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Efficacy of Complementary Nutritional and Herbal Interventions on Peripheral Inflammatory Biomarkers and Clinical Outcomes in Parkinson's Disease: A Systematic Review

Background: Parkinson's disease is a progressive neurodegenerative illness associated with dopaminergic neurone loss, neuroinflammation, oxidative stress, and disturbance of the gut flora. While findings are still inconsistent, probiotics and synbiotics are examples of non-pharmacological adjuvant therapies that have demonstrated potential benefits through regulation of neurotrophic and inflammatory pathways.

Objective: This review was conducted to evaluate the impact of non-pharmacological adjuvant therapy, especially complementary nutritional interventions and herbal agents, such as probiotics, Omega-3 fatty acids, antioxidants/Vitamin E, dietary supplements, and herbal or traditional medicines, on systemic inflammatory biomarkers, neurotrophic factors, metabolic pathways, and clinical outcomes in patients with PD.

Methods: Based on PRISMA 2020 guidelines, this study was conducted and the protocol was registered in PROSPERO (CRD420261395485). Literature from PubMed, ProQuest, ScienceDirect, Springer Nature, and Cochrane Library was screened according to inclusion and exclusion criteria. A total of four RCT were included in the analysis.

Results: Four RCT on probiotics, synbiotics, Zishen Pingchan Granule, and vitamin D3 supplementation in Parkinson's disease were included. The studies showed improvements in inflammatory and neuroprotective biomarkers such TNF-α, IL-6, CRP, BDNF, and α-synuclein, as well as selected motor and non-motor outcomes. No significant treatment-related adverse effects were regularly reported.

Conclusion: Complementary nutrition and herbal therapy could provide anti-inflammatory and neuroprotective benefits in Parkinson's disease. However, the current information available is limited by small sample numbers and methodological heterogeneity. Confirmation of the clinical effectiveness and long-term therapeutic promise requires more standardised studies.

Keywords: Parkinson's disease, Placebo, Non-Pharmacological interventions, Inflammatory biomarkers, Neuroprotective biomarkers

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Introduction

As the fastest-growing neurodegenerative condition globally, Parkinson's disease (PD) represents a chronic and advancing neurological impairment. At the microscopic level, its hallmark pathology is defined by the selective degeneration of dopaminergic pathways within the substantia nigra, alongside the abnormal intracellular accumulation of α-synuclein proteins, which aggregate to form Lewy bodies. From an epidemiological perspective, PD demonstrates a point prevalence of approximately 1 to 2 cases per 1,000 individuals across the general population. The incidence exhibits a sharp, age-dependent trajectory; it comprises roughly 1% of cohorts exceeding 60 years of age, and escalates further to encompass 2% to 3% of elderly populations aged 65 and older. While the vast majority of cases occur sporadically, an underlying hereditary genetic susceptibility serves as the primary etiologic driver in 5% to 10% of the affected patient population.[1]

Crucial motor manifestations of PD, encompassing tremors, rigidity, akinesia, hypokinesia, and bradykinesia, stem directly from a profound dopaminergic deficit within the posterior putamen, leading to subsequent disruption of the central motor circuitry.[2] Beyond its characteristic motor impairments, PD widely compromises non-motor neurological pathways. For instance, dopaminergic depletion within the caudate nucleus, coupled with architectural disruptions in associative circuits, frequently triggers early-onset executive dysfunction, while degeneration of central noradrenergic and serotonergic networks serves as a primary driver for neuropsychiatric manifestations, including severe apathy, generalized anxiety, and depressive mood shifts.[2]

Significant pathological involvement, such as degeneration in the locus coeruleus, raphe nuclei, hypothalamus, and autonomic nervous system structures, may explain the emergence of non-motor symptoms that are often unresponsive to dopamine replacement therapy. Some interconnected mechanisms, such as α-synuclein aggregation, mitochondrial dysfunction, impaired ubiquitin-proteasome and autophagy-lysosome systems, and chronic neuroinflammation, lead to progressive neuronal degeneration in PD.[3]

Given the important role of these mechanisms, particularly neuroinflammation, in disease progression, several non-pharmacological adjuvant therapies have shown potential therapeutic effects in PD through anti-inflammatory, antioxidant, and neuroprotective pathways, including probiotics, synbiotics, Chinese herbal medicine, and vitamin D3, which have been developed. Probiotic therapy has therapeutic and preventive effects via a variety of pathways, including competition for nutrients and binding to the intestinal epithelium, antagonism against pathogenic microbes, and metabolic interactions within the gut microbiota.[4] Besides probiotics, synbiotic therapy could also improve clinical results in PD by modulating the inflammation, oxidative stress, and neurotrophic pathways.[5]

