration, reduced microglial and astroglial activation, and inhibited α-synuclein aggregation[102]. A systematic review of thirty-five preclinical studies confirmed that both UDCA and TUDCA are beneficial in Parkinson's disease and depression models specifically, with TUDCA the most effective BA for neuropsychiatric experimental models[103]. Metabolomic studies in MDD similarly report reduced DCA and LCA levels associated with depressive symptom severity, suggesting partially overlapping BA disturbances between depression and DPD[104].

Microbiota-derived vitamins additionally contribute to metabolic and neurotransmitter homeostasis in PD. B-vitamins function as essential cofactors in amino acid metabolism, KP regulation, homocysteine metabolism, and synthesis of neurotransmitters including serotonin, dopamine, GABA, glutamate, and acetylcholine[105]. Metabolomic analyses further identified dysregulation of folate and tetrahydrobiopterin (BH4) pathways in DPD, findings mechanistically linked to impaired serotonergic and dopaminergic neurotransmitter synthesis because BH4 serves as a critical enzymatic cofactor for both pathways[106]. In addition, microbiota-associated folate metabolism has been implicated in depression-related neurochemical alterations in PD. Clinical evidence also suggests a relationship between vitamin D status and depressive symptomatology in PD. In a cohort of 286 non-demented patients with PD, higher serum 25-hydroxyvitamin D concentrations were associated with lower GDS scores and better cognitive performance[107]. These findings indicate that dysregulation of microbiota-associated BA and vitamin metabolism may contribute to neuroinflammation, neurotransmitter dysfunction, and depressive symptomatology in PD, further supporting the concept of DPD as a metabolically distinct phenotype within the broader PD spectrum.

GUT MICROBIOTA IN THE PATHOGENESIS OF DEPRESSIVE AND NON-DEPRESSIVE PARKINSON'S DISEASE

The gut microbiota is a major regulator of the microbiota-gut-brain axis and contributes to both motor and non-motor manifestations of PD. Through interconnected neural, immune, endocrine, and metabolic pathways, gut microbial dysbiosis influences intestinal permeability, neuroinflammation, neurotransmitter signaling, and α-synuclein pathology, thereby modulating disease progression and vulnerability to depressive symptoms. Increasing evidence suggests that microbiota-derived metabolites and microbiota-associated neurotransmitter pathways contribute differentially to DPD and NDPD, although direct comparative evidence remains limited. Most available studies are cross-sectional, involve relatively small cohorts, or investigate PD and depression independently rather than stratifying patients according to depressive status. Consequently, many proposed microbiota-metabolite mechanisms underlying depressive symptomatology in PD remain associative rather than causally established. The principal microbiota-gut-brain pathways implicated in DPD and NDPD are summarized in Figure 3.

Role of neurological pathways in DPD and NDPD

Neurological dysfunction in DPD and NDPD reflects complex interactions between neurotransmitter disturbances, neuroinflammation, and gut microbiota dysbiosis operating through the microbiota-gut-brain axis. Although dopaminergic degeneration remains a core pathological feature of PD, accumulating evidence suggests that depressive symptoms in PD are more strongly associated with serotonergic and stress-related neurocircuitry alterations than with nigrostriatal dopamine loss alone. Neuroimaging studies demonstrate that patients with DPD exhibit greater reductions in striatal dopamine transporter availability compared with NDPD[23,24]. Importantly, the extent of serotonergic and dopaminergic denervation in DPD appears to worsen with advancing disease stage[108], suggesting that depressive vulnerability may increase as neurochemical

