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Non-pharmacological interventions modulating immune response in Parkinson's disease: where do we stand for future preventive approaches

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ABSTRACT

Parkinson's disease (PD) imposes a growing socioeconomic burden due to its increasing prevalence and lack of a cure. Existing treatment options primarily manage motor and nonmotor symptoms but do not halt or slow disease progression, underscoring the urgent need for more effective and preventative strategies. Growing evidence suggests a strong link between immune system dysfunction, chronic inflammation, and the early pathogenesis of Parkinson's disease, often occurring years before the onset of motor symptoms, thereby indicating a critical window for early intervention. In this review, we examine current evidence on non-pharmacological approaches such as dietary changes, physical activity, and gut microbiome regulation, focusing on their potential to modulate both peripheral and central immune responses, thereby influencing the progression of PD. Besides being complementary to standard pharmacological treatments, these approaches not only reduce systemic inflammation but may also help delay, prevent, or improve clinical management of PD by targeting and modulating its immunological foundations.

Abbreviations list

6-OHDA	6-hydroxydopamine
ALA	α -linolenic acid
BBB	Blood-brain barrier
BDNF	Brain-derived neurotrophic factor
BMI	Body mass index
CD	Cluster of differentiation
CNS	Central nervous system
COMT	Catechol *O*-methyl transferase

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CORDIOPREV	Coronary Diet Intervention with Olive oil and cardiovascular prevention study
CRP	C-reactive protein
DASH	Dietary Approaches to Stop Hypertension
DATATOP	Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism
EEF2	Eukaryotic translation elongation factor-2
ENS	Enteric nervous system
FMD	Fasting-mimicking diets
FMT	Faecal microbiota transplantation
GI	Gastrointestinal
HIIT	High intensity interval training
Iba1	Ionized calcium-binding adaptor molecule 1
IkBa	Inhibitor of kappa light chain gene enhancer in B cells
IL	Interleukin
iNOS	Inducible nitric oxide synthase
LDL	Low-density lipoprotein
MAO-B	Monoamine oxidase B
MAPK	Mitogen-activated protein kinase
MAPKAPK2	Mitogen-activated protein kinase activated protein kinase 2
MDS-UPDRS	Movement Disorder Society – Unified Parkinson's Disease Rating Scale
MeDi	Mediterranean diet
MIND	Mediterranean-DASH Intervention for Neurodegenerative Delay
MPTP	1-methyl-4-phenyl-1,2,3,6tetrahydropyridin
NF-kB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NK	Natural killer
NLRP3	Nucleotide-binding oligomerization domain-, leucine-rich repeat, and pyrin domain-containing 3
Nrf2	NF-E2-related factor 2
PBMCs	Peripheral blood mononuclear cells
PD	Parkinson's disease
PREDIMED	Prevención con dieta mediterránea
RCT	Randomized controlled trial
REM	Rapid eye movement
SCFA	Short-chain fatty acid
SN	Substantia nigra
TGF-β	Transforming growth factor beta
TH	Tyrosine hydroxylase
TLR	Toll-like receptor
TNF-α	Transforming growth factor beta
TNFRSF18	Tumour necrosis factor receptor superfamily member 18
UPDRS	Unified Parkinson's disease rating scale
ZO	Zonula occludens
αSyn	α-synuclein

1. Background

Parkinson's disease (PD) is the second most common multisystemic neurodegenerative condition (Poewe et al., 2017). The progressive and complex nature of PD represents a significant socioeconomic burden worldwide (Ou et al., 2021). As prevalence increases due to an aging population, the direct and indirect costs of PD, including healthcare expenditure, lost productivity, and caregiver burden, have substantially increased in recent decades (Su et al., 2025). The financial burden on patients, families, and healthcare systems emphasizes the urgent need for effective strategies to treat and/or prevent the disease. Despite decades of research, there is still no definitive cure for PD. Current therapeutic approaches are primarily symptomatic and focus on alleviating motor and non-motor symptoms rather than addressing the underlying neurodegenerative process. Pharmacological treatments such as levodopa, dopamine agonists, monoamine oxidase B (MAO-B) or catechol *O*-methyl transferase (COMT) inhibitors are far from optimal, and while being able to provide temporary relief, unfortunately cannot halt disease progression (Church, 2021). The lack of effective disease-modifying therapies highlights the urgent need to explore novel and non-pharmacological strategies that not only address rapid disease progression but also intervene in early mechanisms before irreversible neuronal loss occurs (see Tables 7–9).

Emerging evidence suggests that changes in the immune system and chronic inflammation play a decisive role in the development of PD, with inflammatory changes being detectable more than a decade before the onset of motor symptoms (as previously reviewed in (Roodveldt et al., 2024; Harms et al., 2021)). Epidemiological and biomarker studies have identified systemic and central nervous system immune dysregulation in individuals at high risk for PD, including those with prodromal features such as rapid eye movement (REM) sleep behaviour disorders or genetic predisposition (for review, please see (Roodveldt et al., 2024)). The presence of increased immune activity long before clinical diagnosis indicates a potential window of opportunity for early intervention.

Emerging evidence indicates that immune dysregulation and chronic neuroinflammation play a central role in the pathogenesis of PD, involving a dynamic interplay between innate and adaptive immune mechanisms. Microglia, the resident immune cells of the central nervous system, shift from a homeostatic to a more reactive phenotype, characterized by a sustained release of pro-inflammatory mediators, including tumour necrosis factor alpha (TNF-α), interleukin (IL)-1β, IL-6 and reactive oxygen species (ROS), contributing to dopaminergic neurodegeneration (Isik et al., 2023). Misfolded α-synuclein (αSyn) acts as a damage-associated molecular pattern (DAMP), activating pattern recognition receptors such as toll-like receptor (TLR) 2 and TLR4 and triggering downstream nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signalling, which primes the inflammasome response and promotes caspase-1–dependent maturation of IL-1β and IL-18, thereby amplifying neuroinflammation and inducing pyroptotic pathways (Siddiqui and Bhatt, 2023). In addition to innate immune activation, adaptive immune responses are increasingly recognized, including infiltration of cluster of differentiation (CD)4^+ and $CD8^+$ T cells and the involvement of B lymphocytes, which contribute to antigen presentation, cytokine production and sustained inflammatory signalling (Roodveldt et al., 2024). Peripheral immune alterations, including changes in monocytes and circulating cytokine profiles, further support a systemic inflammatory component that interacts with central mechanisms (Saponjic et al., 2024). Consistently, meta-analytical evidence demonstrates elevated inflammatory biomarkers, such as TNF-α, IL-1β and IL-6, in both cerebrospinal fluid and peripheral circulation, correlating with disease progression and severity (Scott et al., 2023). In addition, crosstalk between neurons, microglia and astrocytes further reinforces this inflammatory network, promoting blood–brain barrier (BBB) dysfunction and facilitating immune cell infiltration (Isik et al., 2023). Collectively, these findings highlight a complex immune-driven network integrating microglial activation, inflammasome signalling and adaptive immune responses, positioning (neuro)inflammation as a key contributor to PD pathophysiology and a promising target for disease-modifying strategies.

Given the prolonged preclinical phase of PD, preventive and/or therapeutic non-pharmacological interventions targeting immune and inflammatory pathways may be a promising strategy to modify the course of the disease. Indeed, lifestyle modifications, including dietary interventions, physical activity and regulation of the gut microbiome, have shown the potential to reduce systemic inflammation and improve neuroprotection (Ghosh et al., 2020; García-Gavilán et al., 2024; Fink et al., 2025; Ni et al., 2025). Understanding the interplay between immune dysfunction and the pathogenesis of PD could pave the way for new non-pharmacological strategies that may prevent or postpone the onset of the disease. By identifying early windows of intervention, we may shift the paradigm towards delaying or preventing PD rather than just treating the symptoms.

This review highlights the latest evidence on different non-pharmacological approaches that can contribute to the mitigation of systemic and brain immune dysregulation, thus having a decisive impact on PD onset, progression, and management. The narrative is focused into non-pharmacological preventive and/or therapeutic interventions (namely preclinical and clinical evidence diet, gut microbiota modulation, and exercise). Special attention is given to the role of the gut-brain axis as a novel potential target for future therapies, along with the

exploration of possible synergistic interventions to more effectively address inflammation throughout the course of the disease.

2. Dietary interventions

Growing evidence suggests that dietary patterns can modulate neuroinflammation, oxidative stress and gut microbiota composition, offering a promising non-pharmacological approach with the potential to slow neurodegeneration and improve quality of life (Mischley et al., 2017; Knight et al., 2022).

To date, different dietary patterns have been associated with a neuroprotective effect in PD (Knight et al., 2022). The same is true for specific nutrient classes, particularly those with proven high antioxidant and anti-inflammatory properties, including vitamins and vitamin-like substances (Zhao et al., 2019; Shults, 2002; Chen et al., 2025a), and (poly)phenols and their metabolites, a group of pleiotropic bioactive compounds with demonstrated neuroprotective properties (Figueira et al., 2017; Carecho et al., 2024; Kujawska and Jodynis-Liebert, 2018). Importantly, changes in the composition of gut bacteria, known as dysbiosis, have been reported in patients (Jackson et al., 2019; Hirschberg et al., 2019), comprising a key link between diet and neuroimmune regulation from the gut to the brain in PD.

The following sections highlight the current clinical and mechanistic evidence for specific dietary interventions and bioactive compounds, focusing on their role in modulating the neuroimmune system and disease progression in PD.

2.1. Mediterranean and Mediterranean-like diets

The Mediterranean diet (MeDi), rich in fruits, vegetables, whole grains, legumes, nuts, olive oil and fish, has been associated with reduced neuroinflammation, oxidative stress and improved cognitive function (Shults, 2002; Figueira et al., 2017; Solch et al., 2022; Maraki et al., 2023) (Table 1). The Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND), a synergy of MeDi and DASH (Dietary Approaches to Stop Hypertension), was also associated with a lower risk and later onset of Parkinsonism (Solch et al., 2022; Maraki et al., 2023; Agarwal et al., 2018; Metcalfe- et al., 2021; van Soest et al., 2024; Zhao et al., 2025; Mischley and Murawska, 2025). Epidemiological studies showed that adherence to a MeDi/MeDi-like diets and a low-processed diet (e.g., MIND diet), may reduce the risk of PD, can delay disease onset and/or reduce motor and non-motor symptoms (Solch et al., 2022; Maraki et al., 2023; Fox et al., 2022; Maraki et al., 2019; Gao et al., 2007; Zhang et al., 2025a; Hajji- et al., 2026). In contrast, Western diets characterized by high consumption of highly processed foods, foods with a high glycaemic index, red meat and added sugar are associated with more severe symptoms and a higher mortality rate in PD (Fox et al., 2022). Consumption of nuts, vegetables, berries, legumes and whole grains together with lower red and processed meat consumption is associated with reduced patient-reported symptomatology and lower mortality (Agarwal et al., 2018; Fox et al., 2022; Zhang et al., 2022a). Interventional trials found that the MeDi appears to improve cognitive function, behaviour, mood and daily activities while reducing intestinal inflammation measured through faecal calprotectin (Paknahad et al., 2020, 2022; Rusch et al., 2021, 2024). However, it must be noted that intervention studies on this topic are limited (Paknahad et al., 2020, 2022; Rusch et al., 2021, 2024). MeDi-like diets may exert their protective effect on PD by reducing systemic inflammation and modulating the expression of genes associated with inflammatory processes. While not specific to PD, mechanistic insights provided by relevant studies suggest positive epigenetic changes in genes such as the eukaryotic translation elongation factor-2 (EEF2) and the mitogen-activated protein kinase (MAPK) activated protein kinase 2 (MAPKAPK2) could be induced by MeDi/MeDi-like diets (Arpón et al., 2016), which are overexpressed post-mortem brain affected by PD and are associated with disease progression and αSyn toxicity (Jan et al., 2018; Zhong et al., 2023), so much so that MAPKAPK2 has been proposed as an early prognostic biomarker of disease associated with the pathological aggregation of αSyn. In addition, it has been shown that MeDi alters miRNA profiles (Marques-Rocha et al., 2016) and suppresses the NF-κB (Camargo et al., 2012), a transcription factor involved in the activation of multiple proinflammatory signalling pathways contributing to neurodegeneration, while strengthening protective factors such as the inhibitor of kappa light chain gene enhancer in B cells (IκBα) (Camargo et al., 2012). Adherence to a MeDi-like diet has been shown to correlate with lower serum inflammatory mediators such as IL-6, IL-1β and C-reactive protein (CRP) (Hart et al., 2021; Koelman et al., 2022), mediators correlated with increased disability and disease progression (Sanjari Moghaddam et al., 2018; Qu et al., 2023). Regarding intestinal inflammation, a randomized controlled trial (RCT) showed that

Table 1
MeDi preclinical (in vivo) and clinical (human) evidence on inflammation modulation with relevance for PD.

Study type	Model/population	Intervention	Main immune/inflammatory outcomes	Reference
Clinical	PD patients with constipation (n = 36) (RCT)	MeDi promotion and constipation standard care	↓faecal calprotectin	Rusch et al. (2024)
Clinical	Aging-brain human evidence (review)	MIND diet	Review supporting neuroinflammatory-prevention framework; no PD-specific immune biomarkers	van Soest et al. (2024)
Clinical	Human PBMCs (non-PD)	MeDi/MeDi-like diet	↓TNF-α, ↓sICAM-1, ↓CRP, ↑VCAM-1 Methylation changes in inflammation-related genes (*EEF2*, *COL18A1*, *IL4I1*, *LEPR*, *PLAGL1*, *IFRD1*, *MAPKAPK2*, *PPARGC1B*)	Arpón et al. (2016)
Clinical	Elderly humans (non-PD)	MeDi	↓NF-κB signalling; ↑IκBα; ↓IL-6, ↓IL-1β and ↓CRP (serum)	Camargo et al. (2012)
Preclinical	Female cynomolgus macaques	MeDi (30 months)	trend for ↑CPT1 expression	Gonzalez-Armenta et al. (2019)
Preclincial	Transgenic AD mice (APP/PS1 double-transgenic)	MeDi (12 weeks)	↑*Lactobacillus* population ↑bacteria-derived lactate production ↑microbiome- and diet-derived metabolites ↓IL-1β, IL-8 (colon) ↓IL-6, IL-1β (brain)	Park et al. (2024)
Preclinical	Rodent neurodegeneration models	MeDi/MeDi-like diet	↓neuroinflammation and oxidative stress; improved cognition; modulated inflammatory-gene expression (↑EEF2; regulated MAPKAPK2)	(Zhao et al., 2019; Shults, 2002; Chen et al., 2025a)

Abbreviations: AD – Alzheimer's disease; APP/PS1 – amyloid precursor protein/presenilin-1 transgenic model; CPT1 – carnitine palmitoyltransferase 1; CRP – c-reactive protein; EF2 – eukaryotic elongation factor 2; IkBa; IL – interleukin; MAPKAPK2 – mitogen-activated protein kinase-activated protein kinase 2; MeDi – Mediterranean diet; MIND; NF-κB – nuclear factor kappa-light-chain-enhancer of activated B cells; PBMCs – peripheral blood mononuclear cells; PD – Parkinson's disease.

promoting a MeDi diet decreases constipation, reflux and diarrhoea and lowers faecal calprotectin levels in people with PD (Rusch et al., 2024). A meta-analysis and systematic review of a total of 24 randomized and crossover trials published between 1989 and 2022, indicated that the MeDi, low-fat and ketogenic diets significantly decreased the Unified Parkinson's Disease Rating Scale (UPDRS) total score and a low-protein diet meaningfully attenuated motor symptoms (Wu et al., 2024). Although MeDi and similar dietary patterns have good palatability (Woodside et al., 2022), they are generally considered safe and associated with good long-term adherence even in older populations, as demonstrated by trials such as the PREvención con DIeta MEDiterránea (PREDIMED) and the CORonary Diet Intervention with Olive oil and cardiovascular PREVention study (CORDIOPREV) (Cano-Ibáñez et al., 2022; Casas et al., 2022) dietary tailoring to individual needs remains necessary, with particular attention to the gradual introduction of fibre and to patients with celiac disease. PD specific trials on MeDi diet and immunity remain scarce, interest in this area is slowly increasing (Pirovano et al., 2025). However, there is an urgent need for longer RCTs with bigger sample sizes to better assess the effectiveness and underlying mechanism of these interventions to identify a target population of people with PD or a specific time window that may allow bigger benefits.