Furthermore, Chinese traditional medicine has shown potential therapeutic effects in PD patients with depression by modulating neurotrophic and inflammatory pathways.[6] Besides Chinese traditional medicine, vitamin D3 supplementation has shown potential therapeutic effects in PD by reducing inflammation and improving functional performance. Patients with PD often have vitamin D insufficiency, which may correlate with increased inflammation and a higher risk of falling.[7]

PD has been treated using some types of non-pharmacological adjuvant therapy that target inflammatory pathways. Nevertheless, choosing the most effective supplementary intervention remains difficult due to variations in mechanisms of action, clinical efficacy, biomarker modification, intervention length, and patient responses among regimens. Some non-pharmacological adjuvant therapies, such as probiotics and synbiotics, have demonstrated potential therapeutic effects by modulating systemic inflammatory markers and enhancing motor and non-motor clinical features of PD. Nonetheless, there are variations across studies regarding the magnitude of the amplitude of biomarker modulation and the depth of clinical improvement as measured by Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) scores, depression measures, and quality-of-life assessments. In addition, most previous studies focused on evaluating a single intervention or comparing it to a placebo, with only a few studies comprehensively evaluating the relationship between inflammatory biomarkers, neurotrophic factors, metabolic signaling pathways, and clinical outcomes in PD patients. Therefore, this systematic review was conducted to evaluate the impact of non-pharmacological adjuvant therapy on systemic inflammatory biomarkers, neurotrophic factors, metabolic pathways, and clinical manifestations in patients with PD.

Method

Protocol and Registration

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines.[8] Prior to conducting the study, the research protocol was prospectively registered and archived in the International Prospective Register of Systematic Review (PROSPERO) under the registration identifier CRD420261395485.

Eligibility Criteria

Study inclusion was strictly governed by a structured PICO framework designed to isolate relevant clinical data. The target population was restricted to patients with a confirmed diagnosis of Parkinson's disease. The interventions included non-pharmacological adjuvant therapies, especially complementary nutritional interventions and herbal agents, such as probiotics, Omega-3 fatty acids, antioxidants/Vitamin E, dietary supplements, and herbal or traditional medicines. Comparators included placebo, standard Parkinson's care (Standard of Care/SoC) without adjuvant therapy, or patients' baseline measurements, depending on the study design.

The investigative endpoints were divided into primary and secondary categories. The primary focus centered on peripheral biomarker alterations, which included down-regulated systemic inflammatory markers (namely TNF-α, IL-6, and IL-1), metabolic signaling shifts involving low-density lipoprotein receptor (LDLR) and peroxisome proliferator-activated receptor gamma (PPAR-γ), and enhanced expression of neurotrophic factors such as brain-derived neurotrophic factor (BDNF). Conversely, secondary parameters evaluated objective clinical changes in motor and non-motor symptom presentation, specifically tracking fluctuations in MDS-UPDRS metrics, psychometric depression scales, and standardized quality-of-life evaluations. To capture a comprehensive body of evidence, the protocol accepted randomized controlled trials (RCTs) because RCTs are considered to provide stronger evidence.

Sources and Search Strategy

A comprehensive literature search was performed across five databases: PubMed, ProQuest, ScienceDirect, Springer Nature, and Cochrane Library, covering all records from database inception to March 2026. The search strategy (Appendix 1) was developed using eight core keywords: Parkinson disease, dietary supplement, probiotics, complementary therapies, adjuvant therapy, inflammation, cytokines, biomarkers. Both Medical Subject Headings (MeSH) and free-text terms were employed and combined using Boolean operators to maximise retrieval sensitivity.

In addition to the database search, a snowballing technique was employed to identify further relevant studies. This involved screening the reference lists of all included articles (backward snowballing) as well as identifying studies that cited the included articles (forward snowballing). This approach was undertaken to ensure that no potentially eligible studies were overlooked. Reference management and duplicate removal were performed systematically before screening.

Selection Process

Study selection was conducted using a two-stage screening process comprising an initial screening of titles and abstracts and a full-text review to determine final eligibility. This approach was undertaken to ensure objectivity and consistency throughout the selection process. Any disagreements were resolved through discussion and consensus. The entire selection procedure was documented in accordance with the PRISMA 2020 guidelines, detailing the number of records identified, screened, excluded, and included in the final analysis.