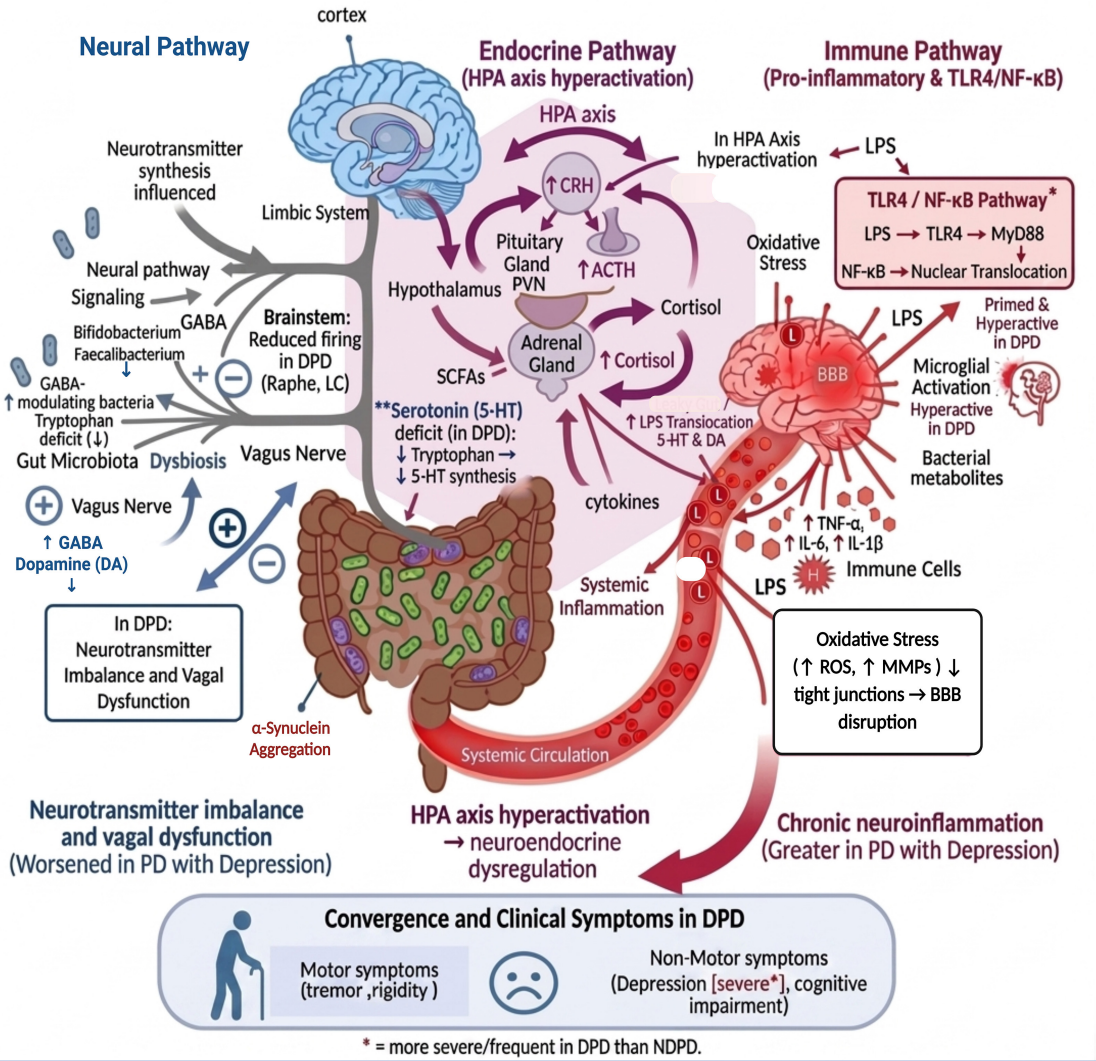

Figure 3. MGBA mechanisms underlying depressive and non-depressive Parkinson's disease. Gut dysbiosis contributes to PD pathogenesis through interconnected neural, neuroendocrine, and immune pathways. In the neural pathway, microbiota-derived neurotransmitters and metabolites modulate vagal signaling, neurotransmitter synthesis, and brainstem-limbic system communication, contributing to neurotransmitter imbalance and vagal dysfunction in DPD. In the endocrine pathway, dysbiosis-associated cytokines and microbial metabolites disrupt HPA axis regulation, promoting cortisol hypersecretion and serotonergic dysfunction. In the immune pathway, increased intestinal permeability permits systemic translocation of LPS and bacterial metabolites, triggering systemic inflammation, blood-brain barrier disruption, microglial activation, oxidative stress, and α-synuclein aggregation. These convergent mechanisms collectively contribute to motor dysfunction and non-motor manifestations, including depression and cognitive impairment, in PD. *Denotes items more severe or frequent in DPD than NDPD. ↑Indicate an increase or up regulation; ↓Indicate a decrease or deficit; →Trace biological pathway cascades. The figure was created with BioRender.com. 5-HT: 5-hydroxytryptamine (serotonin); ACTH: adrenocorticotropic hormone; BBB: blood-brain barrier; CRH: corticotropin-releasing hormone; DA: dopamine; DPD: depressive Parkinson's disease; GABA: gamma-aminobutyric acid; HPA: hypothalamic-pituitary-adrenal; IL-1β: interleukin-1 beta; IL-6: interleukin-6; LPS: lipopolysaccharide; MMPs: matrix metalloproteinases; MyD88: myeloid differentiation primary response 88; NDPD: non-depressive Parkinson's disease; NF-κB: nuclear factor kappa-B; PVN: paraventricular nucleus of the hypothalamus; SCFAs: short-chain fatty acids; TLR4: Toll-like receptor 4; TNF-α: tumour necrosis factor-alpha.

deficits broaden beyond the nigrostriatal system[109]. Structural neuroimaging studies further identified reduced grey matter density within the orbitofrontal cortex, anterior cingulate cortex, medial temporal regions, and parahippocampal gyrus in DPD independent of disease duration[110]. Consistent with these observations, positron emission tomography using serotonin transporter ligands in drug-naïve PD patients demonstrated that depressive and anxiety symptoms correlate with serotonergic denervation within the

anterior cingulate cortex, whereas apathy is associated with orbitofrontal serotonergic loss. Importantly, these alterations were not significantly associated with dopaminergic degeneration, supporting the concept that depressive symptoms in PD involve partially distinct serotonergic mechanisms.