2.2. Ketogenic diet

The ketogenic diet is a dietary pattern characterized by low-carbohydrates and high-fat (usually ranging from 60 to 90% of total energy from fat) inducing nutritional ketosis, a state defined by the production of ketone bodies, reflected into a plasma ketone level between 0.5 and 4.0 mM (Pirovano et al., 2025; Choi et al., 2021).

Two main theories currently explain the benefits of ketone bodies in neurodegenerative diseases (Bohnen et al., 2023). The alternative fuel theory suggests that ketones serve as an energy source for the brain when glucose metabolism is significantly impaired. Ketone bodies have been shown in animal models to exert protective effects in mitochondrial function (Tieu et al., 2003). This effect may be particularly relevant in the patient population with central hypometabolism, who are more likely to experience cognitive decline as the disease progresses (Kalbe et al., 2009; Pilotto et al., 2018). Conversely, the signalling hypothesis proposes that ketone bodies influence cellular pathways, reduce inflammation, oxidative stress, and neurodegeneration, while supporting neurotransmission and neuroplasticity (Bohnen et al., 2023). Considering these pathways, effectiveness of therapeutic ketosis could be studied for early disease stages, impacting progression or for immediate symptom management (Bohnen et al., 2023). Current evidence on inflammation modulation by ketogenic diets for PD is listed in Table 2.

A recent meta-analysis of RCT investigating the ketogenic diet found a significant reduction of TNF-α and IL-6 (Ji et al., 2025). Accordingly, a recent cross-over study comparing the ketogenic and a vegan diet found that the ketogenic one induced a distinct immune signature characterized by upregulation of adaptive immune pathways, including T cell activation, enrichment of B cells, plasma cells, and natural killer (NK) cells (Link et al., 2024a). Moreover, oxidative phosphorylation, which is linked with T cell activation and memory formation, was significantly enriched in a ketogenic diet as compared with a vegan or baseline diet. In fact, ketogenic diet has been used to treat epilepsy since it reduces seizure frequency, being at least partially explained by significant reduction in cytokines and/or chemokines (Wickström et al., 2021; Thambi et al., 2021).

Ketogenic diet has been studied in PD to improve cognition, speech, and voice disorders (Agarwal et al., 2018; Metcalfe- et al., 2021). Studies of ketogenic diet intervention in PD patients have found an improvement in cognitive abilities (Krikorian et al., 2019) and a reduction in both motor and non-motor symptoms (VanItallie et al., 2005; Phillips et al., 2018, Price and Ruppar, 2023). The studied approaches showed more promising evidence regarding improvement in non-motor

Table 2
Ketogenic diet preclinical (in vivo) and clinical (human) evidence on inflammation modulation with relevance for PD.

Study type	Model/ Population	Intervention	Main Immune/ Inflammatory Outcomes	Reference
Clinical	Systematic review of 24 RCTs	Ketogenic diet	↓TNF-α and ↓IL-6	Ji et al. (2025)
Clinical	Overweight women (n = 29)	Low carbohydrate, high fat (4 weeks) High carbohydrate, low fat (4 weeks)	↑CRP, ↑IL-6 ↑IL-6	Rankin and Turpyn (2007)
Clinical	Adults 18-50 (n = 20)	Ketogenic diet and vegan diet (cross-over, 2 weeks)	↑T cell activation, ↑B cells, ↑plasma cells, and ↑NK cells	Link et al. (2024b)
Preclinical	MPTP-injected mice	Ketogenic diet (8 weeks)	↓motor dysfunction Improved DA neuron loss; restored gut microbiota ↓IL-1β, IL-6, TNF-α (striatum) ↓IL-1β, IL-6, TNF-α (plasma) ↓IL-1β, IL-6, TNF-α (colon)	Jiang et al. (2023)
Preclinical	MPTP-injected mice	Medium-chain triglyceride ketogenic diet (5 weeks)	↓DA neuron damage ↑TH expression, ↑DA synthesis, ↓glucose (blood) ↑PI3k-Akt pathway ↓ROS ↓mitochondrial loss ↑ATP levels ↓microglia activation (↓cell ramification, ↓IL-1β, IL-6, TNF-α) Alleviate gut dysbiosis	Zhang et al. (2023a)
Preclinical	LPS-injected rats	Preventive or therapeutic ketogenic diet	↓IL-1β, IL-6, TNF-α ↓microglia activation ($TSPO^{+}$) ↑ $mGluR5^{+}$ microglia phenotype modulation of Akt/GSK-3β/CREB signalling; ↑ H3K9 acetylation at the mGluR5 promoter; ↓PET inflammatory signal (^{18}F-DPA-714). Preventive ketogenic diet produced stronger effects than therapeutic one	Zhu et al. (2022)

Abbreviations: Akt – protein kinase B; CREB – cyclic adenosine monophosphate response element-binding protein; CRP – c-reactive protein; DA - dopamine; GSK-3β – glycogen synthase kinase 3 beta; H3K9 – histone H3 lysine 9; IL – interleukin; LPS – lipopolysaccharide; mGluR5; MPTP – 1-methyl-4-phenyl-1,2,3,6 tetrahydropyridine; NK – natural killer; PI3K – phosphatidylinositol-3-

kinase; PET – positron emission tomography; RCT – randomized controlled trial; ROS – reactive oxygen species; TNF-α – tumour necrosis factor alpha; TSPO – translocator protein.

characteristics but have been classified with low levels of evidence to be generally recommended (Bohnen et al., 2023; Dewsbury et al., 2021). However, the long-term feasibility and adherence to such a diet is questionable, especially in an older population such as people with PD, with an average dropout rate of 14-28%. In a 3-weeks study where a ketogenic diet was supplemented with medium-chain triglyceride oil, ketosis was accelerated, and treatment adherence improved nonmotor symptom severity score (Choi et al., 2024). Similarly, a recent phase II crossover trial, a MeDi supplemented with medium-chain triglyceride oil demonstrated (Link et al., 2024b) improvements in patient-reported outcomes with moderate adherence, compared to MeDi ketogenic diet, highlighting that ketogenic strategies in PD may require adaptation to improve sustainability (Tosefsky et al., 2026).

Importantly, a more recently published RCT (Tağraf et al., 2026) investigating a 6-month plant-rich ketogenic and time-restricted eating intervention, found significant improvements on motor symptomatology apathy and daily living activities, with notably no reported dropouts. However, long-term studies are needed to confirm these results. Relevantly, although the ketogenic diet is generally considered safe, it has been shown to increase CRP (Phillips et al., 2018; Rankin and Turpyn, 2007), which in PD has been correlated with worse life-long prognosis (Sawada et al., 2015). A possible mechanism for an increase in inflammation following ketogenic diet is the increase in oxidative stress, in which the accumulation of ROS perpetuates inflammation via activation of redox-sensitive nuclear transcription factors (e.g. AP-1 and NF-κB), and subsequent increase in expression of inflammatory proteins (Rankin and Turpyn, 2007). Moreover, a recent animal study reported increased expression of the senescence marker p53 in organs such as the heart, kidney and central nervous system (Wei et al., 2024), which is overexpressed in the neurons of people with PD (Sunico et al., 2013). Therefore, warranting caution is needed in ketogenic diets potential clinical application in this population.

2.3. Vegetarian/vegan diet

A vegetarian/vegan diet is defined as a diet that eliminates meat, meat-derived foods and, to varying degrees, other animal products such as eggs and dairy products (Hargreaves et al., 2023). A plant-based diet significantly reduced motor symptoms in just four weeks compared to an omnivorous diet (Baroni et al., 2011). For almost 20 years, epidemiological data on the benefits of plant-based dietary patterns have been accumulating (Gao et al., 2007), and, in particular, for inflammation modulation in PD (Table 3). A recent prospective analysis from the UK Biobank found that plant-based diets, particularly an increased intake of vegetables, nuts, and tea, correlated with a lower risk of PD: this dietary pattern appeared to offer protection only for individuals without genetic risk, while, conversely, an unhealthy plant-based diet, which includes food groups such as refined grains, fruit juices, sugar-sweetened beverages, potatoes, desserts, and sweets, was associated with an increased risk of PD (Tresserra- et al., 2023). The benefits of such a diet can be explained by the same components found in MeDi and a similar diet, as well as by reducing the consumption of food groups such as dairy products that have been associated with increased risk of PD (Olsson et al., 2022; Hughes et al., 2017) and worsening of symptoms (Mischley et al., 2017). Accordingly, a meta-analysis of cross-sectional studies comparing participants following vegan/vegetarian diets with an omnivorous diet found statistically decreased CRP in the vegetarian/vegan group (Menzel et al., 2020). Given that CRP is an established marker of low-grade inflammation, allied with the fact that in retrospective analysis baseline CRP correlated with worse motor-prognosis in PD, this mechanism could be relevant to explain the above-mentioned epidemiological data (Umemura et al., 2015). However, contrasting

Table 3
Vegetarian/vegan diet preclinical (in vivo) and clinical (human) evidence on inflammation modulation with relevance for PD.

Study type	Model/ population	Intervention	Main Immune/ Inflammatory Outcomes	Reference
Clinical	Systematic review and meta-analysis of 21 cross-sectional studies	Vegetarian/ vegan diet or omnivorous diet	↓CRP	Menzel et al. (2020)
Observational	Healthy adults (n = 558, 279 pairs)	Vegetarian diet or omnivorous diet	↓Energy-adjusted inflammatory index ↑TNF-α, ↑IL-6, ↑NLR and ↑PLR	Wang et al. (2024)
Observational	Healthy adults (n = 411)	Short-term dietary restriction of animal products	↓CRP ↓$CD56^+$ NK cells, ↓$CD8^+$ T cells ↑IL-10	Loizidou et al. (2025)
Clinical	Adults 18-50 (n = 20)	Ketogenic diet and vegan diet (cross-over, 2 weeks)	↑T helper cells; ↑NK cells ↑Type I interferon signatures ↑Innate immune signatures ↑Antiviral-response signatures	Link et al. (2024a)

Abbreviations: CD – cluster of differentiation; CRP – c-reactive protein; IL – interleukin; NK – natural killer; NLR – neutrophil-lymphocyte ratio; PLR – platelet-lymphocyte ratio; TNF-α – tumour necrosis factor alpha.

results exist on the topic (Wang et al., 2024), likely due to the dietary composition of the observed study population.

Relevantly, not all vegan and/or vegetarian diets necessarily have health benefits. Recent years have seen an increase in the commercialisation of animal-protein substitutes, therefore according to observational studies vegetarian and vegan nowadays consume more ultra processed foods compared to omnivores (Gehring et al., 2021; Chang et al., 2024). However, mechanistically restriction of animal protein seems to confer specific immunological and metabolic benefits. A recent large quasi-interventional study in people who restrict animal protein for religious reasons found, short-term restriction of meat, fish, dairy, and eggs for 3-4 weeks resulted in rapid reductions in total and low-density lipoprotein (LDL) cholesterol, liver and renal function markers (namely, reducing alanine aminotransferase and gamma-glutamyl transferase; and urea and creatinine, respectively), and a striking 73% reduction in circulating CRP levels (Loizidou et al., 2025). Importantly, comprehensive immune profiling revealed a diet-associated reduction in pro-inflammatory and senescent immune cell subsets, including non-classical monocytes, $CD56^+$ NK cells, and $CD8^+$ memory T cells, alongside an increased IL-10 response following immune stimulation, indicating enhanced immunoregulatory capacity (Loizidou et al., 2025). Moreover, as referred above, in a recent controlled cross-over study in healthy adults, it was shown that vegan diet selectively upregulated innate immune and antiviral pathways as compared with the ketogenic one: by multi-omic immune profiling, the vegan intervention increased signatures of neutrophil-driven innate immunity, type I interferon responses, and pathways related to host-viral interactions (Link et al., 2024a).

Together, these findings suggest that even short-term restriction of animal products can modulate systemic inflammation, providing a plausible biological mechanism linking plant-forward dietary patterns to neurodegenerative diseases. Still, caution is warranted when

recommending such dietary regimens, particularly the vegan diet, as it may be deficient in essential micronutrients such as vitamin B12 (Lederer et al., 2019), especially since PD patients have often already reduced B12 (Dong and Wu, 2020). Therefore, targeted supplementation should be carefully considered to prevent exacerbation of deficiency-related complications. Moreover, vegan and vegetarian diets, although rich in the omega-3 fatty acid α-linolenic acid, contain little to no eicosapentaenoic acid and docosahexaenoic acid; notably, the conversion of α-linolenic acid into eicosapentaenoic and docosahexaenoic acid is limited in humans and appears to be further reduced under chronic inflammatory conditions (Yin et al., 2023).

2.4. Fasting and caloric restriction

Fasting and caloric restriction, in their various iterations, have attracted increasing scientific and clinical attention in recent years (Chen et al., 2022) due to their pleiotropic effects on metabolism, inflammation, and longevity (Longo and Mattson, 2014). Fasting is defined as voluntary abstinence from some or all foods, with or without beverages. Fasting-mimicking diets (FMD) are a structured caloric restriction providing between 25 and 50% habitual energy intake, whilst intermittent fasting is a repetitive fasting period lasting less than 48 h (Koppold et al., 2024). A comprehensive consensus on the classification and definition of the different iterations of fasting has been previously proposed (Koppold et al., 2024).

Moreover, fasting has attracted considerable interest in the field of neurodegenerative diseases due to its potential neuroprotective properties (Longo and Mattson, 2014). Similar to ketogenic diets, FMDs, including intermittent fasting and caloric restriction, may also influence the pathogenesis of PD by affecting intestinal peptide production, the nucleotide-binding oligomerization domain-, leucine-rich repeat, and pyrin domain-containing 3 (NLRP3) inflammasome, insulin sensitivity and brain-derived neurotrophic factor (BDNF) production (Figueira et al., 2017; Jackson et al., 2019; Mattson et al., 2017) – Table 4.

Table 4
Fasting and caloric restriction preclinical (in vivo) and clinical (human) evidence on inflammation modulation with relevance for PD.