Data Collection Process

Data extraction included study characteristics (author, year, country, and study design), sample characteristics (sample size), eligibility criteria for PD, intervention and comparator regimens, and outcomes of interest, including changes in inflammatory cytokines (TNF-α, IL-1, IL-6), neurotrophic factors (BeDNF), metabolic pathway markers (PPAR-γ and LDLR), motor symptom severity, depression scores, and quality-of-life measures in patients with PD.

Risk of Bias Assessment

The risk of bias in the included studies was assessed using the Cochrane Risk of Bias 2 (RoB 2) tool.[9] This tool evaluates five domains of bias, including bias arising from the randomization process, bias due to deviations from intended intervention, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported result. The assessment was conducted independently by two

reviewers to ensure objectivity and consistency. Each domain was judged as 'low risk', 'some concerns', or 'high risk' of bias, in accordance with the RoB 2 guidance. Any disagreements between the reviewers were resolved through discussion and consensus, with consultation from a third reviewer where necessary.

As shown in Figure 2, no study was judged to have a high risk of bias. Most studies showed a low risk of bias in the domains related to the randomization process (D1), deviations from intended interventions (D2), and outcome measurement (D4). However, all included studies were rated as having some concerns in the domains of missing outcome data (D3) and selection of the reported result (D5). These judgements primarily reflected insufficient reporting regarding the handling of missing data and the lack of clear evidence that the reported outcomes were prespecified in a published protocol or statistical analysis plan. Consequently, the overall risk of bias for all included studies was judged as some concerns, in accordance with the RoB 2 guidance.

Result

Study Selection

A total of 1,373 records were identified through database searching. After removing duplicates and records marked as ineligible by automation tools, 183 studies remained for title and abstract screening. A total of 179 records were excluded due to the wrong population, intervention, comparison, and outcomes. Ultimately, 4 studies were included in this systematic review

Study Characteristics

The included studies consisted of four randomized controlled trials (RCTs) conducted between 2023 and 2025 across several countries, such as the United Kingdom, Sweden, China, and Poland. All studies involved patients diagnosed with PD, with varying participant characteristics based on disease stage, age range, and specific inclusion criteria. Most studies involved adults with mild to moderate PD, while one

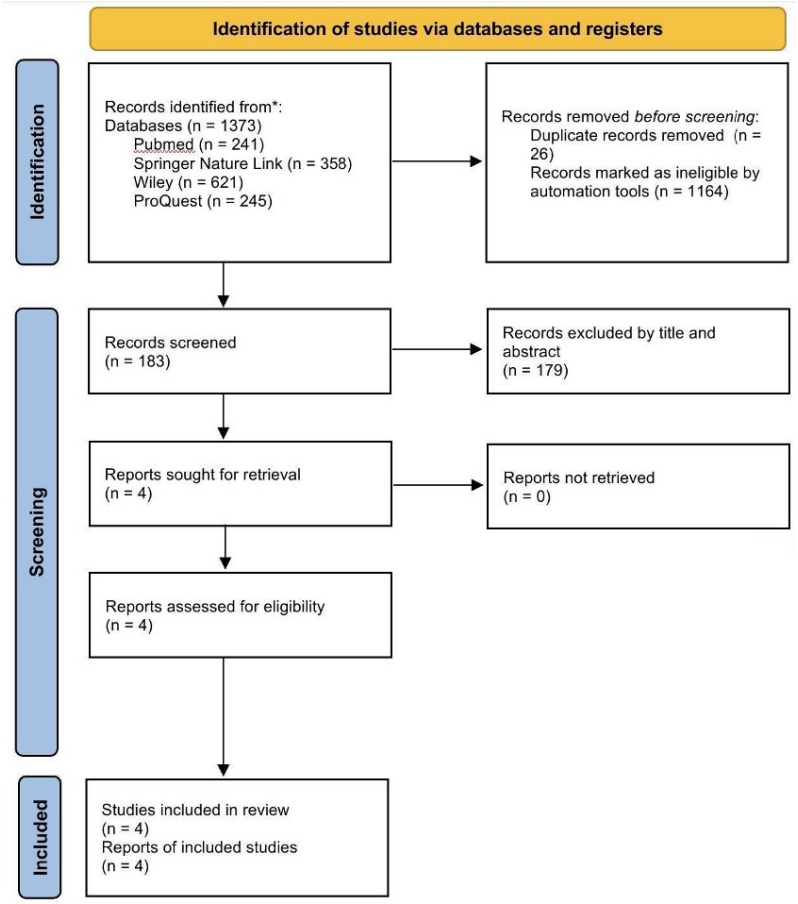

Figure 1: Diagram Flow of Literature Search Strategy

study specifically included patients with PD and comorbid depression. Participant sample sizes ranged from 40 to 74 participants.