The vagus nerve represents a major communication pathway linking the gut microbiota with central neurophysiological processes[111]. Several gut microbial taxa, particularly *Lactobacillus* and *Bifidobacterium* species, possess glutamate decarboxylase activity and can produce GABA within the intestinal environment[112,113]. Experimental administration of *Lactobacillus rhamnosus* JB-1 altered central GABA receptor expression and reduced corticosterone levels in mice[114], effects abolished following vagotomy, thereby highlighting vagal signaling as a critical mediator of microbiota-gut-brain communication[115].

Although GABA does not efficiently cross the blood-brain barrier, microbiota-derived GABA may indirectly modulate CNS function through vagal afferent signaling, immune pathways, HPA regulation, and microbiota-derived metabolites influencing hypothalamic GABAergic metabolism[116].

Microbial dysbiosis associated with reduced diversity and depletion of beneficial taxa has also been linked to depressive vulnerability in PD[117]. Reduced abundances of *Faecalibacterium prausnitzii* and *Bifidobacterium infantis* have been reported in both PD and depressive disorders, although studies directly comparing DPD and NDPD remain limited[74,118]. Preclinical studies further demonstrated that B. infantis supplementation restores brainstem norepinephrine levels, normalizes immune responses, and attenuates depressive-like behaviors, supporting its potential psychobiotic relevance, although these findings have not yet been validated specifically in DPD cohorts[119,120].

In NDPD, pathological progression is primarily characterized by nigrostriatal dopaminergic degeneration and α-synuclein aggregation[121]. Gut dysbiosis-associated depletion of SCFA-producing bacteria may impair intestinal barrier integrity, promoting a "leaky gut" state and facilitating local α-synuclein accumulation within the ENS[122]. The presence of Lewy body pathology in enteric neurons further supports the hypothesis that α-synuclein pathology may originate in the gut and subsequently propagate to the CNS through vagal pathways[120,123]. Altered GABAergic neurotransmission may additionally contribute to axial motor dysfunction in PD, potentially exacerbated by reduced microbial GABA production[124,125].

Gut microbial metabolites also influence neurotrophic signaling pathways relevant to both DPD and NDPD. Butyrate functions as a histone deacetylase inhibitor capable of regulating brain-derived neurotrophic factor (BDNF) transcription through epigenetic mechanisms[126]. Reduced butyrate availability in PD may therefore impair histone acetylation at the BDNF promoter, resulting in decreased neuroplasticity. Consistent with this mechanism, serum BDNF concentrations are significantly reduced in PD and further decreased in DPD, where lower BDNF levels correlate with greater depressive symptom severity[127]. These findings support the concept that depressive symptoms in PD reflect biologically distinct neurochemical and microbiota-associated mechanisms rather than solely psychological responses to motor disability. However, longitudinal and depression-stratified studies integrating microbiome, metabolomic, and neuroimaging analyses remain necessary to clarify the causal interactions linking gut dysbiosis with neurological dysfunction in DPD and NDPD.

Role of neuroendocrine pathways in DPD and NDPD

The neuroendocrine system, particularly the HPA, is a central component of the microbiota-gut-brain axis regulating stress responses, mood, intestinal permeability, and immune homeostasis[128]. In PD, chronic stress and HPA axis dysregulation are associated with elevated cortisol levels, impaired negative feedback regulation, altered gut motility, and disruption of intestinal barrier integrity[129,130]. Increased intestinal

permeability facilitates systemic translocation of microbial products such as LPS[131,132], thereby promoting peripheral and central inflammatory responses[133].

Evidence suggests that HPA axis dysfunction is more pronounced in DPD than in NDPD. Although Lewy body pathology has been identified within the adrenal glands and peripheral autonomic nervous system, its direct contribution to adrenal dysfunction remains unclear[134,135]. Nevertheless, progressive neuroendocrine dysregulation is thought to contribute substantially to the high prevalence of depressive symptoms in PD.

Gut dysbiosis further amplifies HPA axis activation through immune-mediated mechanisms[129,136]. As discussed in Section 3.3, translocated LPS activates TLR4, inducing NF-κB-dependent production of pro-inflammatory cytokines including IL-1β, IL-6, and TNF-α. These cytokines influence hypothalamic corticotropin-releasing hormone (CRH) secretion, stimulating adrenocorticotropic hormone (ACTH) release and adrenal cortisol production, thereby sustaining HPA axis hyperactivation and stress responsiveness[129,137]. Microbiota-derived metabolites also participate directly in neuroendocrine regulation. Reduced SCFA concentrations, particularly butyrate, have been associated with depressive symptoms in PD[53,138]. Altered BA profiles linked to specific microbial shifts, including increased Verrucomicrobia abundance, have likewise been reported in depression-associated phenotypes[139]. In addition, microbiota-mediated modulation of GABA signaling contributes to HPA axis feedback regulation and stress resilience, with *Bifidobacterium* species implicated in these effects[129]. Emerging evidence further suggests that gut microbial alterations may influence ghrelin and related neuropeptides involved in appetite regulation, stress adaptation, and neuroprotection[140].