Study type	Model/population	Intervention	Main Immune/Inflammatory Outcomes	Reference
Clinical	PD patients (n = 31)	Prolonged fasting (~350 kcal/day, 7 days) followed by 16:8 time-restricted eating (12 months)	Clinical endpoints: −34% UPDRS Part III and −36% NMSS ($P < 0.01$), sustained over 12 months; ↓BMI, ↓heart rate Proposed mechanism: ↓pro-inflammatory signalling via ↓insulin/IGF-1/mTOR, ↑autophagy/ketogenesis, gut microbiome reset.	Hansen et al. (2025)
Observational	PD patients (n = 24)	Ramadan dawn-to-dusk fasting (~1 month)	Feasibility/safety endpoint (no inflammatory markers): no serious adverse effects; no significant change in PDQ-39, NMSS, or clinical severity vs pre-Ramadan.	Kamel et al. (2019)
Preclinical	MPTP-injected mice	ADF or weekly (2 weeks)	↓GFAP; ↑PI3K; ↑Akt; ↑ERK1/2; ↑CREB; ↑BDNF; ↑GDNF	Ojha et al. (2023)
Preclinical	MPTP-injected mice	FMD - 3 days fasting, 4 days feeding 1 (3 cycles)	↑BDNF ↓TNF-α, ↓IL-1β ↓GFAP, ↓Iba-1 ↑SCFA	Zhou et al. (2019a)
Preclinical	MPTP-injected mice	ADF or Ad libitum (16 weeks)	↓NLRP3, ↓caspase1, ↓IL-1β Maintained IL-18 and IL-1β (gut)	Wang et al. (2025a)
Preclinical	rAAV-αSyn mice	ADF (4 weeks)	↓GFAP, ↑Iba-1, ↓activated microglial morphology ↓*Nos2*, ↓*Tnfa*, ↑*Il-4*, ↑*RETNLB*, ↑*Chil3* ↑*Ccl17*, ↑*Cdkn1a*, ↓*l1rl2*, ↓*Pla2g4a*	Szegő et al. (2025)
Preclinical	MPTP-induced rhesus monkeys (*Macaca mulatta)*	30% CR or Ad libitum (6 months)	↑GDNF Maintenance of motor activity; Attenuate DA depletion and DA metabolites (striatum)	Maswood et al. (2004)
Preclinical	MPTP-injected mice	IF (alternate-day fasting) (13 weeks)	↓TNF-α, ↓IL-1β (gut); ↓astrocyte and microglial activation; ↓TLR4/NF-κB signalling (colon and SN); ↑SCFA; ↓*Proteobacteria*, ↓*Desulfovibrio*; ↑*Lactobacillus murinus*; Restored gut and BBB integrity	Qu et al. (2026)
Preclinical	Rotenone-injected mice	IF (24 h alternate-day fasting) Alone or with rotenone (28 days)	**Exacerbated** neurodegeneration: ↑DA neuron loss, ↑αSyn accumulation (SN); ↑excitatory amino acids; ↑inflammatory lysophospholipids and sphingolipids; impaired motor performance	Tatulli et al. (2018)
Preclinical	MPTP-injected mice Aged (1-year-old)	DR (60% intake) (3 months)	No inflammatory markers assessed. No neuroprotection in striatal DA and DOPAC Baseline DA lower in DR mice. Age-dependent loss of the protective effect.	Morgan et al. (2003)
Preclinical	MPTP-injected mice (subchronic)	DR (alternate-day fasting) initiated AFTER toxin (21 days)	No inflammatory markers assessed. Reversed the MPTP-induced decrease in striatal extracellular glutamate; no change in GLT-1; no DAergic rescue	Holmer et al. (2005)
Preclinical	MPTP-injected mice (adult)	DR (alternate-day fasting) or 2-deoxy-D-glucose	No cytokine data. ↓oxidative stress, preserved mitochondrial function; ↓dopaminergic neuron loss (SN), improved motor outcome	Duan and Mattson (1999)
Preclinical	*SNCA* (A53T α-synuclein) transgenic mice	IF (alternate-day) vs high-calorie diet vs Ad libitum	No cytokine data. IF restored autonomic control of heart rate (↑parasympathetic/cardiovagal tone, normalised elevated HR) and preserved DMNV neuron function; High-calorie diet ↑autonomic dysfunction; brainstem αSyn accumulation unaffected	Griffioen et al. (2013)

Abbreviations: ADF – alternate-day fasting; Akt – protein kinase B; BBB – blood-brain barrier; BDNF – brain-derived neurotrophic factor; BMI – body mass index; CR – caloric restriction; CREB – cyclic adenosine monophosphate response element-binding protein; DA - dopamine; DMNV – dorsal motor nucleus of the vagus; DOPAC - 3,4-dihydroxyphenylacetic acid; DR – dietary restriction; ERK – extracellular signal-regulated kinase; FMD – fast mimicking diet; GDNF – glial-derived neurotrophic factor; GFAP – glial fibrillary acidic protein; GLT-1 – glutamate transporter 1; HR – heart rate; Iba-1 – ionized calcium-binding adaptor molecule 1; IF – intermittent fasting; IGF-1 – insulin-like growth factor 1; IL – interleukin; MPTP – 1-methyl-4-phenyl-1,2,3,6 tetrahydropyridine; mTOR; NF-κB – nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP3 – nucleotide-binding oligomerization domain-, leucine-rich repeat, and pyrin domain-containing 3; NMSS – non-motor symptoms scale; PD – Parkinson's disease; PDQ-39 – PD questionnaire-39 (quality of life assessment); PI3K – phosphatidylinositol-3-kinase; SCFA – short-chain fatty acid; SN – substantia nigra; *SNCA* – synuclein alpha (gene encoding for α-synuclein); TLR – toll-like receptor; TNF-α – tumour necrosis factor alpha; UPDRS – Unified Parkinson's Disease Rating Scale; aSyn – alpha synuclein.

FMDs trigger autophagy and can reduce neuroinflammation and mitochondrial dysfunction (Neth et al., 2021; Zhao et al., 2022a). In one of the most widely used animal models of PD (*i.e.*, mice injected with the neurotoxin 1-methyl-4-phenyl-1,2,3,6tetrahydropyridine, MPTP), fasting and intermittent fasting increased retention of motor function and decreased SN neurodegeneration (Ojha et al., 2023; Zhou et al., 2019a). This effect is likely mediated by FMD-induced increases in brain BDNF and reductions in neuroinflammation through attenuations in reactive glial cells and pro-inflammatory cytokines such as the TNF-α and IL-1β, as well as increases in neuroprotective pathways such as phosphatidylinositol-3-kinase and protein kinase B (Ojha et al., 2023; Zhou et al., 2019a). Moreover, the FMD regulates the microbiome, shifting it towards taxa associated with short-chain fatty acids (SCFA) production such as Firmicutes, Tenericutes, and Opisthokonta, whilst lowering Proteobacteria, and increasing faecal SCFA (Zhou et al., 2019a). In another MPTP mouse model, alternate-day fasting, through a time-dependent effect, reduced nigrostriatal neurodegeneration, improved motor performance, and decreased α-synuclein aggregation, also reducing the NLRP3–caspase-1–IL-1β/IL-18 axis and microglial activation (Wang et al., 2025a). Again, the protective effect of fasting appears to act mechanistically through the gut-brain axis, via increases in zonula occludens (ZO)-1 and occludin, decreases in intestinal cytokines, and amelioration of villus architecture, as well as decreases in pathogens such as Helicobacter and Desulfovibrio and increases in potential beneficial bacteria such as Alistipes and Lactobacillus[93]. Accordingly, in the recombinant adeno-associated viral vectors)- αSyn mouse model, intermittent fasting decreased nigrostriatal neurodegeneration through enhanced autophagic capacity, thereby increasing α-synuclein clearance, where transcriptome analysis highlighted the modulation of inflammation-related genes and of glial activation (Szegő et al., 2025).

Although both 6-hydroxydopamine (6-OHDA) and MPTP are widely used models for studying different aspects of PD pathology, each has distinct advantages and limitations. The 6-OHDA model enables precise and reproducible control of dopaminergic neurodegeneration and closely mimics motor symptoms of PD; however, it is limited by its rapid, non-progressive nature, weak and transient neuroinflammation, and the absence of αSyn/Lewy body pathology. In contrast, the MPTP model better reflects certain features of human PD, particularly mitochondrial dysfunction and peripheral immune involvement, and is well suited for studying molecular pathways and aspects of disease progression. Nevertheless, it is constrained by variability and a tendency for recovery after intoxication (for a review in the theme, see (Saponjic et al., 2024)). From a translation perspective, early evidence from a rhesus monkey model of PD demonstrated that caloric restriction allowed retention of higher striatal dopamine levels, motor function, and increased levels of neurotrophic factors supporting dopaminergic neuron survival in the caudate nucleus (Maswood et al., 2004). Relevantly, a recent one-arm study, ExpoBiome (Hansen et al., 2023), investigated a one-year-long time-restricted eating window following a one-week prolonged fast and found protracted amelioration of motor and non-motor symptoms and a reduction of depressive symptoms (Hansen et al., 2025). Importantly, preliminary clinical evidence supports the feasibility and safety of fasting-based interventions in PD, as fasting is common across several religious practices; notably, Ramadan fasting appears safe and well tolerated in people with PD (Kamel et al., 2019). Importantly to stress, dietary restrictions are not recommended for older adults (Zhao et al., 2022a) once constraining food choice and eating pleasure may lead to low dietary intake, an underlying cause for malnutrition, also related to high requirements and impaired energy and nutrient bioavailability (Volkert et al., 2019). Particularly, caloric restrictions (i.e., regimens where energy requirements are not met), if not framed in specific obesity-targeting strategies represent an increased risk for weight and free-fat mass loss and functional decline (Zhao et al., 2022a). Considering PD patients' characteristics such as age, weight-loss and symptomatology, any investigation or recommendation of fasting and restrictive regimens such as caloric restriction should take this into consideration (Li et al., 2024a).

2.5. Vitamin supplementation

In addition to specific dietary patterns, several nutrients and vitamins with putative neuroprotective and immunomodulatory properties may be of interest. Regarding vitamins (Table 5), vitamin D, omega-3 fatty acids, co-enzyme Q10, vitamin E and vitamin B12, have been found to be consistently decreased in PD patients compared to controls, and often correlate with PD motor and non-symptoms (Etminan et al., 2005; McCarter et al., 2019; Ding et al., 2013; Negida et al., 2016). Despite the potential benefits, there is currently a lack of robust clinical evidence regarding the benefits of vitamin supplementation in inflammation in the context of PD (see Table 6).

Vitamins such as vitamin E and vitamin C are known to contribute to protect against the development of PD (Etminan et al., 2005; Moretti et al., 2017). Vitamin B12 and folate are involved in homocysteine metabolism, which deficiency is associated with cognitive decline and neurodegeneration (McCarter et al., 2019), particularly pertinent once chronic levodopa therapy has been shown to increase homocysteine, leading to vitamin B12/folate deficiency (O'Suilleabhain et al., 2004; Lökk, 2003), however, is there is no evidence of the effect of B vitamin supplementation in immune marker in PD.

The strongest evidence supports the benefits of vitamin D (Pignolo et al., 2022), which crosses the BBB and is associated with its immunomodulatory role in innate and adaptive immunity, including pattern recognition receptors, cytokines and induction of antimicrobial peptide secretion (Zali et al., 2024a; Asbaghi et al., 2020; White, 2022). Moreover, low vitamin D levels have been associated with an increased PD risk (Ding et al., 2013; Zali et al., 2024a; Wang et al., 2015a). Calvello et al., showed that supplementation of vitamin D for 10 days in an MPTP-induced preclinical mouse model of PD significantly attenuated the toxin-induced loss of tyrosine hydroxylase (TH)-positive neuronal cells, microglial cell activation (Ionized calcium-binding adaptor molecule 1 (Iba1)-immunoreactive), inducible nitric oxide synthase (iNOS) and TLR4 expression, typical hallmarks of the pro-inflammatory activation of microglia. In the same study, vitamin D supplementation also decreased pro-inflammatory cytokines mRNA expression in the brain, upregulated anti-inflammatory cytokines [IL-10, IL-4 and transforming growth factor beta (TGF-β)] mRNA levels, as well as increasing the expression of CD163, CD206 and CD204, considered to be part of anti-inflammatory signalling pathways. In a clinical study with PD patients with deep brain stimulation were allocated to a 12-week body mass index (BMI)-based supplementation of vitamin D3: after the intervention, there was a significant decrease in serum TNF-α concentrations, while IL-6 levels remained relatively stable (Bytowska et al., 2023).

To date, there are no human clinical studies investigating the independent role of omega-3 or vitamin E supplementation on motor symptoms or inflammatory markers in PD, as they are often co-supplemented. A randomized, double-blind, placebo-controlled clinical trial with 40 PD participants[91] showed that a 12-week intervention, co-supplementation with omega-3 fatty acids and vitamin E significantly downregulated TNF-α gene expression in the peripheral blood mononuclear cells (PBMCs) of participants with PD compared to the placebo group. However, no significant effects were observed for IL-1 and IL-8 expression. They also found that omega-3 and vitamin E co-supplementation significantly decreased UPDRS part I compared with the placebo though it did not affect other parts of UPDRS. In a separate study from the same team, a 12-week intervention of omega-3 and vitamin E co-supplementation led to a significant improvement in UPDRS and decreased serum high-sensitivity CRP, compared with the placebo (Taghizadeh et al., 2017). The largest known study with vitamin E supplementation was conducted by the Parkinson Study Group, in a prospective, placebo-controlled, double-blind trial of 800 drug-naive PD

Table 5
Vitamin supplementation preclinical (in vivo) and clinical (human) evidence on inflammation modulation with relevance for PD.

Study type	Model/Population	Intervention type	Impact on Immune/Inflammatory Outcomes	Reference
Clinical	PD patients (n = 16)	Vitamin D3 (BMI-based dosing) (12 weeks; post-DBS)	↓TNF-α; IL-6 unchanged (serum)	Bytowska et al. (2023)
Clinical	PD patients (n = 40) (RCT)	Omega-3 + vitamin E co-supplementation (12 weeks)	↓*TNF-α* (PBMCs); ↓ hs-CRP; IL-1, IL-8 unchanged; ↓UPDRS part I	Borzabadi et al. (2018)
Clinical	PD patients drug-naïve (RCT, n = 800; DATATOP)	Vitamin E (α-tocopherol) ± deprenyl	No effect on disease-progression rate; no inflammatory marker measured	Effects of Tocopherol and Deprenyl (1993)
Clinical	Patients with PD/inflammatory conditions (meta-analysis)	Coenzyme Q10	↓CRP, IL-6, TNF-α in some trials	Fan et al. (2017)
Clinical	PD patients (meta-analysis)	Coenzyme Q10	No benefit on motor symptoms	Zhu et al. (2017)
Clinical	Early PD patients (RCT) (n = 600)	Coenzyme Q10 (high dose)	No clinical benefit vs placebo	Beal et al. (2014)
Preclinical	MPTP-injected mice	Vitamin D (calcitriol) (10 days)	↓ Iba-1$^+$ microglia, iNOS, TLR4; ↓ TNF-α, IL-1β; ↑ IL-10, IL-4, TGF-β; ↑ CD163/CD206/CD204; preserved TH$^+$ neurons; M1→M2 shift	Calvello et al. (2017)
Preclinical	MPTP-injected mice (129SV)	Vitamin C (ascorbate) (10 days)	↓ TH$^+$ cell loss, microglial activation, astrogliosis; ↓ IL-6, TLR4, TNF-α, iNOS, CD40; ↑ IL-10, CD163, TGF-β, IL-4; ↓ NLRP3	De Nuccio et al. (2021)
Preclinical	PD rodent models	Nicotinamide (vitamin B3)	↑ locomotor behaviour; ↓ oxidative biomarkers; direct immunomodulatory role under study	(Zhao et al., 2019; Shults, 2002; Chen et al., 2025a)

Abbreviations: BMI – body mass index; CD – cluster of differentiation; CRP – c-reactive protein; DBS – deep brain stimulation; Iba-1 – ionized calcium-binding adaptor molecule 1; IL – interleukin; iNOS – inducible nitric oxide synthase; M1 - classically activated macrophage/microglia phenotype; M2 - alternatively activated macrophage/microglia phenotype; MPTP – 1-methyl-4-phenyl-1,2,3,6 tetrahydropyridine; NLRP3 – nucleotide-binding oligomerization domain-, leucine-rich repeat, and pyrin domain-containing 3; PD – Parkinson's disease; RCT – randomized controlled trial; TGF – transforming growth factor; TH – tyrosine hydroxylase; TLR – toll-like receptor; TNF-α – tumour necrosis factor alpha; UPDRS – Unified Parkinson's Disease Rating Scale.

patients – Deprenyl and tocopherol antioxidative therapy of parkinsonism (DATATOP) study (Effects of Tocopherol and Deprenyl, 1993). The study investigated the effect of deprenyl (a MAO-B inhibitor) and vitamin E: in this population, vitamin E failed to delay the rate of disease progression compared with placebo, whether administered alone or in combination with deprenyl. However, an epidemiological study showed that vitamin E consumption is associated with decreased risk of PD, but only in its dietary form, suggesting that vitamin E's benefits may be enhanced when taken in naturally occurring dietary forms (Zhang et al., 2002). Studies with co-enzyme Q10, a vitamin-like substance, have also shown positive effects on the reduction of pro-inflammatory cytokines, namely CRP, IL-6 and TNF-α (Fan et al., 2017; Abdollahzad et al., 2015; Lee et al., 2012, 2013; Sanoobar et al., 2015) but despite some encouraging evidence (Yoritaka et al., 2015), a meta-analysis of RCTs have failed to show positive effects of co-enzyme Q10 supplementation on PD motor symptoms (Zhu et al., 2017; A randomized clinical trial of, 2007; Beal et al., 2014).

Further studies are certainly needed to investigate the effect of vitamin D and other vitamins on the immune regulation of people with PD at different stages of the disease. Moreover, precision medicine concepts should be applied to vitamin supplementation and clinical trials should account for ethnic background, as nutritional requirements can vary significantly across different populations (Koulman et al., 2026). Importantly to stress, it is known that vitamin B6 (pyridoxine) can reduce the efficacy of levodopa if administered without the combination with a decarboxylase inhibitor (e.g., carbidopa, benserazide): indeed, vitamin B6 is a L-amino acid decarboxylase cofactor, acting by increasing peripheral conversion of levodopa into dopamine, and, consequently, reducing the amounts of levodopa able to reach the CNS (Klawans et al., 1971; Lizárraga and Lang, 2022). On the other hand, it has been reported that vitamin C can alter levodopa absorption/-pharmacokinetics by increasing its bioavailability in elderly PD patients – a potential combinatory treatment (Nagayama et al., 2004).