A variety of non-pharmacological adjuvant interventions were assessed, including probiotics, synbiotics, traditional Chinese herbal medicine, Zishen Pingchan Granule (ZPG), and Vitamin D3 supplementation. Comparator groups generally received placebo treatment alongside standard Parkinson's care. The assessed outcomes primarily focused on inflammatory and neurotrophic biomarkers, including TNF-α, IL-1β, IL-6, CRP, BDNF, α-synuclein, and oxidative stress markers, as well as clinical outcomes, including changes in MDS-UPDRS, Hamilton Depression Scale (HAMD), and functional status scores. Several studies also explored alterations in gut microbiota composition and systemic inflammatory regulation following intervention.

Overall, the interventions showed typically positive safety profiles, with most studies reporting no serious adverse reactions. Some trials noted that the frequency of adverse events was comparable between intervention and placebo groups, while others reported no significant treatment-related complications. Although the included studies consistently suggested potential benefits of complementary nutritional and herbal therapies in improving inflammatory profiles and clinical symptoms in PD, direct comparisons across studies remain limited because of differences in intervention types, biomarker assessments, follow-up duration, and outcome reporting methods.

The methodological quality and overall risk of bias varied across the selected literature. Methodological evaluations indicated that a majority of the included trials exhibited a robust design with a low risk of bias within three primary evaluation areas: the initial randomization process (D1), adherence to intended therapeutic interventions (D2), and the objective measurement of clinical outcomes (D4). Specifically, Leta et al. (2025)[10] and Bytowska et al. (2023)[7] were generally assessed as having low risk in D1, D2, and D4, although some concerns remained regarding missing outcome data (D3) and selection of the reported result (D5). Similarly, Ning et al. (2023)[6] showed low risk in deviations from intended interventions (D2) and outcome measurement (D4), but some concerns were identified in the randomization process (D1), missing outcome data (D3), and selective reporting (D5).