In NDPD, neuroendocrine disturbances are also evident but appear less pronounced. Reduced abundance of SCFA-producing bacteria, including Prevotella and Faecalibacterium, may impair signaling pathways linked to neuroprotective peptides such as growth hormone-releasing peptide (GHRP)[42,141], potentially compromising dopaminergic neuron survival and contributing to disease progression[141,142]. These findings indicate that although neuroendocrine dysregulation occurs across PD phenotypes, DPD is characterized by greater HPA axis activation, amplified inflammatory signaling, and impaired inhibitory feedback mechanisms, which together may contribute to increased stress vulnerability and depressive symptomatology.

Immune-pathway mediated neuroinflammation

Immune-mediated neuroinflammation is a major mechanism linking gut dysbiosis with both neurodegenerative and depressive manifestations of PD[143]. However, direct comparative evidence between DPD and NDPD remains limited, as most available studies are cross-sectional or preclinical in nature. Consequently, the extent to which inflammatory alterations specifically distinguish DPD from NDPD is not yet fully established.

Clinical studies nevertheless indicate that DPD is associated with greater inflammatory activation than NDPD[144]. CSF TNF-α concentrations are significantly elevated in DPD and correlate positively with depression severity while correlating negatively with dopamine levels, suggesting a link between inflammatory activation and dopaminergic dysfunction in depressive symptomatology[62]. Similarly, increased CSF IL-6, IL-8, and IL-17 levels have been associated with depression and anxiety in newly diagnosed PD cohorts[145]. A systematic review further identified IL-17A as the inflammatory marker most consistently associated with depressive symptoms in PD, whereas associations involving C-reactive protein (CRP), IL-10, TNF-α, and IL-6 were more heterogeneous and context-dependent[146].

These findings align with the cytokine hypothesis of depression, whereby pro-inflammatory cytokines alter monoaminergic neurotransmission by diverting tryptophan metabolism from serotonin synthesis toward the KP, thereby increasing neurotoxic metabolites such as QA while reducing neuroprotective kynurenines[62,147]. This mechanism provides a plausible link between immune activation and depressive symptomatology in PD.

Gut dysbiosis may further amplify these inflammatory pathways through disruption of intestinal barrier integrity. Increased gut permeability facilitates systemic translocation of LPS derived from Gram-negative bacteria. LPS activates TLR4, triggering myeloid differentiation primary response 88 (MyD88)- and TIR-domain-containing adapter-inducing interferon-β (TRIF)-dependent signaling cascades that converge on NF-κB activation and the subsequent transcription of pro-inflammatory cytokines including TNF-α and IL-1β[148,149]. These inflammatory pathways contribute to systemic immune activation, blood-brain barrier disruption, and microglial activation within the CNS[143,150]. Activated microglia release reactive oxygen species and pro-inflammatory mediators that promote dopaminergic neuronal injury within the substantia nigra, thereby exacerbating both motor dysfunction and depressive manifestations in PD[151,152].

In contrast, beneficial gut microbes and their metabolites exert anti-inflammatory effects. SCFA-producing taxa, including *Faecalibacterium*, reduce systemic inflammation, whereas Bifidobacterium and lactic acid bacteria produce neuroprotective indole derivatives capable of attenuating microglial activation and inflammatory signaling[143]. Inflammatory dysbiosis may additionally facilitate α-synuclein pathology. A pro-inflammatory intestinal environment promotes α-synuclein misfolding and aggregation within the ENS, potentially enabling prion-like propagation to the brain via the vagus nerve[117,153]. Furthermore, microbiota-associated alterations in GABA signaling may influence microglial activation states within PD-relevant brain regions, including the substantia nigra and striatum, thereby accelerating neurodegeneration and worsening depressive symptomatology[154].

Overall, current evidence supports immune-mediated neuroinflammation as a central mechanistic interface linking gut dysbiosis with PD progression and depressive symptoms, as illustrated in Figure 3. However, longitudinal and depression-stratified studies integrating microbiome, metabolomic, and immune profiling remain necessary to determine whether these inflammatory pathways represent causal drivers or secondary consequences of DPD.

POTENTIAL OF GUT DYSBIOSIS AS A THERAPEUTIC TARGET FOR DPD

Increasing evidence suggests that gut dysbiosis contributes to both motor and depressive manifestations in PD through disruption of the microbiota-gut-brain axis. Altered microbial composition and metabolite production influence neuroinflammation, neurotransmitter homeostasis, intestinal barrier integrity, and neuroendocrine signaling, thereby contributing to depressive symptoms in DPD. Consequently, microbiota-targeted interventions including probiotics, prebiotics, dietary modulation, and faecal microbiota transplantation (FMT) have emerged as potential adjunctive therapeutic strategies [Figure 4]. Unlike conventional antidepressants, which primarily target monoaminergic neurotransmission and often demonstrate variable efficacy in PD patients, microbiota-directed therapies may exert broader effects by simultaneously modulating inflammatory, metabolic, and neuroendocrine pathways.