2.6. (Poly)phenol supplementation

(Poly)phenols and their metabolites are increasingly being studied in PD with respect to protection of nigrostriatal dopaminergic neurons (Figueira et al., 2017; Datla et al., 2007; Zhou et al., 2019b) and hallmarks of PD such as neuroinflammation (Datla et al., 2007; Zhou et al., 2019b; Lofrumento et al., 2014). They comprise a group of non-essential plant phytochemicals/bioactive compounds characterized by the presence of one or more phenol groups (*i.e.* the (poly)phenols), also highly abundant in healthy dietary patterns such as the MeDi. (Poly)phenols have been described as pleiotropic with widely reported anti-inflammatory and immunomodulatory effects, acting on key molecular signalling pathways involved in PD progression, such as oxidative stress, protein aggregation, mitochondrial dysfunction and (neuro) inflammation (Figueira et al., 2017; Carecho et al., 2024; Kujawska and Jodynis-Liebert, 2018; Datla et al., 2007; Gahtani et al., 2024; Carregosa et al., 2022).

While poor nutritional status and reduced quality of life were found in people with PD, higher consumption of flavonoids (*i.e.* a class of dietary (poly)phenols), particularly anthocyanins and flavan-3-ols, and flavonoid-rich foods (such as berries and red wine) has been associated with a lower risk of patient mortality (Zhang et al., 2022b). In addition, increased (poly)phenol consumption has been associated with a lower risk of developing PD (Gao et al., 2012; Bianchi et al., 2023), whilst flavonoid intake was associated with reduced cognitive decline and reduced mortality in PD patients (Zhang et al., 2022a, 2022b). A systematic review by Kujawska and Jodynis-Liebert (2018) gathered evidence from in vivo studies showing that (poly)phenols increase dopamine levels and protect dopaminergic neurons, reduce neuroinflammation by inhibiting NF-κB and pro-inflammatory cytokines (Sharma and Nehru, 2018), and attenuate oxidative stress by upregulating antioxidant enzymes and suppressing ROS(22). One of the primary immune-related mechanisms through which (poly)phenols act is via the inhibition of NF-κB, responsible for the upregulation of proinflammatory cytokines such as TNF-α, IL-1β and IL-6, reported to be elevated in people with PD and contributing to neurodegeneration (Mamun et al., 2024; Karunaweera et al., 2015). In addition, (poly) phenols have been shown to improve antioxidant defence by activating the Nrf2 pathway (Yasuda et al., 2024), which upregulates endogenous antioxidant enzymes and reduces ROS, which are a major cause of oxidative stress and mitochondrial dysfunction in PD neurons (Karunaweera et al., 2015; Sharifi-Rad et al., 2023). Furthermore, Zhang

Table 6
(Poly)phenol supplementation preclinical (in vivo) and clinical (human) evidence on inflammation modulation with relevance for PD.

Study type	Model/population	Intervention	Main Immune/Inflammatory Outcomes	Reference
Clinical	PD patients (n = 60)	Curcumin nanomicelle (80 mg/day) (oral, 9 months)	No significant UPDRS/PDQ-39 change (trend part III). **No inflammatory markers measured**	Ghodsi et al. (2022)
Clinical	PD patients (n = 50)	Curcumin nanomicelle (80 mg ×2/day) (oral, 3 months)	↑Sleep quality (PSQI); ↑quality of life (PDQ-39); no effect on fatigue. **No inflammatory markers measured**	(Maghbooli et al., 2019)
Clinical	PD patients (n = 40)	Curcumin phospholipid (Meriva) (2 g/day) (oral, 12 months)	↑Non-motor scales (COMPASS-31, NMSS); trend ↓ skin-nerve p-αSyn; curcuminoids cross BBB (CSF). **No inflammatory markers measured**	Donadio et al. (2022)
Preclinical	MPTP-injected mice	Resveratrol (50 mg/kg/day) (gavage, 21 days)	↓GFAP; ↓CD11 ↓IL-1β; ↓IL-6; ↓TNF-α ↓*IL-1Rβl*, ↓*TNF-αRI* and ↓*IL-6Rα* ↑*SOCS-1*	Lofrumento et al. (2014)
Preclinical	LPS-injected rats	Curcumin (40 mg/kg) (i.p., 21 days)	↓GFAP, ↓NADPH oxidase, ↓NF-κB, ↓TNF-α, ↓IL-1β, ↓IL-1α, and ↓iNOS	Sharma and Nehru (2018)
Preclinical	Rotenone-injected mice	*Ecklonia cava* (poly)phenols	↑AMPK/Nrf2-ARE signalling, ↑NQO1, ↑Nrf2 nuclear translocation, ↑TH	Yasuda et al. (2024)
Preclinical	MPTP-injected mice	EGCG (25 & 50 mg/kg) (gavage, ≈26 d)	↓TNF-α/IL-6 (serum); restored CD4+/CD8+ T-cell ratio; protected TH^+ neurons (SN); ↑motor performance	Zhou et al. (2018)
Preclinical	Intranigral LPS-injected mice	Quercetin (30 & 60 mg/kg) (i.p., 10 d)	↓Microglial activation via NLRP3–mitophagy interplay; ↓IL-1β; restored mitochondrial quality control	Han et al. (2021)
Preclinical	Rotenone-induced mice (oral, chronic)	Quercetin (30 mg/kg/day) (gavage, 60 d)	↑IL-6 (serum); ↑GFAP (SN, hippocampus); ↓TH^+ fibers; improved memory & motor	Jain et al. (2022)
Preclinical	MPTP-injected mice	Quercetin (60 mg/kg/day) (i.p., 8 d)	↓Ferroptosis via Nrf2; ↓lipid ROS/MDA; ↑GSH/SOD; ↑GPX4/SLC7A11/FTH; ↑TH	Lin et al. (2022)
Preclinical	MPTP-injected mice	Baicalein (140/280/560 mg/kg/day) (intragastric, 9 d)	↓IL-1β/IL-18/IL-6/TNF-α; ↓NLRP3/caspase-1/GSDMD pyroptosis; ↓MGnD microglia (IBA1+APOE)	Rui et al. (2020)
Preclinical	MPTP-injected mice	Fisetin (100 ng/kg) (oral, 30 d)	↑TH; ↓apoptosis; gut microbiota remodelling (16S). Anti-inflammatory inferred via gut–brain axis only; **cytokines/microglia not measured**	Chen et al. (2020)
Preclinical	6-OHDA mouse model (intrastriatal)	Hesperidin (50 mg/kg) (p.o., 28 d)	↓Striatal TNF-α/IFN-γ/IL-1β/IL-2/IL-6; ↑neurotrophic factors; ameliorated anxiety/depressive-like behaviour	Antunes et al. (2020)
Preclinical	MPTP-injected mice	Isoliquiritigenin (20 & 40 mg/kg) (gavage, 10 d)	↓iNOS/COX2; ↓p-JNK/AKT/NF-κB/IκBα (SN, striatum); suppressed microglial neuroinflammation	Bai et al. (2023)
Preclinical	6-OHDA mouse model (stereotaxic SN)	Isoliquiritigenin (20 mg/kg) (i.p., 14 d)	↓Iba1; ↓IL-1β/IL-6/TNF-α; ↑Nrf2/NQO1; ↑TH; ↓αSyn; ↑motor performance	Huang et al. (2022)
Preclinical	MPTP-injected mice	Neohesperidin (25 & 50 mg/kg) (gavage, 24 d)	↓IL-6/IL-1β/TNF-α (midbrain/colon/serum); ↓Iba-1 & OX42; ↓NF-κB p65 & MAPK; gut microbiota regulation	He et al. (2024)
Preclinical	MPTP-injected mice	Rhein (20 mg/kg) (i.v., every 2 d × 1 month)	↓IL-1β/IL-6/TNF-α (SN/striatum, serum); ↓Iba1; ↓M1 markers CD16/32/86; ↓p-P38/JNK/IκB; ↑TH; ↓αSyn	Qin et al. (2024)
Preclinical	MPTP-injected mice	Nootkatone (2 & 5 mg/kg) (i.p., 3 d)	↓iNOS/COX2/TNF-α/IL-1β/IL-6; ↓GFAP/Iba-1; ↑Nrf2/HO-1/NQO1 (astrocytes); ↓TLR2/TLR4; ↑IL-10/TGF-β; ↑TH	Park et al. (2023a)
Preclinical	MPTP-injected mice	Urolithin A (20 mg/kg) (i.p., 7 d pre-MPTP)	↓NLRP3 inflammasome activation; ↑mitophagy; ↓pro-inflammatory responses; ↓dopaminergic loss	Qiu et al. (2022)
Preclinical	MPTP-injected mice	Morin, dietary (34 d)	↓GFAP/Iba-1; ↑TH; (glia in vitro: ↓TNF-α/IL-6/IL-1β, ↓ERK & p65/NF-κB)	Hong et al. (2022a)
Preclinical	MPTP-injected mice (SN + striatum)	Silybin (100 mg/kg), (gavage, post-MPTP × 5 d)	↓TNF-α/IL-1β/IL-6 (basal); ↑IL-10 & IL-4 (SN); ↑fractalkine/CX3CL1; ↑BDNF & IGF-1; ↓MDA	Ramírez-Carreto et al. (2023)
Preclinical	MPTP-injected mice (subacute)	Silibinin (70/140/280 mg/kg) (gavage, 24 d)	↓NLRP3/caspase-1/IL-1β/TNFα; ↓MDA; ↑GSH-PX; ↑TH/DA; ↑PINK1/Parkin/LC3 (mitophagy); ↓αSyn	Liu et al. (2021a)
Preclinical	MPTP-injected mice (acute)	Cinnamaldehyde (150/300/600 mg/kg) (gavage, 14 d)	↓*iNOS/TNF-α/IL-1β* ↓iNOS & NF-κB p65; ↓IBA1 & GFAP; ↑*GDNF*	Jiao et al. (2024)
Preclinical	MPTP-injected mice	Apigenin (50 mg/kg) (i.p., 5 d -prophylaxis or treatment)	Reversed ↑TNF-α/IL-1β/IL-6 and ↓IL-10 (brain); stronger in prophylaxis; ↑TH^+ neurons	Yarim et al. (2025)
Preclinical	Rotenone-injected rats	Apigenin (10 & 20 mg/kg) (i.p., 14 d)	↓*TNF-α/IL-6*/NF-*κB/iNOS*-1 (striatum); ↓NO; ↑TH; ↑BDNF/GDNF; ↓αSyn; Restored complex-I and GSH/SOD/CAT/GPx	Anusha et al. (2017)
Preclinical	Intranigral LPS-injected mice	Luteolin (40 mg/kg/day) (i.p., 9 d)	Shifted microglial M1→M2 (↓CD32/iNOS/TNF-α; ↑Arg-1/CD206/IL-10); ↓IL-6/TNF-α/IL-1β; ↓IBA-1; via TLR4/NF-κB p65	Xie et al. (2024)
Preclinical	MPTP-injected mice	Luteolin-7-O-glucoside (30 mg/kg) (gavage, 15 d)	↓GFAP & ↓Iba1 (SN) – attenuated gliosis; ↑TH + neurons & fibers; ↑ERα/ERβ & ERK1/2/STAT3/c-Fos; ↑Bcl-2/Bax	Qin et al. (2019)
Preclinical	MPTP-injected mice	Pterostilbene (20 mg/kg) (oral, daily)	↓Microglial (CD11b) & astrocyte (GFAP) activation (SN); ↓*TNF-α/IL-1β* mRNA ↑striatal DA; ↓αSyn	Fan et al. (2024)
Preclinical	MPTP-injected mice	Chlorogenic acid (25/50/100 mg/kg) (oral, 24 d)	↓GFAP (SN + striatum); ↓TNF-α/iNOS; ↓IL-1β/TNF-α mRNA, ↑IL-10 mRNA; ↓NF-κB; ↑TH; ↓oxidative stress	Singh et al. (2018)
Preclinical	MPTP-injected mice	Mangiferin (12.5/25/50 mg/kg) (oral, 2 weeks)	↓GFAP/IBA-1; ↑GIT1; ↑Nrf2/HO-1, ↓Keap1; ↓ROS, ↑GSH/SOD; ↑motor performance	Zhou et al. (2023)

(*continued on next page*)

Table 6 (*continued*)

Study type	Model/population	Intervention	Main Immune/Inflammatory Outcomes	Reference
Preclinical	6-OHDA rat model (hemi-parkinsonism)	Genistein (50 mg/kg) (gavage)	↓TNF-α (basal ganglia) ↑SOD, ↓MDA, ↓DNA fragmentation; ↑SN neurons	Bagheri and Salari (2025)
Preclinical	MPTP-injected mice	Daidzein (50 & 75 mg/kg) (oral, 30 d)	↓TNF-α/IL-1β/IL-6 (brain); ↓peripheral immune-cell infiltration; ↑DA; ↑motor performance	Wu et al. (2022)
Preclinical	MPTP-injected mice	Rosmarinic acid (1/4/16 mg/kg) (i.p., daily)	↓TNF-α/IL-1β/IL-6 (ventral midbrain); ↓Iba-1; ↓α-syn; via HMGB1/TLR4/MyD88/p65	Lv et al. (2019)
Preclinical	6-OHDA mouse model (intrastriatal)	Sulforaphane (5 mg/kg) (i.p., 2×/week × 4 weeks)	↑GSH & GST/GR (Nrf2/phase-II); ↓DNA fragmentation & caspase-3; ↓pERK1/2; ↑TH + neurons; ↑motor performance	Morroni et al. (2013)
Preclinical	MPTP-injected mice	Isobavachalcone (10 & 50 mg/kg) (gavage, 7 d)	↓IL-6/IL-1β; ↓Iba-1/GFAP; ↓NF-κB p65	Jing et al. (2017)
Preclinical	MPTP-injected mice	Ellagic acid (10 mg/kg) (1-week pre-MPTP)	↓IL-1β/IL-6/TNF-α; ↓COX-2/iNOS (striatum); ↓Iba-1/GFAP; DA neurons rescue	Ardah et al. (2020)

Abbreviations: 6-OHDA – 6-hydroxydopamine; AKT – protein kinase B; AMPK – AMP-activated protein kinase; ARE – antioxidant response element; Arg-1 – arginase-1; Bax – Bcl-2 associated X protein (pro-apoptotic); Bcl-2 – B-cell lymphoma 2 (anti-apoptotic); BDNF – brain-derived neurotrophic factor; CAT – catalase; CD – cluster of differentiation; COMPASS-31 – composite autonomic symptom score 31; COX2 - cyclooxygenase-2; CSF – cerebrospinal fluid; CX3CL1 – C-X3-C motif chemokine ligand 1 (fractalkine); DA - dopamine; EGCG – epigallocatechin gallate; ER – endoplasmic reticulum; ERK – extracellular signal-regulated kinase; FTH – ferritin heavy chain; Fos - FBJ murine osteosarcoma viral oncogene homolog (c-Fos); GDNF – glial-derived neurotrophic factor; GFAP – glial fibrillary acidic protein; GIT1 – G protein-coupled receptor kinase-interacting protein 1; GPx – glutathione peroxidase; GSDMD – gasdermin D; GSH – glutathione; GST – glutathione S-transferase; GR – glutathione reductase; HO-1 – heme-oxigenase 1; Iba-1 – ionized calcium-binding adaptor molecule 1; IGF-1 – insulin-like growth factor 1; IL – interleukin; IκBα – inhibitor of NF-κB alpha; iNOS – inducible nitric oxide synthase; JNK - c-Jun N-terminal kinase; LC3 – microtubule-associated proteins 1A/1B light chain 3; LPS – lipopolysaccharide; M1 - classically activated macrophage/microglia phenotype; M2 - alternatively activated macrophage/microglia phenotype; MAPK - mitogen-activated protein kinase; MDA – malondialdehyde; MPTP – 1-methyl-4-phenyl-1,2,3,6 tetrahydropyridine; MyD88 – myeloid differentiation primary response 88; NADPH – nicotinamide adenine dinucleotide phosphate; NF-κB – nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP3 – nucleotide-binding oligomerization domain-, leucine-rich repeat, and pyrin domain-containing 3; NMSS – non-motor symptoms scale; NQO1 – NAD(P)H quinone dehydrogenase 1; Nrf2 – nuclear factor erythroid 2–related factor 2; P38 - p38 mitogen-activated protein kinase; p65 – NF-κB p65 subunit; PD – Parkinson's disease; PDQ-39 – PD questionnaire-39 (quality of life assessment); PINK – PTEN-induced kinase; PSQI – Pittsburgh sleep quality index; ROS – reactive oxygen species; SLC – solute carrier; SN - Substantia nigra; SOCS-1 – suppressor of cytokine signaling 1; SOD – superoxide dismutase; STAT - Signal transducer and activator of transcription; MGnD – microglia neurodegenerative phenotype; OX42 - CD11b/c integrin marker; TGF – transforming growth factor; TH – tyrosine hydroxylase; TLR – toll-like receptor; TNF-α – tumour necrosis factor alpha; UPDRS – Unified Parkinson's Disease Rating Scale; aSyn – alpha synuclein.

et al. (2023) highlighted that (poly)phenols may modulate gut bacteria by increasing beneficial SCFA-producing species and may counteract gut inflammation, potentially influencing disease progression (Zhang et al., 2023b). Clinical and pre-clinical studies have linked the consumption of (poly)phenols, particularly blueberries and grapes, to improved cognitive function and memory (Krikorian et al., 2010, 2012; Bensalem et al., 2019). Similarly, (poly)phenol intake was shown to contribute to improved neurocognitive function in older adults and may slow the onset and progression of neurodegenerative diseases (Nurk et al., 2009). Importantly to mention, dietary (poly)phenols present relatively low bioavailability and fast excretion, whilst their metabolites, mainly resulting from gut microbiota catabolism, can be several orders of magnitude higher found in circulation in the bloodstream (Carregosa et al., 2022; Le Sayec et al., 2023); in fact, after ingestion, only 5-10% of the parent/dietary (poly)phenols present in food are absorbed in the small intestine, whereas the great majority reach the colon being extensively metabolized/catabolized by the gut microbiota into low-molecular-weight (poly)phenol metabolites (Carregosa et al., 2022; Cardona et al., 2013), some reaching concentrations between nanomolar to low micromolar in healthy individuals (Pimpão et al., 2015). Consequently, most recent evidence points to the role of such metabolites as the true bioactive molecules acting against systemic and/or brain inflammation in PD, rather than parent (poly)phenols originally present in the different food matrices (Carecho et al., 2022; Marques et al., 2024; Carregosa et al., 2020). Importantly, it has already been shown that some bloodstream bioavailable (poly)phenol metabolites, such as that phenolic sulphates, can derive from different (poly)phenol-rich sources, regardless of crops, regions, season (Carregosa et al., 2022), which further supports them as ideal candidates to be explored for their health benefits. In addition, individuals can exhibit variability in their ability to absorb dietary (poly)phenols, influenced by factors such as age, gender, gut health, and specific transporters and enzymes (Scalbert et al., 2005; Del Rio et al., 2013), as well as how (poly)phenols are consumed (raw vs. cooked) and overall diet composition, such as the presence of fat (Manach et al., 2004; Rodriguez-Mateos et al., 2014). The gut microbiota's role in metabolizing (poly)phenols into more bioactive metabolites also varies among individuals, affecting the compounds' bioavailability and overall potential biological activity (Rodriguez-Mateos et al., 2014; Williamson and Clifford, 2010), factors that collectively determine (poly)phenol metabolites bioavailability, a paradigm yet to be fully disclosed in PD patients. Nevertheless, to exert a significant role against systemic/brain inflammation in nutritional terms, these metabolites need to either transpose the BBB or be effective at the borders of the BBB, in concentrations comparable to those found in the bloodstream/to the ones reported to be transported across the BBB (Figueira et al., 2017; Carecho et al., 2024; Rendeiro et al., 2015). What is known for the time being is that, in fact, some (poly)phenol metabolites can cross the BBB and reach the brain, both in vivo and in humans (Carecho et al., 2024; Le Sayec et al., 2023; Gasperotti et al., 2015), though the exact mechanism(s) behind such transport is yet to be fully understood ((Marques et al., 2024; Carecho et al., 2020) for detailed reviews in the subject). Remarkably, (poly)phenol metabolites tested in concentrations comparable as the ones bioavailable have already shown promising effects in attenuating (neuro)inflammation and PD-related hallmarks in vitro (Figueira et al., 2017; Carecho et al., 2022; Carregosa et al., 2020), reinforcing the hypothesis of their potential neuroprotective role in vivo and in PD patients.

Caution should also be taken regarding potential PD pharmacotherapy interactions with (poly)phenol-rich food sources. Flavonoids, stilbenes, and phenolic acids can either lead to pharmacokinetic interactions altering drug bioavailability or metabolism, or via pharmacodynamic/neuroprotective actions that may complement PD treatments. For instance, epigallocatechin-3-gallate and quercetin exhibit catechol structures, capable to bind and inhibit COMT, prolonging levodopa half-life and increasing brain dopamine availability (Kang et al., 2010; Singh et al., 2003). Contrarily, grapefruit flavanones

Table 7
Protein and fibre intake preclinical (in vivo) and clinical (human) evidence on inflammation modulation with relevance for PD.

Study type	Model/Population	Intervention	Main Immune/Inflammatory Outcomes	Reference
Clinical	Human evidence (PD risk) (meta-analysis)	Macronutrient intake (protein, carbohydrate, cholesterol, energy, PUFA)	Protein, carbohydrate, cholesterol, energy not independently associated with PD risk; higher PUFA inversely associated **No immune marker measured**	Wang et al. (2015b)
Clinical	General population & PD patients (meta-analysis)	Dairy/milk intake	↑ PD risk with higher dairy (≈+11% per 200 g/day total dairy); ↓ 12% cognitive impairment per 200 g/day	Talebi et al. (2023)
Clinical	Adults restricting animal protein	Animal-protein restriction (meat, fish, dairy, eggs) (quasi-interventional, 3–4 weeks)	−73% circulating CRP; ↓ non-classical monocytes, $CD56^{+}$ NK, $CD8^{+}$ memory T cells; ↑ IL-10 response (enhanced immunoregulation)	Loizidou et al. (2025)
Clinical	PD patients (n = 10)	Prebiotic fibre bar (resistant starch, rice bran, resistant maltodextrin, inulin) (10 g/serving) (open-label, 10 days)	↓ faecal calprotectin and zonulin; ↑ faecal SCFA; improved dysbiosis; ↓ UPDRS (exploratory) No changes in HMGB-1 and BDNF; ↓NfL	Hall et al. (2023)
Clinical	PD patients (n = 30)	Synbiotic (*L. paracasei* + inulin) (open-label single-arm, 12 weeks)	↑ SCFA-producing taxa; improved non-motor/GI symptoms; faecal SCFA increase not significant	Andreozzi et al. (2024)
Clinical	PD patients (n = 72)	Propionate + butyrate (SCFA) + prebiotic (2′-fucosyllactose) (RCT, 6 months, n = 72)	↑ MDS-UPDRS motor and some non-motor outcomes; ↓ ex vivo faecal inflammatory activity; ↑ gut-barrier markers	Hegelmaier et al. (2025)
Preclinical	MPTP-injected mice	Animal vs. plant protein (casein vs. soy)	Soy: ↓ microgliosis/astrogliosis, ↓ IL-1β, IL-6; ↑ IL-4, IL-10; preserved gut barrier. Casein: barrier injury, systemic inflammation, worse motor deficits	Zeng et al. (2020)
Preclinical	MPTP-injected mice	Casein (intragastric)	↑ Iba-1, CD4, IL-22 (midbrain/ileum); intestinal barrier injury; ↓ dopamine, ↓ TH	Liu et al. (2021b)
Preclinical	MPTP-injected mice (convalescent)	Casein-rich diet	Intestinal inflammation; ↑ Firmicutes/Bacteroidetes; ↓ α-diversity; ↓ dopamine; GI dysfunction	Pu et al. (2023)
Preclinical	GBA1-transgenic mice ($Gba1^{L444P/+}$)	Calcium- and casein-rich (dairy-rich) diet	Hepatic αSyn aggregation; mitochondrial oxidative stress; αSyn propagation via liver–brain axis	Chen et al. (2025b)
Preclinical	αSyn-overexpressing mice (Thy1-αSyn; ASO; line 61)	Prebiotic (fermentable) fibre diet	↑ faecal SCFA; ↓ central αSyn aggregation; ↓ motor deficits; effect mediated by microglia	Abdel-Haq et al. (2022)
Preclinical	αSyn-overexpressing mice (B6.D2-Tg(Thy1-SNCA)14Pjk)	Dietary fibre deprivation	Gut dysbiosis; ↑ αSyn aggregation; accelerated disease	Schmit et al. (2023)

Abbreviations: BDNF – brain-derived neurotrophic factor; CD – cluster of differentiation; CRP – c-reactive protein; IL – interleukin; GI – gastrointestinal; GBA – glucocerebrosidase beta acid; Iba-1 – ionized calcium-binding adaptor molecule 1; HMGB-1 - high mobility group box 1; MPTP – 1-methyl-4-phenyl-1,2,3,6 tetrahydropyridine; NfL – neurofilament light chain; NK – natural killer; PD – Parkinson's disease; PUFA – polyunsaturated fatty acid; SCFA – short-chain fatty acid; TH – tyrosine hydroxylase; UPDRS – Unified Parkinson's Disease Rating Scale; aSyn – alpha synuclein.

(naringin, naringenin) and furocoumarins irreversibly inhibit intestinal CYP3A4, having negative effects on bromocriptine and some MAO-B inhibitors leading to toxic levels and even excessive dopaminergic or side effects (Bailey et al., 2013). Nevertheless, evidence supports for increased consumption of fruits (including berries), vegetables, tea and coffee as significantly beneficial in PD. While observational studies have associated high (poly)phenol intake with better brain health, controlled intervention studies are needed to prove causality (Gahtani et al., 2024).

2.7. Macronutrients: protein and fibre intake

The importance of certain macronutrients in the management of neurodegenerative diseases, such as PD, is currently a topic of considerable controversy. A 2015 meta-analysis on macronutrients and PD risk found that protein, carbohydrate, cholesterol, and energy intake are not independently associated with PD risk, while higher polyunsaturated fatty acid intake may be inversely associated with PD risk (Wang et al., 2015b). In fact, the evidence on the different effects of animal protein sources in the diet on the risk of neurodegenerative diseases is still contradictory. A meta-analysis of prospective cohort studies found that the risk of developing PD was significantly higher with increased milk and dairy product consumption: each 200g increase in the total daily amount of dairy products consumption was associated with an 11% higher risk of PD and a 12% lower risk of cognitive impairment (Talebi et al., 2023). There was also a strong linear association between fish consumption and a lower risk of dementia (Talebi et al., 2023). Several other studies have shed light on the association of milk consumption and risk of PD (Olsson et al., 2022; Hughes et al., 2017; Park et al., 2005; Chen et al., 2007), although it is not yet clear whether these associations reflect an increased inflammatory status of patients or a causal role of milk consumption in the development of PD. Such observations may be due, at least in part, to the contribution of casein phospholipoprotein. In an MPTP mouse model, it was observed that casein administration resulted in persistent dyskinesia that decreased dopamine content in the striatum and TH expression in the midbrain and ileum, while the expression of Iba-1, CD4 and IL-22 in the midbrain and ileum continuously increased with persisted intestinal histopathology and intestinal barrier injury, suggesting involvement of nigrostriatal and intestinal inflammation (Liu et al., 2021b). The same observations were subsequently confirmed where casein resulted in decreased motor coordination, gastrointestinal dysfunction, decreased dopamine content and induced intestinal inflammation, with significant disruption of gut microbiota homeostasis by increasing Firmicutes/Bacteroidetes ratio, decreasing α-diversity and abnormal changes in faecal metabolites in MPTP-convalescent mice (Pu et al., 2023). Furthermore, a recent human study found in two people with PD carrying GBA1 L444P, the most common genetic risk factor in PD, hepatic accumulation of phosphorylated α-synuclein and they both presented elevated dairy consumption, which seems to create a permissive environment for phosphorylated αSyn (Bohnen et al., 2023). Further experimental models in mice demonstrated that a calcium- and casein-rich diet induced αSyn aggregation in liver macrophages, promoted mitochondrial oxidative stress and autophagy impairment, and facilitated the propagation of αSyn pathology to the brain via a neural liver–brain axis (Chen et al., 2025b). These studies suggest that casein and calcium may exacerbate PD-related symptoms by stimulating intestinal inflammation and unbalanced intestinal flora, which are potential risk factors for PD. Whether this is also true for PD patients and exactly how, is yet to be

Table 8
Probiotics and FMT preclinical (in vivo) and clinical (human) evidence on inflammation modulation with relevance for PD.

Study type	Model/ Population	Intervention	Main Immune/ Inflammatory outcomes	Reference
Clinical	PD patients (n = 46)	Probiotic cocktail with vitamin D supplements	↓IL-1β, INF-γ, IL-6, and MDA ↑IL-10 and TAC (serum)	Zali et al. (2024b)
Clinical	PD patients (n = 74)	Probiotic cocktail	↓TNF-α and IL-6 (plasma)	Leta et al. (2025)
Preclinical	Rotenone-iinjected mice	FMT	↓GFAP$^+$ cells, Iba-1$^+$ cells, TNF-α, IL-1β, IL-6, iNOS, and COX2 ↑ZO-1, occludin, and claudin-5 (SN); ↓histological score, TNF-α, IL-1β, IL-6, iNOS, and COX2, ↑ZO-1, occludin, and claudin-5 (colon); ↓FD4, TNF-α, IL-1β, and IL-6 (serum)	Zhao et al. (2021b)
Preclinical	MPTP-injected mice	FMT	↓GFAP$^+$ cells and Iba-1$^+$ cells (SN); ↓TLR4/TBK1/NF-κB/TNF-α signalling (colon and SN)	Sun et al. (2018b)
Preclinical	MPTP-injected mice	*Lacticaseibacillus rhamnosus* GG	↑GDNF ↓Bax/Bcl-2 (striatum)	Liu et al. (2022b)
Preclinical	MPTP-injected rat	*Bifidobacterium breve* Bif11	↑glutathione ↓MDA, nitrite, iNOS, IL-6, IL-1β, NF-κB, and CRP (midbrain	Valvaikar et al. (2024)
Preclinical	LPS-injected rat	Probiotic cocktail	↓microglial activation	Parra et al. (2023)
Preclinical	*SNCA* A53T transgenic mouse	Engineered *Lactococcus* lactis strain	↓LPS, LBP, TNF-α, IL-1β, and IL-6 (serum); ↓TLR4, MyD88, p65, COX2, and iNOS ↓Iba1, C3, IL-1α, TNF, C1qα, GFAP, and C3d levels (SN)	Yue et al. (2026)
Preclinical	MPTP or rotenone-injected mice	Probiotic cocktail	↓ GFAP$^+$ cells and Iba-1$^+$ cells (SN); ↑BDNF and GDNF (SN)	Srivastav et al. (2019b)
Preclinical	MPTP-injected mice	*Clostridium butyricum* WZMC1016	↑ synapsin I and GLP-1R (SN); ↑GLP-1 and GPR41/43 (colon)	Sun et al. (2021b)
Preclinical	MPTP-injected mice	*Pediococcus pentosaceus* WMU002	↑GABA, SOD1, GPx1, and Nrf2 ↓Keap1 (SN)	Pan et al. (2022b)
Preclinical	Rotenone-injected mice	*Lactobacillus acidophilus* SLAM_LAA02	↑ occludin, ↓NF-κB, TNF-α, and IL-1β (colon); ↓Bax and Casp-3, ↑Bcl2, and BDNF (brain)	Kim et al. (2026)
Preclinical	Aged SAMP8 mouse	Probiotic cocktail	↑SYN, claudin-1, occludin, and ZO-1 ↓Iba-1, GFAP, TNF-α, IL-6, NF-kB, and LPS (brain); ↑ claudin-1, occludin, and ZO-1 ↓TNF-α and IL-6 (intestine); ↓TNF-α, IL-6, and LPS (plasma)	(Wang et al., 2022) (Wang et al., 2021a)
Preclinical	MPTP-injected mice	*Lactobacillus plantarum* DP189	↑SOD, GSH-Px, IL-10, p-ERK1/2, Nrf2, HO-1, GCLC, PGC-1α, UCP2, MnSOD, Bcl-2, ERK2, AKT, and mTOR ↓ MDA, ROS, TNF-α, IL-6, IL-1β, NLRP3, Bax, Casp-1, Casp 3, and IL-1β in (SN)	Chu et al. (2023)
Preclinical	Rotenone-injected mice	*Lactobacillus plantarum* CCFM405	↓Iba-1 and GFAP in SN; ↓IL-1β, IL-6, and TNF-α in midbrain; ↑ZO-1 and occludin ↓IL-1β, IL-6, and TNF-α (colon)	Fang et al. (2019)
Preclinical	MPTP-injected mice	An engineered bacterium MG1363-pMG36e-GLP-1	↓ GFAP, TLR4, TNF-α IL-6, and IL-1β (SN)	Li et al. (2022)
Preclinical	MPTP-injected mice	*Bifidobacterium breve* CCFM1067	↓Iba-1 and GFAP ↑ BDNF and GDNF (striatum); ↓TNF-α, IL-1β, and IL-6 ↑ IL-10, ZO-1, occludin, and claudin-1 (SN and colon)	Wang et al. (2023)
Preclinical	MPTP-injected mice	An engineered Clostridium butyricum-GLP-1	↑GLP-1, Beclin-1, PINK-1, Parkin, Atg7, LC3B, LAMP-1, SOD, and GSH-Px ↓MDA (SN); ↑SOD, and GPx ↓MDA (serum); ↑GPR41, GPR43, ZO-1, and occludin (colon)	Liao et al. (2020)
Preclinical	MPTP-injected mice	*Lactobacillus plantarum* PS128	↓corticosterone (serum); ↑GFAP, Iba-1, SOD, GSH, catalase, and GPx ↓m-BDNF, NGF, TNF-α, IL-1β, and IL-6 (striatum); ↑SOD, GSH, and catalase ↓TNF-α, IL-1β, and IL-6 (midbrain)	