Probiotics

Probiotics are live microorganisms that confer health benefits when administered in adequate amounts and are increasingly investigated for their ability to restore microbial homeostasis and regulate microbiota-gut-brain axis signaling[155,156]. Among the most extensively studied probiotic genera in depression-related disorders are *Lactobacillus* and *Bifidobacterium*, both of which influence neurotransmitter synthesis, immune regulation, and intestinal barrier integrity[157].

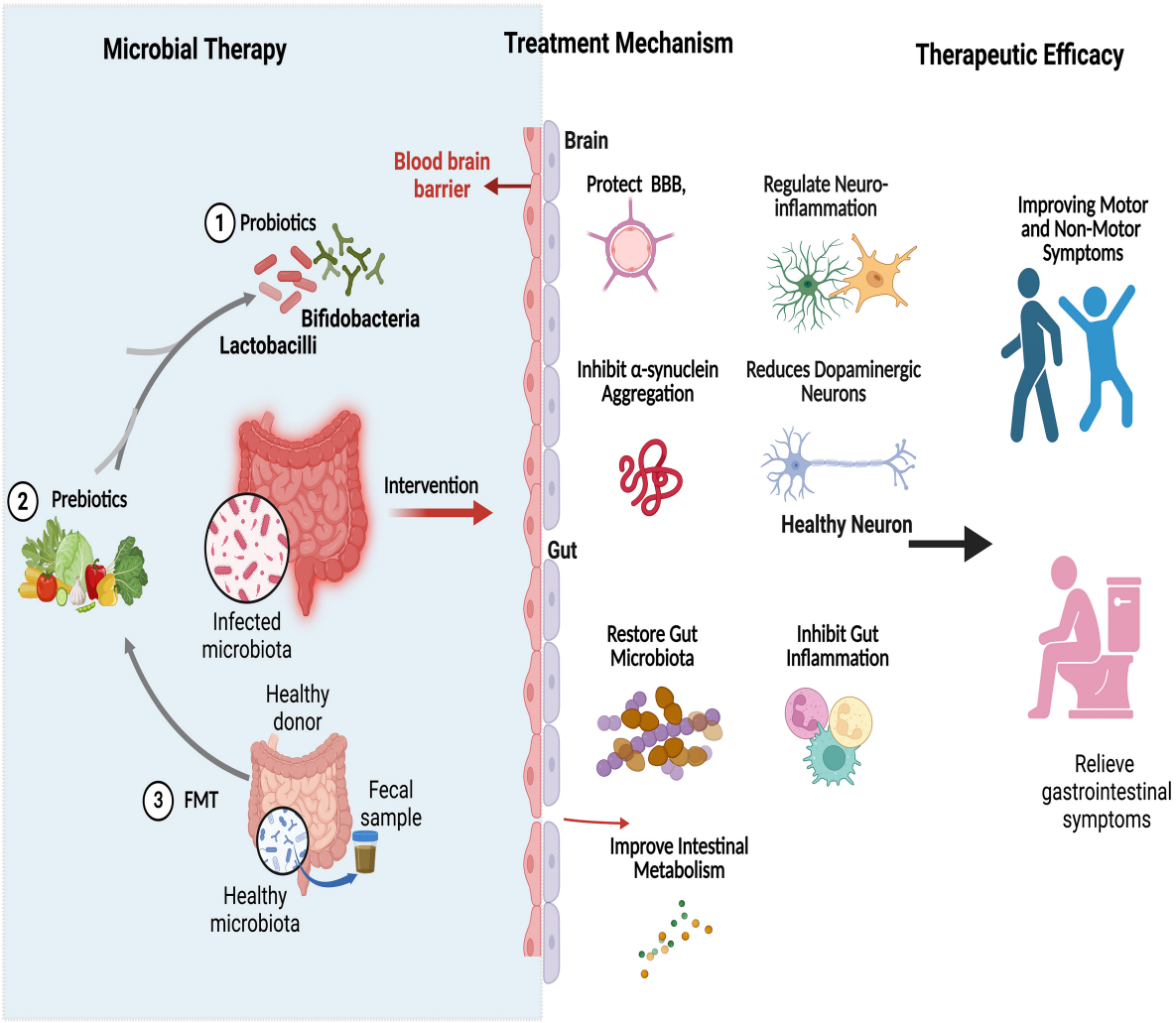

Figure 4. Microbiota-targeted therapeutic strategies. Microbial therapies, including probiotics, prebiotics, and FMT, modulate gut microbial composition and restore intestinal homeostasis. Proposed therapeutic mechanisms through the microbiota-gut-brain axis include restoration of intestinal physiology, suppression of gut inflammation, preservation of blood-brain barrier integrity, inhibition of α-synuclein aggregation, regulation of neuroinflammation, and reduction of dopaminergic neuronal loss. Potential clinical outcomes of microbiota-directed interventions, including improvement of gastrointestinal dysfunction, motor symptoms, and depression-associated non-motor manifestations in PD. The figure was created with BioRender.com. PD: Parkinson's disease; FMT: faecal microbiota transplantation.