Abbreviations: AKT – protein kinase B; Atg – autophagy-related gene; Bax – Bcl-2 associated X protein (pro-apoptotic); Bcl-2 – B-cell lymphoma 2 (anti-apoptotic); BDNF – brain-derived neurotrophic factor; C1qα – complement C1q subcomponent subunit alpha; C3 – complement component 3; C3d – complement component 3d; Casp – caspase; COX2 - cyclooxygenase-2; CRP – c-reactive protein; ERK – extracellular signal-regulated kinase; FD4 – fluorescein isothiocyanate–dextran 4 kDa; FMT – faecal microbiota transplantation; GABA – gamma-aminobutyric acid; GCLC – glutamate-cysteine ligase catalytic subunit;

GDNF – glial-derived neurotrophic factor; GFAP – glial fibrillary acidic protein; GLP – glucagon-like peptide; GPx – glutathione peroxidase; HO-1 – heme-oxigenase 1; Iba-1 – ionized calcium-binding adaptor molecule 1; IL – interleukin; IFN – interferon; Keap1 – Kelch-like ECH-associated protein 1; iNOS – inducible nitric oxide synthase; LAMP-1 – lysosome-associated membrane protein 1; LBP – lipopolysaccharide-binding protein; LC3 – microtubule-associated proteins 1A/1B light chain 3; LPS – lipopolysaccharide; MDA – malondialdehyde; MnSOD – manganese superoxide dismutase (SOD2); MPTP – 1-methyl-4-phenyl-1,2,3,6 tetrahydropyridine; mTOR – mammalian target of rapamycin; MyD88 – myeloid differentiation primary response 88; NF-κB – nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP3 – nucleotide-binding oligomerization domain-, leucine-rich repeat, and pyrin domain-containing 3; Nrf2 – nuclear factor erythroid 2–related factor 2; p65 – NF-κB p65 subunit; PD – Parkinson's disease; PGC-1a – peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PINK1 – PTEN-induced kinase 1; SAMP8 – Senescence-accelerated mouse prone 8; SN – substantia nigra; *SNCA* – synuclein alpha (gene encoding for α-synuclein); SNGPR – single nucleotide polymorphism genotyping platform/region; SOD1 – superoxide dismutase 1; SYN – synaptophysin; TAC – total antioxidant capacity; TBK1 – TANK-binding kinase 1; TLR – toll-like receptor; TNF-α – tumour necrosis factor alpha; UCP2 – uncoupling protein 2; ZO – zonula occludens.

fully understood. What is known is that dietary protein intake has a significant impact on levodopa therapy. The interaction is predominantly competitive and pharmacokinetic – protein-derived amino acids (e.g., leucine, isoleucine, valine, phenylalanine, tyrosine, tryptophan) compete with levodopa for absorption and transport, reducing its bioavailability and causing motor fluctuations in susceptible individuals (Wang et al., 2017; Rusch et al., 2023). The evidence is insufficient to conclusively recommend low-protein diet, and, importantly, PD patients are often older and prone to malnutrition, so cutting protein has risks (e.g., muscle waste, frailty), so recommendations advise taking levodopa 30 min before or 1-2h after meals.

MeDi and healthy plant-based diets also provide an increased intake of dietary fibre (Barrea et al., 2021). Dietary fibers have long been recognized as an essential modulator of many disease (Burkitt, 1974), and its deficiency is a major risk factor for non-communicable disease (O'Keefe, 2019). It has been shown that dietary fibre fermentation contributes to the maintenance of a healthy gut barrier due to the bacterial production of SCFA, as these are the primary source of energy for colonocytes (Duan et al., 2024). Moreover, intestinal inflammation is thought to contribute to pathological aggregation of αSyn in the gut and brain (Espinosa- et al., 2024). Dietary fibre could reduce the pathological burden of αSyn by regulating intestinal inflammation. In an alpha-synuclein overexpressing mouse model of PD, various prebiotic diets increased faecal SCFAs, reduced central alpha-synuclein aggregation and motor and behavioural deficit (Abdel-Haq et al., 2022). Interestingly, this protective effect appeared to be mediated by microglia (Abdel-Haq et al., 2022). Accordingly, fibre deprivation leads to gut dysbiosis and increased alpha-synuclein aggregation (Schmit et al., 2023). An open-label, controlled, non-randomized study investigated a 10-day supplementation of prebiotic fibre in the form of a bar containing resistant starch, rice bran, resistant maltodextrin and inulin, providing PD patients with a total of 10 g of fibre per serving (Hall et al., 2023).

Table 9
Physical exercise preclinical (in vivo) and clinical (human) evidence on inflammation modulation with relevance for PD.

Study type	Model/Population	Intervention	Main Immune/Inflammatory Outcomes	Reference
Clinical	PD patients (n = 19)	Cycling (individualized protocol) (1 month)	↑IL-10	Cadet et al. (2003)
Clinical	PD patients (n = 12)	Cycling (1h/session, 3×/week) (8 weeks)	↓TNF-α, ↓sVCAM-1	Zoladz et al. (2014)
Clinical	PD patients (n = 27)	Multimodal exercise (90min/session, 3x/week) (8 weeks)	↑IL-10, IL-10/TNF-α ratio	Landers et al. (2019)
Clinical	PD patients (n = 40)	Tai chi, Multimodal exercise (1h/session, 2×/week) (12 weeks)	↓T-cell receptor signaling and T-cell activation pathways (CD3E, ZAP70, TNFRSF18); ↑TNF-α	Hu et al. (2020b)
Clinical	PD patients (n = 62)	Balance exercise (60 min/session, 3×/week) (12 weeks)	↑IL-10, TGF-β1, fractalkine, ↓TNF-α	Szymura et al. (2020)
Clinical	PD patients (n = 28)	Cycling (60min/session, 3×/week) (12 weeks)	↓TNF-α, neutrophils, NLR, NMR, SII, ↑IL-10	Malczynska-Sims et al. (2022)
Clinical	Early-stage PD patients (n = 32)	Tai chi (60 min/session, 2×/week) (12 months)	↓IL-1β, IL-5, IL-7, IL-9; ↓eotaxin	Li et al. (2024b)
Clinical	PD patients (n = 17)	Qigong (1 h/session, once weekly) (12 weeks)	↓IL-1β, IL-6 (serum)	Zali et al. (2024b)
Preclinical	MPTP-injected mice	Treadmill exercise (1 h/day, 5×/week) (4 weeks)	↓Iba-1	Churchill et al. (2017)
Preclinical	MPTP- injected mice	Treadmill exercise (60 min/session, 5×/week) (8 weeks)	↓TLR2/MyD88/NF-κB signaling, TNF-α, IL-1β, Iba-1 expression	Koo et al. (2017)
Preclinical	6-OHDA-injected rats	Treadmill exercise (40 min/day, 3×/week) (4 weeks)	↓GFAP, CD11b/c, iNOS, ROS production, ↓astrocyte and microglial activation	Real et al. (2017)
Preclinical	MPTP-injected mice	Treadmill exercise (60 min/day, 5×/week) (6 weeks)	↓ NLRP3, ASC, caspase-1 and IL-1β; ↓ Iba-1^{+} microglial activation; ↓TLR4/MyD88/NF-κB signaling	Wang et al. (2021b)
Preclinical	Rotenone-injected mice	Treadmill exercise (30 min/day, daily) (21 days)	↓IL-1β, TNF-α; ↑IL-4, IL-10	Kumar et al. (2025)
Preclinical	MPTP- injected mice	Treadmill exercise (40 min/session, 5×/week) (10 weeks)	↓GFAP, Iba-1b and CD11b staining (SN and striatum), ↓astrocyte/microglial activation	Palasz et al. (2025)

Abbreviations: 6-OHDA – 6-hydroxydopamine; ASC – caspase recruitment domain; CD – cluster of differentiation; GFAP – glial fibrillary acidic protein; Iba-1 – ionized calcium-binding adaptor molecule 1; IL – interleukin; iNOS – inducible nitric oxide synthase; MPTP – 1-methyl-4-phenyl-1,2,3,6 tetrahydropyridine; MyD88 – myeloid differentiation primary response 88; NF-κB – nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP3 – nucleotide-binding oligomerization domain-, leucine-rich repeat, and pyrin domain-containing 3; PD – Parkinson's disease; ROS – reactive oxygen species; SN – substantia nigra; TGF – transforming growth factor; TLR – toll-like receptor; TNF-α – tumour necrosis factor alpha; TNFRSF18 – tumour necrosis factor receptor superfamily member 18; VCAM-1 – vascular cell adhesion molecule 1; ZAP70 – zeta chain associated protein kinase 70.

The prebiotic intervention was found to be safe and well tolerated and resulted in an improvement in gut dysbiosis, an increase in faecal SCFA, a decrease in faecal calprotectin and zonulin levels and alleviation of gut symptomatology (Hall et al., 2023). An exploratory analysis also indicated a decrease in the UPDRS score, although a placebo effect cannot be ruled out (Hall et al., 2023). Another open-label, single-arm study investigated the effects of 12 weeks of supplementation with a commercially available symbiotic containing the probiotic strain *Lacticaseibacillus paracasei* and the prebiotic fibre inulin, founding significant improvements in non-motor and gastrointestinal symptoms (Andreozzi et al., 2024). In addition, the symbiotic appeared to promote an increase in SCFA-producing bacterial taxa and SCFAs in faeces, although the increase in the latter was not statistically significant (Andreozzi et al., 2024). Although the results appear promising, double-blind, placebo-controlled studies are needed to substantiate the results. To date, fibre does not appear to interact with PD medications in the classic sense of chemical drug-drug interactions; instead, its effects are largely physiological, influencing how PD drugs are absorbed, and mitigating GI-related side effects of both the disease and the medications (Fernandez et al., 2005; Crozier et al., 2026). Current clinical and preclinical evidence on the effects of protein and fiber intake on inflammation in PD is summarized in Table 7.

Importantly to stress, while environmental and dietary triggers - such as per- and polyfluoroalkyl substances, microplastics, and high-fat/high-sugar diets - may exacerbate pro-inflammatory pathways in PD, an exhaustive analysis of these risk factors remains beyond the scope of this review, which focuses strictly on interventional strategies.

3. Gut-immune-brain axis

Although PD is clinically defined by motor impairment, non-motor symptoms related to gastrointestinal (GI) tract dysfunction, such as leaky gut syndrome and defecation disorders have been frequently reported (Seguella et al., 2020; Lubomski et al., 2020). Moreover, in PD patients, αSyn accumulates not only in the brain, but also in peripheral areas such as the neurons of enteric nervous system (ENS), and these findings are particularly relevant when we consider the communication between the ENS and the central nervous system (CNS) (Paillusson et al., 2013; Bu et al., 2019).

There is a growing consensus that the GI microbiota communicates with the brain, forming the so-called gut-brain axis, and that signalling occurs between the gut microbiota, the GI tract, the ENS, and the CNS (Pan et al., 2019; Gamage et al., 2023; Mayer et al., 2022). In addition, the gut microbiota has been found to be involved in neuronal plasticity in adulthood, e.g. microglial activation and neurogenesis, and are important for healthy brain development and function in adulthood (Stilling et al., 2015; Ogbonnaya et al., 2015; Desbonnet et al., 2015). Conversely, the brain modulates gut functions via the hypothalamic-pituitary-adrenal axis, the autonomic nervous system and the ENS by altering epithelial integrity, mucosal immunity, luminal secretion and neurotransmitter release (Mayer et al., 2022; Hartstra et al., 2020; Sun et al., 2018a).

Disruption of gut-brain interaction is known to be associated with various neurodegenerative diseases, and several studies have shown that the gut microbiota may play a role in PD development and progression via the modulation of neuroinflammation (Bedarf et al., 2017; Morais et al., 2021). The importance of the gut-brain axis in conjunction with immunomodulation for physiological functions can hardly be underestimated, as the gut microbiota is closely involved in the regulation, induction and function of local and systemic immunity. Physiological processes of functional GI disorders are thought to be involved in the dysregulation of the bidirectional gut-brain interaction by causing microbiome dysbiosis as well as a disturbed gut barrier and inflammation (Black et al., 2020; Ning et al., 2022). Stool samples from people with PD have been compared to their matched controls and it was found that the composition of their gut microbiome was altered (Bedarf et al., 2017; Hill- et al., 2017; Unger et al., 2016; Scheperjans et al., 2015). In general, a decrease was observed in the populations of the *Prevotellaceae* and *Bacteroidetes*, while an increase was observed in the populations of *Akkermansia*, *Enterobacteriaceae*, *Lactobacillaceae*, and *Bifidobacteriaceae.* However, altered populations have shown to vary depending on the animal model used (Aktas et al., 2024). This should be considered when designing experiments exploring the gut-brain axis, and microbial change should be evaluated in comparison to matched healthy controls. Recent meta-analyses have shown that one of the most consistent findings in studies linking PD to microbiome composition is a decrease in the number of SCFA producing bacteria (Boertien et al., 2019; Romano et al., 2021). Stool samples from PD have been shown to have significantly lower concentrations of SCFA such as acetate, propionate, and butyrate compared to healthy control groups (Unger et al., 2016; Hirayama et al., 2023). In addition, intestinal integrity was also already reported to be decreased in people with PD and resulted in a leaky gut (Hasegawa et al., 2015; Schwiertz et al., 2018). Recent studies using PD animal models suggest that the GI tract may be a possible starting point for αSyn aggregation, the pathology of which can be transmitted to the brain via the vague nerve (Kim et al., 2019). The transmission of gut-derived αSyn fibrils from the gut to the brain, which is associated with nigral dopaminergic neurodegeneration and PD-like motor symptoms, has been demonstrated in aged mice but not in young mice (Challis et al., 2020). In a study of intestinal biopsies from people with PD and matched controls, an accumulation of phosphorylated αSyn was detected in upper and lower GI tract several years before the onset of motor symptoms and is maintained throughout the course of the disease (Hilton et al., 2014). In addition, complete truncal vagotomy, which is associated with a lower risk of developing PD, has also endured the involvement of the gut in PD progression (Svensson et al., 2015).