Several probiotic strains have demonstrated antidepressant-like effects in experimental and clinical studies. *Bifidobacterium breve* CCFM1025, *Bifidobacterium longum*, *Lactobacillus rhamnosus*[158,159], and *Lactobacillus helveticus* have been associated with reduced depressive symptoms, improved stress resilience, and modulation of serotonergic signaling pathways[160,161]. Experimental evidence indicates that *Bifidobacterium* species may enhance tryptophan metabolism and increase production of serotonin-related metabolites, whereas *Lactobacillus* species strengthen epithelial barrier integrity, reduce inflammatory cytokine production, and modulate BDNF signaling[162]. In particular, *Lactobacillus rhamnosus* has been shown to influence GABA receptor expression through vagus nerve-dependent mechanisms, supporting its relevance to mood regulation within the microbiota-gut-brain axis[163]. Similarly, *Bifidobacterium strains* have been shown to enhance serotonin biosynthesis through tryptophan metabolism and normalise HPA axis hyperactivity in patients with MDD[164,165], suggesting potentially relevant mechanisms that have not yet been directly validated in PD populations. Whether these findings translate to DPD warrants investigation in PD-specific clinical trials.

Recent interest has also focused on next-generation probiotics, including *Akkermansia muciniphila* and *Faecalibacterium prausnitzii*, owing to their anti-inflammatory and SCFA-producing properties[119,166]. Preclinical studies suggest that these taxa may attenuate neuroinflammation, improve intestinal barrier integrity, and reduce depressive-like behaviors. Similarly, butyrate-producing organisms such as *Butyricicoccus pullicaecorum* may exert neuroprotective effects through epigenetic and immunomodulatory mechanisms[167,168].

A 3-month randomized controlled trial in 82 PD patients receiving conventional medication. Adjuvant *Bifidobacterium animalis* subsp. *Lactis* ProbioM8 (3×10^{10} CFU/day) significantly improved sleep quality, alleviated anxiety, and improved gastrointestinal symptoms, along with increased serum acetic acid and dopamine levels[169].

Despite these promising findings, several limitations remain. Probiotic efficacy appears highly strain-specific, and therapeutic outcomes vary substantially according to dosage, treatment duration, disease stage, and host microbial composition. Most available studies involve relatively small cohorts and short follow-up periods, limiting conclusions regarding long-term efficacy and safety. As shown in Table 1, Dosage ranges studied in clinical trials have varied considerably, typically between 10^8 and 10^{11} colony-forming units (CFU) per day, with treatment durations ranging from four to twelve weeks in most published studies[170]. Regarding safety, short-term probiotic use appears generally well tolerated in most PD patients, with mild gastrointestinal side effects such as bloating and flatulence being the most commonly reported adverse events. However, potential risks in immunocompromised individuals and theoretical concerns regarding bacteremia with certain strains, particularly in patients with compromised intestinal barrier integrity as is common in PD, warrant careful safety monitoring in future trials.

Prebiotics and dietary modulation

Prebiotics are non-digestible dietary substrates, including fructooligosaccharides (FOS), galactooligosaccharides (GOS), and inulin, that selectively promote the growth of beneficial gut microbiota and enhance microbial metabolite production[171,172]. Through fermentation by gut bacteria, prebiotics increase SCFA production, improve intestinal barrier integrity, and reduce systemic inflammation, mechanisms that may be particularly relevant to depressive symptoms in PD.

Experimental studies demonstrate that prebiotic supplementation can partially reverse gut dysbiosis and improve neurobehavioral outcomes in PD models. In a rotenone-induced PD model with depressive-like behaviors, administration of FOS and GOS reduced the abundance of Proteobacteria and *Helicobacter hepaticus* while increasing beneficial taxa including *Bacteroides*, *Alistipes*, and *Lactobacillus reuteri.* These microbial changes were associated with increased butyrate production, restoration of serotonin levels, attenuation of neuroinflammation, and improvement in depressive-like behaviors[54].

Beyond classical fibres, several dietary phytochemicals exhibit prebiotic-like effects. Polyphenols such as quercetin, chlorogenic acid, and resveratrol selectively promote the growth of *Bifidobacterium* and *Lactobacillus* species while suppressing pathogenic taxa[173,174]. Medicinal plant-derived compounds, including ginsenosides and polysaccharides, have also demonstrated antidepressant-like and neuroprotective effects through modulation of gut microbial composition and neurotransmitter regulation[175]. Dietary patterns rich in fibre, polyphenols, and omega-3 fatty acids, particularly Mediterranean-style diets, may further enhance microbial diversity, increase SCFA production, and reduce oxidative stress associated with α-synuclein pathology[176,177].

Table 1. Consolidated summary of probiotic and prebiotic doses used in studies relevant to PD and depression

Intervention	Type	Dose	Study model	Main findings	Ref.
Lactobacillus rhamnosus JB-1	Probiotic	10^9 CFU/day, 28 days	Mouse	Reduced depressive-like behavior and stress-induced corticosterone response; effects were strain-dependent and comparable to fluoxetine in responsive mice	[114]
Faecalibacterium prausnitzii	Probiotic	10^8 CFU, twice weekly for 15 weeks	Thy1-ASO α-synuclein PD mice	Improved motor and gastrointestinal function, reduced α-synuclein aggregation, enhanced anti-inflammatory responses, and restored gut microbial balance	[74]
Bifidobacterium breve CCFM1025	Probiotic	10^{10} CFU/day, 4 weeks	Human RCT (MDD patients, *n* = 45)	Reduced depression severity, improved gastrointestinal symptoms, and modulated tryptophan metabolism and gut microbiota composition	[165]
Multi-strain probiotic (*B. bifidum*, *B. longum*, *L. rhamnosus*, *L. rhamnosus* GG, *L. plantarum* LP28, *Lc. lactis* subsp. *lactis*)	Probiotic	10^{10} CFU/mouse/day, 16 weeks	PD mice model	Improved motor performance and preserved nigral dopaminergic neurons	[170]
Bifidobacterium animalis subsp. *lactis* Probio-M8	Probiotic	3×10^{10} CFU/day, 3 months	Human RCT (PD patients, *n* = 82)	Improved anxiety, sleep quality, and gastrointestinal symptoms; increased serum dopamine and acetic acid levels	[169]
Inulin or oligofructose (FOS)	Prebiotic	20 g/day, 30 days	Human pilot study (PD patients, *n* = 5)	Improved nutritional parameters, altered gut microbiota composition, and modestly improved stool consistency	[179]
FOS + GOS	Prebiotic	FOS 3 g/kg/day + GOS 4 g/kg/day	Rotenone-induced PD mice	Improved motor and depressive-like behaviors, increased serotonin and butyrate levels, enhanced gut barrier integrity, reduced neuroinflammation, and promoted neuroprotection	[54]

CFU: Colony-forming units; FOS: fructo-oligosaccharides; GOS: galacto-oligosaccharides; MDD: major depressive disorder; PD: Parkinson's disease; RCT: randomized controlled trial.

Similarly, ketogenic diets have shown beneficial effects in experimental PD models through modulation of inflammatory pathways and microbial metabolism[178]. Prebiotic doses used in experimental studies have generally ranged from 5 to 20 grams per day for fibres such as FOS and inulin, summarized in Table 1[179, 180], although optimal dosing for PD populations has not been systematically investigated. Nevertheless, the translational relevance of prebiotics in DPD remains incompletely established. Human interventional studies remain limited, and substantial variability exists regarding fibre composition, dosage, and treatment duration. Moreover, gut microbial metabolism may alter the bioavailability and efficacy of PD medications, including levodopa, complicating interpretation of therapeutic outcomes. Additional longitudinal and mechanistic studies are therefore required to define optimal dietary strategies and identify microbial biomarkers predictive of treatment responsiveness.

FMT

FMT involves the transfer of faecal microbiota from healthy donors to recipients with the aim of restoring intestinal microbial homeostasis[181,182]. Because gut dysbiosis is increasingly implicated in PD pathogenesis and depression-related neuroinflammation, FMT has emerged as a potential experimental therapeutic strategy for DPD.

Preclinical studies support a causal relationship between gut microbiota composition and depressive phenotypes. Transfer of microbiota from depressed individuals into germ-free or antibiotic-treated rodents induces depressive-like behaviors, altered tryptophan metabolism, and neurochemical abnormalities in

recipient animals[183,184]. In PD models, FMT has been shown to improve intestinal dysbiosis, suppress TLR4/TANK-binding kinase 1 (TBK1)/NF-κB/TNF-α inflammatory signaling, reduce neuroinflammation, and enhance striatal dopamine and serotonin levels[185,186]. The most rigorous clinical evidence to date comes from a double-blind, placebo-controlled randomized controlled trial (RCT) by Scheperjans *et al.* (2024), which enrolled 47 patients with PD[181]. The primary outcome did not differ significantly between FMT and placebo groups, and secondary outcomes showed stronger improvement in the placebo arm. Gastrointestinal adverse events were significantly more frequent in the FMT group (53% *vs.* 7%). The authors concluded that FMT was safe but did not offer clinically meaningful improvements in PD. Earlier preliminary observations, including the first documented FMT case in PD, which reported improvement in constipation and partial reduction in tremor severity, and small-scale pilot studies reporting improvements in NMS at two months post-FMT[187], should therefore be interpreted as hypothesis-generating observations only. Post-FMT microbial alterations in these earlier studies frequently included enrichment of SCFA-producing taxa such as *Blautia* and members of *Lachnospiraceae*[188,189], but whether these microbial changes translate to sustained clinical benefit remains unestablished in light of the negative RCT findings.