3.1. Probiotics and the gut-immune-brain-axis

Modulating the composition of the gut microbiota through functional foods or faecal transplantation has been shown to influence brain function and cognitive behaviour by altering neurotransmitter activity in animals (Sun et al., 2018a, 2021a). Certain dietary components, particularly (poly)phenols and fibre, have been shown to modulate gut microbiota diversity, promote anti-inflammatory bacterial species and increase the production of SCFA, which contribute to the regulation of neuroimmune function (Hirschberg et al., 2019; Zhang et al., 2022a; Filosa et al., 2018; Riegelman et al., 2024). Probiotics are one of the approaches to restructure the imbalanced gut microbiota (Li et al., 2020; Aktas et al., 2015). They will not only manage the gut dysbiosis but also help to maintain the health of the immune system (Bonfrate et al., 2020; Gao et al., 2021). The effects of probiotics have been studied extensively, particularly in inflammation related diseases and have been shown to affect intestinal permeability, strengthening the epithelial barrier and reducing permeability by increasing the production of tight junction proteins such as occludin, claudin, and ZO (Chen et al., 2010; Corridoni et al., 2012; Madsen et al., 2001). Studies targeting altered gut microbiota with probiotics in PD animal models have shown that probiotic application has been able to be neuroprotective regarding the dopamine lost in the brain of animals with PD and improve motor deficits as well as intestinal integrity, which indicates that the gut microbiota can play an important role in promoting dopamine production via gut-brain axis (Aktas et al., 2024; Pan et al., 2022a; Srivastav et al., 2019a).

Regarding evidence from human subjects, in a study of healthy individuals with no gastrointestinal or psychiatric symptoms, a probiotic cocktail was administered, and brain function was monitored using functional magnetic resonance imaging (Tillisch et al., 2013). Probiotic intake has also been shown to improve Movement Disorder Society – Unified Parkinson's Disease Rating Scale (MDS-UPDRS) scores in people with PD, as well as inflammatory biomarkers, and metabolism (Park et al., 2023b). In a randomized, double-blind, placebo-controlled study investigating the effects of a probiotic cocktail with four different

strains on people with PD, the administration of probiotics significantly decreased plasma levels of TNF-α and IL-6. In addition, the results showed improvements in both motor and non-motor symptoms (Leta et al., 2024). In another study, after a 12-week intervention, compared with the placebo, probiotic intake significantly downregulated gene expression of IL-1, IL-8 and TNF-α in PBMCs of subjects with PD (Borzabadi et al., 2018). A more recent study showed that co-administration of probiotics and vitamin D resulted in an anti-inflammatory effect by lowering serum levels of INF-γ, IL-6, IL-1β and malondialdehyde while increasing IL-10 in people with PD, alleviating disease severity, anxiety and gastrointestinal symptoms in PD patients compared to the placebo group (Zali et al., 2024a). The use of probiotics has also been shown to be synergistic with conventional treatment and to improve clinical efficacy in people with PD by altering the gut microbiota, gut microbiome-related metabolites and serum metabolites (Sun et al., 2022). For PD pharmacotherapy, the primary interactions with probiotics are indirectly positive: by restoring healthy gut motility and microbiota balance, probiotics tend to support and *synergize* with drug therapy by ensuring the gut is not a limiting factor in drug delivery, creating a more pro-dopamine environment in the body, and helping to optimize the absorption and efficacy of PD medications (especially levodopa (Sun et al., 2022; Tan et al., 2021)). There are also early signs of direct pharmacodynamic benefits (e.g. reduced neuroinflammation, enhanced neurotransmitter production (Hong et al., 2022b)). Importantly, no serious adverse interactions have been documented; theoretical risks (like *Enterococcus* species found to inactivate levodopa via tyrosine decarboxylase activity (van Kessel et al., 2019; Maini et al., 2019)) are being studied but have not manifested in clinical trials.

Although probiotics have been proposed as potential therapeutics in PD due to their ability to modulate the gut microbiota, there are still only few clinical trials comprehensively investigating their effects on PD via the gut-brain axis.

3.2. Faecal microbiota transplantation

Faecal microbiota transplantation (FMT) has also been used as a microbiota-targeted strategy to treat diseases associated with dysbiosis. It has previously been shown that faecal microbiota from people with PD resulted in impaired motor function when transplanted into mice (Sampson et al., 2016). FMT was found to improve motor and non-motor symptoms in PD and modulate the gut microbiota, a potential promising strategy in PD to enhance the efficacy of conventional treatment for cognitive function (Cheng et al., 2023). In an MPTP-induced mouse model, FMT from healthy mice resulted in a decrease in elevated short-chain fatty acids and restoration of the disrupted gut microbiota (Sun et al., 2018a). Moreover, FMT decreased the microglia and astrocytes activation in the substantia nigra and downregulated the expression of the proteins involved in TLR4/TNF-α signalling pathway in both gut and brain.

Whilst there is evidence of beneficial impact of FMT in immune function in animal models of PD (e.g. (Sun et al., 2018a; Zhao et al., 2021a),), FMT studies in PD patients still overlook cytokine alterations and immune cell modulation (Sadowski et al., 2023), which certainly deserves further attention. Intervention strategies targeting gut microbial modulation in neurological disorders and related clinical trials are still ongoing (Liu et al., 2022a). Further studies related to the gut microbiota would be important for understanding the mechanism of PD and the development of alternative therapeutics for the disease prevention or/and progression.

3.2.1. Considerations and clinical recommendations

Although a growing body of research supports the beneficial effects of dietary interventions in modulating neuroinflammation, oxidative stress, and gut-brain axis dynamics in PD (Mischley et al., 2017; Tosefsky et al., 2024), several important considerations must guide clinical application.

While adherence to a MeDi or MeDi-like diet has been consistently associated with a lower risk of PD and slower disease progression (Solch et al., 2022; Maraki et al., 2023), the limited number of intervention studies (Paknahad et al., 2020; Rusch et al., 2024) underscores the need for caution in translating epidemiological findings directly into clinical practice tough representing a valid starting point for personalized improvements (van Soest et al., 2024). For example, the minimum daily amount of 400 g of fruit and vegetables, preferably leafy green vegetables, being sources of fibre, polyphenols and vitamins, such as C and E (Davis et al., 2015); the preference for whole grains, to reach fibre recommendations of at least 25 g per day (Davis et al., 2015; Volkert et al., 2022); the use of extra virgin olive oil, rich in monounsaturated fatty acids with antioxidant proprieties (Angeloni et al., 2017) for seasoning and cooking; the daily inclusion of 30 g – 60 g of nuts and seeds, considering individual susceptibility, contributing for recommendations and consequent referred benefits of vitamin E, fibre, phenolic compounds, monounsaturated and polyunsaturated fatty acids (Davis et al., 2015; Gonçalves et al., 2023); and fish consumption (Angeloni et al., 2017), for example, two portions, 100 g each of a fatty fish such as salmon per week, to reach the general adult recommendation of 250 mg per day of docosahexaenoic acid and eicosapentaenoic acid (Gonçalves et al., 2023).

Concerns remain about ketogenic and fasting diets long-term adherence and safety in older populations (Wei et al., 2024): ketogenic diets can yield greater improvements in non-motor symptoms compared to low-fat diets, but these benefits are often shadowed by unfavourable lipid profile changes, including increases in LDL cholesterol, and a higher frequency of adverse effects (Phillips et al., 2018). Consequently, the “promise” of these diets must be weighed against the risk of inducing low-grade systemic inflammation and metabolic disturbances, which are particularly threatening for the aging populations who are most at risk for cognitive decline. Importantly, a plant-based diet may have a protective effect through anti-inflammatory nutrient profiles (Tresserra- et al., 2023), but may be deficient in key micronutrients such as vitamin B12 and docosahexaenoic acid, particularly in patients with levodopa-induced malabsorption (Clemente-Suárez et al., 2025; Rekik et al., 2024).

When designing recommendations and interventions for older patients, protein daily intake should be at least 1 g/kg of body weight, even in a protein redistribution regimen designed to maximize levodopa absorption and efficacy in PD patients reporting motor fluctuations and taken 30 min before meals due to known amino acids-levodopa interaction (KASIAN et al., 1986; Burgos et al., 2018). Importantly, certain food components, such as casein, have been associated with exacerbation of neuroinflammation and alteration of gut microbiota homeostasis in PD models (Liu et al., 2021b; Pu et al., 2023), suggesting that individualized assessment of dietary protein sources is required.

In addition, modulation of the gut microbiota through dietary fibre, (poly)phenols, probiotics, and even FMT has been shown to have the potential to restore gut integrity and reduce inflammatory markers in PD (Zali et al., 2024a; Hall et al., 2023; Cheng et al., 2023), although larger, placebo-controlled trials are needed. Probiotics are considered safe especially for PD patients experiencing constipation (Volkert et al., 2022). Fluid intake is also critical and besides water, tea consumption may also represent an interesting strategy for fluid intake improvement due to its polyphenol content (Zhou et al., 2019b). Current clinical and preclinical evidence on the effects of probiotics and FMT on inflammation in PD is summarized in Table 8.

Given these nuances, healthcare professionals should take a personalized nutritional approach that considers the patient's disease stage, microbiota profile, nutritional status, and comorbidities. To be effective and safe, dietary recommendations should also consider preferences, compliance capacity, promote the management of body weight, that tends to be lower in PD patients (Li et al., 2024a) to avoid malnutrition that might be underreported (Volkert et al., 2022) and promote

quality of life. Careful monitoring and targeted supplementation, in particular for vitamin D and B, may be necessary to optimize the therapeutic potential of the diet while minimizing nutritional risks.

. Since energy and nutrient intake are inherently dependent on total food consumption, future studies should take this into account at either the design or analysis stage, assessing and monitoring dietary intake trough Food Frequency Questionnaires, 24 h dietary recalls or food diaries. Protocol implementation should also be accompanied by trained nutritionists to safely guarantee compliance and follow-up, including meal plans and educational sessions/written information.

A major barrier to the clinical translation of dietary interventions is the lack of validated, sensitive, and reproducible biomarkers that reliably capture dietary exposure, adherence, as well physiological and immune responses to interventions. Many currently used biomarkers in inflammation, such metabolites and cytokines, are highly variable between individuals, or insufficiently specific to distinguish meaningful biological effects from background metabolic noise (Liu et al., 2021c) and extreme careful should be taken when designing such trials and proper collection/storing of patients' samples ((Muñoz-Delgado et al., 2025) for detailed guidelines in the subject). Although emerging multi-omics approaches offer promise (Fu et al., 2026), most remain exploratory and lack standardisation, longitudinal validation, and clear clinical relevance. Without robust biomarkers and standardized design of clinical trials to monitor inflammatory alterations in PD patients, it remains difficult to accurately stratify patients, monitor treatment efficacy, or generate the high-quality evidence needed for widespread clinical implementation of nutrition-based therapies.

4. Exercise interventions

Physical activity is defined as any bodily movement that results in energy expenditure (WHO guidelines on physical activity, 2020). This broad definition includes the sub-category of exercise, which refers to planned, structured, and repetitive bodily movement to improve or maintain physical fitness. Beyond general health benefits, exercise has been extensively studied for its therapeutic effects on neurodegenerative diseases, particularly in PD, where it has been linked to a reduced risk of disease development (Gilat et al., 2021; Zhen et al., 2022; Ernst et al., 2023; Yang et al., 2015). Research has demonstrated that exercise improves motor functions, including gait and balance, and decreases rigidity in people with PD (Fishel et al., 2025; Ge et al., 2024). Aerobic exercise, particularly endurance-enhancing activities, has been found to improve motor skills (Fisher et al., 2008), whereas resistance exercises contribute to increased muscle strength and speed of movement (Corcos et al., 2013). Similarly, stretching exercise has been found effective for improving mobility and alleviating motor symptoms (Duñabeitia et al., 2025). Moreover, exercise has been shown to significantly improve not only motor but also non-motor symptoms of PD, demonstrating its effectiveness in enhancing cognition, supporting sleep quality, and reducing depressive symptoms (Moratelli et al., 2025; Amara et al., 2020). Alternative and multimodal exercise approaches have gained increasing attention in PD, particularly given their potential to target multiple symptom domains simultaneously. In this context, unconventional exercise modalities that incorporate multidimensional and multisensory training strategies, such as dance, Tai Chi, Qigong, Baduanjin, exergaming, and robotic-assisted gait training, have shown advantages over conventional approaches in certain domains (Mao et al., 2025; Lou et al., 2025; Yapei et al., 2025; Zhang et al., 2025b). Dance-based interventions have been identified as particularly effective for improving balance and depressive symptoms, while mind–body approaches such as Tai Chi, yoga, and Qigong appear to be particularly beneficial for postural control, cognitive function, and psychological outcomes, including anxiety (Lou et al., 2025; Pinto et al., 2024; Meliani et al., 2026). Similarly, exergaming interventions, which integrate interactive, technology-assisted movement training, have demonstrated benefits for gait and motor improvement. Boxing-based interventions have also been explored, with some studies reporting improvements in both motor and non-motor symptoms alongside high adherence, but findings remain inconsistent, with other analyses reporting limited or no significant effects on physical and mental outcomes, including balance, cardiorespiratory fitness, or quality of life (Wang et al., 2025b; González-Devesa et al., 2024; Hernandez-Martinez et al., 2025). Overall, these findings suggest that different exercise modalities may preferentially target distinct symptom domains, highlighting the need for individualized, multimodal exercise prescriptions in PD.

Accumulating evidence indicates that regular exercise exerts neuroprotective effects by promoting immune homeostasis, reducing neuroinflammation, and enhancing neuroplasticity (Szymura et al., 2020; Hirsch and Hunot, 2009). Indeed, across prospective studies, medium levels of physical activity, heavy leisure-time physical activity, and moderate-to-vigorous physical activity have consistently been associated with a lower risk of Parkinson's disease (Yang et al., 2015; Sääksjärvi et al., 2014; Thacker et al., 2008; Xu et al., 2010). Additionally, emerging evidence suggests that exercise interventions may help mitigate chronic neuroimmune and neuroinflammatory responses in individuals with PD, making it a promising adjunct to conventional pharmacological treatments (Bloem et al., 2015). Given these multifaceted benefits, integrating exercise into clinical management strategies could provide symptomatic relief and long-term neuroprotection, ultimately improving the quality of life for people with PD. Current clinical and preclinical evidence on the effects of protein and fiber intake on inflammation in PD is summarized in Table 9.

4.1. Exercise on pharmacokinetics of common PD drugs

There is currently limited evidence on the complementary effects of exercise on mediation in PD patients, with current literature available focusing on the combined effects of exercise and levodopa. In this regard, Studies have shown no significant impact of exercise on levodopa plasma concentration (Mouradian et al., 1987; Figura et al., 2024). No significant changes to antiparkinsonian response when levodopa was paired with exercise interventions were also observed across several studies (Mouradian et al., 1987). In contrast, participation in resistance (Dibble et al., 2015), and low-to-moderate intensity endurance exercises (Reuter et al., 2000; Muhlack et al., 2007) demonstrated benefits when administered with levodopa on motor and mobility scores (Dibble et al., 2015). Although the mechanistic pathways have yet to be fully elucidated, it could be suggested that the absence of statistically significant results could be linked to evidence showing counter-active levodopa pharmacokinetics and pharmacodynamics, where there is a tendency for improved levodopa absorption, but for increased levodopa demand during exercise (Reuter et al., 2000). It could be suggested that the increased absorption of levodopa across the BBB and/or increase endogenous dopamine synthesis and release into the nigrostriatal regions improves motor response (Muhlack et al., 2007). The inconclusive results may be attributed to the insufficient differentiation between patient sub-types during clinical trials. Exercise may exert varying effects on clinical symptoms and the pharmacokinetics of levodopa, contingent upon disease severity and/or treatment duration. Notably, a higher mean residence time was observed in levodopa-naïve patients at rest compared to post-exercise, in contrast to healthy controls and individuals with advanced PD (Figura et al., 2024). Further research is required to fully understand the pharmacokinetics and clinical effects of levodopa when paired with exercise during PD stages. It was also observed that there were no significant effects, entacapone, a COMT inhibitor, on maximal workload or cardiorespiratory response during exercise (Lyytinen et al., 2002). Although this could suggest no significant vice versa effect of exercise on the pharmacokinetic and pharmacodynamics of COMT inhibitors, more research is needed to elucidate underlying mechanisms and combined effects of physical exercise and COMT inhibitors on PD progression.

4.1.1. Exercise and inflammation: mechanistic insights and evidence

Exercise and inflammation have been closely linked, with responses that differ substantially between acute and chronic exercise. While a single bout of exercise acts as a physiological stressor that transiently activates immune pathways, repeated exposure through regular training has been reported to promote longer-term anti-inflammatory adaptations (Cerqueira et al., 2019).

During acute exercise, skeletal muscle acts as a secretory organ, releasing myokines such as IL-6 in response to contraction (Febbraio and Pedersen, 2005; Ostrowski et al., 2000). Circulating IL-6 has been reported to increase approximately 145% following moderate-to-high-intensity exercise (Brown et al., 2015). Despite its well-established role in inflammation, IL-6 released during exercise appears to exert predominantly anti-inflammatory effects. Exercise-induced IL-6 stimulates the production of IL-10 and interleukin-1 receptor antagonist (IL-1ra), which suppress pro-inflammatory cytokines, including TNF-α, IL-1β, and IL-1α (Pedersen and Fischer, 2007; Steensberg et al., 2003; Lancaster and Febbraio, 2014). Therefore, it is fair to say that acute exercise induces a transient inflammatory response characterized by short-lived increases in cytokines such as IL-6, followed by a compensatory anti-inflammatory phase. While IL-6 levels typically return to baseline within hours, anti-inflammatory mediators such as IL-1ra remain elevated for longer, extending the post-exercise anti-inflammatory effect (Cavalcante et al., 2017; Kandola et al., 2019).

With repeated exercise bouts, these acute responses lead to cumulative adaptations that reduce basal inflammation. Comprehensive review of meta-analyses across endurance, resistance, and combined training interventions indicates that moderate-to-vigorous exercise, performed regularly over several weeks, can significantly reduce chronic low-grade inflammation, including circulating markers such as IL-6, IL-18, CRP, leptin, fibrinogen, and angiotensin II (Fedewa et al., 2018; Ding and Xu, 2021; Zheng et al., 2019; Sardeli et al., 2018; Kim and Yeun, 2022; Zhao et al., 2022b). Several mechanisms have been proposed to explain how chronic exercise contributes to a sustained anti-inflammatory environment (Gleeson et al., 2011). One of the most commonly described pathways involves reductions in visceral adiposity, leading to decreased secretion of pro-inflammatory adipokines such as IL-6, TNF-α, and leptin, alongside increased levels of anti-inflammatory adiponectin (Ouchi et al., 2011; Ben Ounis et al., 2009; Mujumdar et al., 2011). In parallel, repeated exercise-induced IL-6 release may reinforce anti-inflammatory signalling, consistent with its role in inducing IL-10 and IL-1ra (Keller et al., 2003; Scheller et al., 2011). Additionally, chronic exercise has been associated with reduced expression of TLR4 on monocytes, which may contribute to reduced production of pro-inflammatory cytokines (Flynn et al., 2003; Flynn and McFarlin, 2006; Koo et al., 2017; Gleeson et al., 2006; Favere et al., 2021). Beyond these pathways, exercise may also affect inflammation through alterations in immune cell profiles, including shifts toward anti-inflammatory phenotypes such as an increased M2-to-M1 macrophage ratio in adipose tissue (Kawanishi et al., 2010, 2013). While overall evidence is strong, inconsistencies between studies have also been documented (Bigseth et al., 2023; Feng et al., 2025; Schuch et al., 2016). These inconsistencies may reflect both methodological and individual-level variability. Exercise-induced immune responses depend on factors such as exercise type, intensity, duration, and training status, as well as participant characteristics including age, sex, fitness level, clinical condition, and additional factors such as hormonal status, environmental conditions, and measurement protocols may also contribute (Cerqueira et al., 2019; Gonçalves et al., 2019; Monteiro-Junior et al., 2018).

In summary, exercise seems to induce a biphasic inflammatory response, characterized by an initial transient activation followed by a compensatory anti-inflammatory phase. Repeated exposure to these responses is believed to result in long-term adaptations that decrease basal inflammation and support immune homeostasis.

4.1.1.1. Exercise and neuroinflammation in PD.

Neuroinflammation is a central feature of PD pathology, characterized by sustained activation of glial cells and increased production of pro-inflammatory mediators (Chen et al., 2026). This process triggers the release of pro-inflammatory cytokines and chemokines that may impair BBB integrity and promote neuronal injury and apoptosis (Huang et al., 2021). Research indicates that exercise interventions can actively modulate neuroinflammatory pathways in PD, offering a promising non-pharmacological strategy to complement conventional treatments (Koo et al., 2017; Real et al., 2017; Wang et al., 2021b). Additionally, exercise has also been shown to strengthen BBB integrity by reducing inflammatory signalling and improving endothelial function (Su and Su, 2025). Preclinical studies demonstrate that exercise interventions attenuate neuroinflammatory responses in PD models through modulation of glial activation, inflammatory cytokine production, oxidative-inflammatory pathways, and innate immune signalling (Koo et al., 2017; Real et al., 2017; Kumar et al., 2025; Churchill et al., 2017; Palasz et al., 2025). Specifically, treadmill exercise has been shown to reduce neuroinflammatory responses in PD models, including decreases in pro-inflammatory mediators such as IL-1β and TNF-α (Koo et al., 2017; Real et al., 2017; Zhang et al., 2019). Mechanistically, these effects seem to involve suppression of innate immune signalling pathways, including TLR2/4–MyD88–NF-κB signalling and, NLRP3 inflammasome activity, thereby reducing microglial reactivity and limiting complement-mediated synaptic vulnerability (Koo et al., 2017; Chen et al., 2026; Wang et al., 2021b) These pathways are closely linked to the regulation of inflammation-associated neuronal damage and apoptosis, further supporting the role of exercise in modulating neuroinflammatory processes. In addition to these central mechanisms, exercise-induced circulating factors, known as myokines, have emerged as key mediators of muscle-brain crosstalk (Kumar et al., 2025). Among them, irisin has been shown to attenuate microglial activation and inflammatory signalling, while promoting neurotrophic pathways such as BDNF, thus linking peripheral muscle activity to central neuroimmune regulation (Yang et al., 2026; Kamidai et al., 2026). Other myokines, including BDNF, IGF-1, IL-6, also participate in this regulatory network, affecting inflammatory balance (Yang et al., 2026). Beyond direct effects on the brain, exercise may also modulate peripheral immune responses relevant to PD pathogenesis. Transcriptomic analyses of blood leukocytes from PD patients before and after 12 weeks of exercise revealed significant downregulation of genes involved in T-cell receptor signalling, T-cell activation, and leukocyte migration (Hu et al., 2020a). Genes such as CD3E, ZAP70, and TNFRSF18, central to T-cell activation, were notably downregulated following exercise interventions. Since increased T-cell activation and infiltration have been observed in post-mortem PD brain tissues, these findings suggest that exercise may protect dopaminergic neurons by reducing peripheral immune overactivation and limiting neuroinflammation. Clinical evidence further supports the anti-inflammatory effects of exercise in PD (Szymura et al., 2020; Li et al., 2024b; Landers et al., 2019; Moon et al., 2024; Cadet et al., 2003; Malczynska-Sims et al., 2022; Zoladz et al., 2014). Exercise interventions lasting 4–12 weeks have been associated with reductions in circulating TNF-α levels and increases in the anti-inflammatory cytokine IL-10 in people with PD (Szymura et al., 2020; Cadet et al., 2003; Malczynska-Sims et al., 2022; Zoladz et al., 2014). Supporting this, people with PD who participated in a 12-week high-intensity interval training (HIIT) program exhibited a 22% reduction in serum TNF-α levels and a 30-fold increase in IL-10 concentration post-exercise (Malczynska-Sims et al., 2022). Similarly, increased IL-10 concentrations were observed following an 8-week high-intensity multimodal exercise intervention in people with PD (Landers et al., 2019). Exercise interventions have also been associated with reductions in several additional pro-inflammatory mediators, including IL-1β, IL-5, IL-6, IL-7, IL-9, and eotaxin in people with PD (Li et al., 2024b; Moon et al., 2024). Together, these findings suggest that exercise may attenuate systemic inflammatory responses and contribute to

the modulation of PD-related neuroinflammation.

4.1.1.2. Oxidative stress and neuroprotection. In addition to modulating neuroinflammation and peripheral immune responses, exercise may also exert its therapeutic effects in PD by mitigating oxidative stress, a key contributor to disease progression. Research suggests that oxidative damage and neuroinflammation are closely intertwined (Park et al., 2013; Tapias et al., 2017), and exercise-induced antioxidant mechanisms could provide additional neuroprotection. Indeed, treadmill exercise has been associated with increased antioxidant enzyme activity and reduced oxidative damage, accompanied by a concomitant decrease in αSyn of PD-induced 6-OHDA rodents that underwent treadmill running compared to unexercised controls (Tuon et al., 2012). This is supported by evidence from human-based RCT demonstrating that an 8-week resistance exercise program was associated with significant reductions in a biomarker of oxidative stress of serum hydrogen peroxide levels by 16% in people with PD patients compared to no-exercise controls (Bloomer et al., 2008). Exercise is also widely acknowledged in the regulation of BDNF production, which promotes neuroprotection and neurodegeneration by enhancing the survival of dopaminergic neurons, improving dopaminergic neurotransmission, and supporting motor performance in animal models of PD (Palasz et al., 2019; Costa et al., 2017). Moderate-to-vigorous intensity exercise intervention studies have demonstrated significant increases in serum BDNF levels in people with PD, ranging from 16% to 80% post-exercise, which has been associated to improvements in UPDRS scores by 32% to 41% potentially due to attenuated neuroinflammation (Szymura et al., 2020; Zoladz et al., 2014; Frazzitta et al., 2014). A recent meta-analysis confirmed the aforementioned findings, highlighting an increase in BDNF levels in people with PD patients regardless of the type of exercise, with more intense exercise correlating with greater increases in BDNF (Paterno et al., 2024).

4.1.1.3. Exercise, gut microbiota modulation, and PD progression. Beyond its effects on oxidative stress and neuroprotection, exercise also influences systemic factors such as the gut microbiome, which plays a critical role in neuroimmune modulation. Emerging research highlights the role of systemic factors in modulating neuroimmune responses, with growing evidence pointing out the gut microbiome as a key player in this process (Elfil et al., 2020; Claudino dos Santos et al., 2023). Gut dysbiosis has been linked to a wide range of neurodegenerative diseases, including PD, while exercise appears to positively influence microbial diversity and mitochondrial performance, though the underlying mechanisms remain largely unknown (Zhang et al., 2020). Relatedly, a study using AAV-αSyn rat showed that nigral αSyn pathology disrupts the enteric nervous system and gut microbiota, while voluntary exercise protects enteric neurons and partly normalizes microbial profiles, pointing out exercise's modulatory role in the gut–brain axis in PD (O'Donovan et al., 2020). Consistent with these mechanistic findings, evidence suggests that people with PD who engage in a more physically active lifestyle experience less severe constipation, and reduced walking performance is associated with greater constipation severity (Chtioui et al., 2025; Frazzitta et al., 2019). By promoting an anti-inflammatory microbiota and supporting healthy bowel movements, exercise may not only help reduce neuroinflammatory mediators and neuroimmune responses but also contribute to lowering PD risk and slowing its progression. Moreover, it has been suggested that gut microbiota dysbiosis in PD is closely linked to increased BBB permeability, allowing peripheral immune cells and inflammatory mediators to infiltrate the central nervous system (Nakhal et al., 2024). Regular physical activity has been shown to enhance tight junction protein expression (e.g., occludin, claudin-5) in the BBB, reducing its permeability and preventing excessive immune cell infiltration (Sun et al., 2025). Furthermore, exercise-induced shifts in gut microbiota toward an anti-inflammatory profile may help restore gut and BBB integrity, thereby mitigating neurodegenerative progression in PD (Heithoff et al., 2021).

4.2. Considerations and clinical recommendations

Although current research has extensively documented the positive effects of exercise in regulating clinical outcomes and inflammatory biomarkers, much uncertainty remains on determining the appropriate mode, frequency, and intensity that is necessary to elucidate the positive benefits of exercise in preventing and improving the progression of PD (McGinley and Nakayama, 2024), and standardised exercise prescriptions for PD prevention and treatment remain underutilised in clinical practice (Xu et al., 2025). Although high levels of physical exercise were associated with lower risk of PD, this was notably only apparent in men (Fang et al., 2018). Research also demonstrate that the optimal benefits of various types of exercise for PD patients are only apparent at certain doses (Xie et al., 2025), with different exercise types shown to regulate different inflammatory markers (see Section 3.1). Additionally, despite the well-documented benefits of exercise in modulating PD progression, significant time is required to complete prescribed regimens. Hence, many patients find it challenging to continuously adhere to training programs (Xu et al., 2025). One explanation could be the lack of tailored intensity and amount required for different stages of PD (Song et al., 2022), and risk of adverse events increasing when individuals are exposed to strenuous exercise protocols without gradual build-up and close monitoring (Franklin et al., 2020; Lin et al., 2021). Taken together, these findings highlight the importance of carefully modulating exercise intensity, duration, and type in individuals with PD. Accordingly, exercise prescriptions should be personalized, considering the individual's age, fitness level, disease stage, and even inflammatory profile. Future research is needed to determine whether inflammatory biomarkers can be reliably integrated into personalized exercise strategies in PD. Finally, exercise interventions should also be aligned with appropriate levodopa dosing during training to optimize benefits while minimizing potential risks.

Although current literature highlighted potential biomarkers to track exercise-related changes (Hacker et al., 2023; Lee et al., 2017), research in this topic to support clinical translation of exercise interventions is very limited, with current investigations focusing on biomarkers as practical tools for monitoring general health and recovery and supporting mechanistic research (Hacker et al., 2023). Furthermore, high variability of exercise responses between individuals complicates the efficient and standardisation for the efficient use of blood-based biomarkers to support clinical translation of exercise interventions (Hacker et al., 2023). Hence, there is not only a need to evaluate and validate putative biomarkers of clinical relevance from exercise interventions but also account for the combined use of multiple markers (Hacker et al., 2023), characterisation of biomarker performance for clinical application based on efficacy, cost-effectiveness, and individual variations in exercise response (Lee et al., 2017; Perlis, 2011).

5. Conclusion

PD is a complex neurodegenerative, multisystemic disorder increasingly understood through the lens of neuroinflammation, immune dysregulation, and gut-brain axis dysfunction. Non-pharmacological interventions, namely dietary strategies or exercise, offer promising avenues to target these mechanisms in both preventive and therapeutic contexts. A key advantage of these approaches lies in their compatibility with pharmacological treatments, enabling them to serve as adjunctive therapies that can be integrated throughout the disease course and potentially even applied preventively in at-risk populations. Each of these interventions provides distinct yet complementary immunomodulatory and anti-inflammatory benefits. Dietary interventions, including Mediterranean, ketogenic, and fibre-rich diets, influence systemic immunity and gut microbiota composition, restoring

barrier integrity and modulating neuroimmune signalling. Moreover, exercise has demonstrated robust effects in reducing central and peripheral inflammation, enhancing antioxidant capacity, and improving both motor and non-motor symptoms. However, the potential clinical application of these strategies must be personalized, accounting for disease stage, inflammatory profile, age, comorbidities, and patient preferences and needs. While strong preclinical and observational data support their use, future research should focus on large-scale, placebo-controlled trials, long-term outcome studies, and biomarker-guided approaches to identify responders and optimize timing and dosage.

In contrast to physical exercise, now considered a cornerstone of PD management (Ernst et al., 2024), dietary interventions remain comparatively under-investigated, despite rising interest in their therapeutic potential (e.g., (Study Details NCT07187739; Study Details NCT06463769; Study Details NCT05437640; Study Details NCT07213856; Study Details NCT06171360)). Beyond single-component strategies, future interventions are adopting integrated, multi-component approaches (Study Details NCT06669455; Study Details NCT06755645)) combining dietary modification and physical exercise, potentially yielding synergistic benefits on functional capacity, inflammation, and long-term disease trajectories (Alnes et al., 2026). Particular attention should be given to protocol standardization, mechanistic validation, and integration with genetic and microbiome profiling. For clinicians, these interventions represent low-risk, scalable tools that may enhance patient outcomes and slow disease progression. For researchers, they offer a platform to deepen our understanding of neuroimmune interactions in PD. And for patients, they empower active participation in managing their health. When applied thoughtfully, non-pharmacological therapies hold transformative potential of inflammation modulation in reshaping the future of PD care.

Data availability

Not applicable.

Code availability

Not applicable.

CRediT authorship contribution statement

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Declaration of competing interest

Hereby we declare that this is an original publication, that was not published or submitted elsewhere.

The authors alone are responsible for the content enclosed in the manuscript.

All the authors declare to have no conflict of interest.

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