However, despite promising preliminary findings, FMT remains an experimental intervention with significant unresolved challenges. Therapeutic outcomes may vary substantially according to donor microbial composition, transplantation protocols, route of administration, and frequency of treatment. Concerns also remain regarding long-term microbial engraftment, safety, and the potential transmission of opportunistic pathogens. Reported adverse events in PD-related FMT studies have included transient gastrointestinal discomfort, fever, and, in rare cases, serious infections, underscoring the necessity of rigorous donor screening protocols. Furthermore, the optimal route of administration, whether via colonoscopic infusion, nasojejunal tube, or oral capsule delivery, the required frequency of transplantation, and the minimum effective donor microbial diversity threshold remain undefined for PD populations. Long-term follow-up data beyond twelve months are currently absent from the literature, making it impossible to assess whether initial clinical improvements are sustained or whether repeated transplantation is necessary to maintain therapeutic effects. Moreover, current clinical studies are limited by small sample sizes, short follow-up durations, and lack of standardized depression-specific outcome measures. Large, rigorously controlled, longitudinal clinical trials are therefore necessary before FMT can be considered a clinically applicable therapy for DPD.

LIMITATIONS AND FUTURE DIRECTIONS

Although an increasing body of evidence has established a link between gut dysbiosis and both the motor and depression-related manifestations of PD, numerous challenges still impede the precision and translational significance of current research findings. Substantial clinical and microbial heterogeneity, arising from disparities in genetics, disease stage, motor subtypes, medication exposures, and baseline microbiome composition, complicates efforts to define reproducible microbial signatures across cohorts. This variability is further magnified by methodological inconsistencies, such as differences in sample handling, sequencing platforms, analytic pipelines, and the clinical criteria used to diagnose depression. A particularly significant shortcoming is that few studies directly compare gut microbial profiles between depressed and non-depressed PD patients, limiting the field's ability to identify depression-specific alterations. Furthermore, existing studies rarely stratify patients by disease stage or motor subtype, such as tremor-dominant versus PIGD subtypes, limiting understanding of how microbial alterations evolve across the disease continuum and whether distinct dysbiosis signatures characterize early versus advanced PD with or without depression.

Moreover, it remains arduous to disentangle the influence of confounding factors, including diet, lifestyle, geography, aging, and the use of antidepressants or dopaminergic therapies, from disease-driven microbial changes. The current exclusive focus on bacterial taxa also leaves the contributions of other microbial

kingdoms, such as fungi and viruses, unexamined. These kingdoms may play significant roles in gut-brain signaling. Addressing these limitations necessitates a coordinated transition toward more rigorous and integrative research strategies. Longitudinal human studies tracking microbial trajectories from the prodromal phase through advanced disease are essential for establishing temporality and determining whether dysbiosis is a driver or a consequence of depressive symptoms in PD.

Mechanistic understanding will be enhanced by multi-omics frameworks that combine metagenomics, metabolomics, and transcriptomics with neuroimaging and immunophenotyping to delineate how specific gut-derived metabolites and neuroactive compounds shape neural circuits, mood regulation, and neuroendocrine-immune interactions. Parallel efforts to identify robust microbial or metabolic biomarkers capable of stratifying patients by depression risk or predicting therapeutic response will be crucial for advancing precision medicine. Progress in personalized therapy will rely on customizing probiotics, prebiotics, and FMT protocols to individual genetic backgrounds, disease stages, medication profiles, and microbial baselines. Ultimately, large-scale, randomized controlled trials with long-term follow-up are needed to determine the safety, durability, and clinical value of microbiota-targeted interventions for depression in PD and to transform the potential of gut-brain research into effective, individualized care.

CONCLUSION

Gut microbiota dysbiosis and the consequent alterations in metabolites are central modulators in the pathophysiology of DPD and NDPD. These changes influence disease progression through intricate, overlapping mechanisms involving neurotransmitter metabolism, neuroinflammation, and neuroendocrine signaling. Distinct microbial signatures and metabolite profiles, including SCFAs, tryptophan derivatives, and TMAO, interact with key signaling pathways such as the TLR4/NF-κB pathway, GABAergic circuits, and the HPA axis, to shape divergent motor and mood-related phenotypes. Elucidating these gut-brain interactions is crucial for understanding the shared and distinct pathophysiological underpinnings of DPD and PD-ND and for identifying novel targets for microbiota-directed interventions. Future longitudinal, mechanistic, and interventional studies are essential to translating these insights into effective precision therapies that address both motor dysfunction and depressive comorbidities in PD.

DECLARATIONS

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Authors' contributions

Writing original draft, investigation, methodology, formal analysis, visualization, data curation, and conceptualization: Noor U

Review & editing, investigation, methodology, and data curation: Khan I (Imran Khan), Khan I (Ikram Khan), Zheng W

Review & editing, conceptualization, validation, funding acquisition, and supervision: Li S

All authors critically reviewed and approved the final version of the manuscript for submission.

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During the preparation of this manuscript, the AI tool DeepSeek (version latest, released 2025-01-20) was used solely for language editing. The tool did not influence the study design, data collection, analysis, interpretation, or the scientific content of the work. All authors take full responsibility for the accuracy, integrity, and final content of the manuscript.

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