Ramadan et al. (2025)[5] demonstrated low risk in the

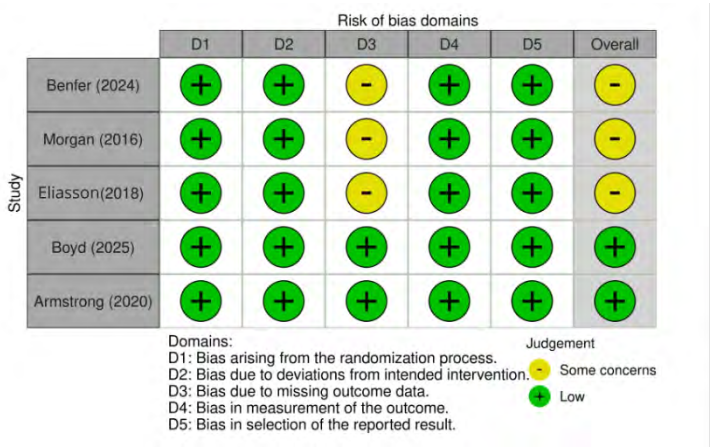

Figure 2: Risk of Bias domains of RCT studies

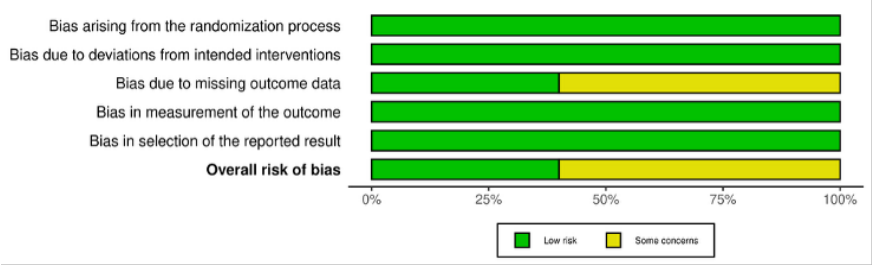

Figure 3: Overall risk of bias of RCT studies

Table 1. Study Characteristics of Included Studies

Authors (Year)	Country	Study Design	N (groups)	Population	Intervention vs Control	Key Outcomes	Adverse Events
Leta et al. (2025)[10]	UK and Sweden	RCT	74 (35 vs 39)	Adults ≥18 with MDS-diagnosed PD	Probiotic vs Placebo	Gut microbiota change at 12 wks (primary); inflammatory markers (TNF-α, IFN-γ, IL-6, IL-8, IL-10)	11 events in each arm; 3 vs 2 dropouts due to AEs
Ramadan et al. (2025)[5]	UK	RCT	66 (33 vs 33)	Adults 45–65, de novo PD, Hoehn-Yahr stage 1–4	Synbiotic vs Placebo	MDS-UPDRS motor/non-motor scores (primary); TNF-α, MDA, BDNF, α-synuclein	NR
Ning et al. (2023)[6]	China	RCT	80 (40 vs 40)	Adults 40–80, PD (Hoehn-Yahr 1–4) with mild-moderate depression (HAMD 8–24).	ZPG vs Placebo	HAMD and UPDRS-III scores; BDNF, IL-1β, IL-6, CRP, TNF-α	No serious adverse reactions
Bytowska et al. (2023)[7]	Poland	RCT	42 (21 vs 21)	PD patients on STN-DBS, no prior vitamin D supplementation, no major comorbidities.	Vitamin D3 vs Placebo	Serum vitamin D levels; motor/ mobility function; systemic inflammation	NR

RCT, randomized controlled trial; PD, Parkinson's disease; MDS, Movement Disorder Society; MDS-UPDRS, Movement Disorder Society–Unified Parkinson's Disease Rating Scale; HAMD, Hamilton Depression Rating Scale; BDNF, brain-derived neurotrophic factor; TNF-α, tumor necrosis factor-alpha; IFN-, interferon-γ gamma; IL-1β/6/8/10, interleukin-1beta/6/8/10; CRP, C-reactive protein; MDA, malondialdehyde; α-Syn, alpha-synuclein; ZPG, Zishen Pingchan Granule; STN-DBS, subthalamic nucleus deep brain stimulation; N, total sample size; AE, adverse event.

randomization process (D1), while several concerns remained in domains related to deviations from intended interventions (D2), missing outcome data (D3), outcome measurement (D4), and selection of the reported result (D5). Across all included studies, the most common concerns were associated with missing outcome data (D3) and selective reporting (D5), as all studies showed some concerns in these domains.

Overall, the included studies were predominantly judged as having "some concerns" rather than a high risk of bias. The summary risk-of-bias assessment demonstrated that most studies had low risk in randomization, intervention deviations, and outcome measurement domains, whereas concerns related to incomplete outcome data and reporting bias remained relatively common across the included trials.

Discussion

Principal Findings and Clinical Signal

The evidence from four randomised controlled trials (RCTs) assessing complementary nutritional and herbal interventions–such as probiotic supplementation, synbiotic therapy, traditional Chinese herbal medicine (Zishen Pingchan Granule), and vitamin D3 supplementation–in patients with PD was compiled in this systematic review. Together, these studies evaluated biological and clinical results, focusing on neurotrophic markers, oxidative stress markers, peripheral inflammatory biomarkers, and validated clinical scales measuring the burden of motor and non-motor symptoms.[5,6,7,10]

Complementary nutritional and herbal therapies may have potentially helpful anti-inflammatory and neuroprotective benefits in PD, according to the collected research. Several interventions were linked to favourable modulation of systemic inflammatory markers across the reviewed studies. These included improvements in oxidative stress parameters and neurotrophic markers like brain-derived neurotrophic factor (BDNF), as well as decreases in pro-inflammatory cytokines like TNF-α, interleukin-1 beta (IL-1ß), interleukin-6 (IL-6), and C-reactive protein (CRP). Modulation of disease-relevant biomarkers, such as alpha-synuclein, has also been identified in several studies, indicating potential mechanistic significance beyond general systemic inflammation. In some trials, these biomarker changes were accompanied by improvements in selected clinical outcomes, including MDS-UPDRS scores and depressive symptom measures. However, these findings were not consistent across all included studies. [5,6,7,10]

Despite these positive results, the research as a whole is still preliminary and should be evaluated carefully. Significant methodological heterogeneity, such as variations in intervention type, participant characteristics, biomarker selection, outcome measuring techniques, and follow-up duration, limits direct comparison between trials. Additionally, the very small sample sizes in each of the included trials limit the generalizability of results and lower statistical power. Therefore, there is currently insufficient evidence to conclude that complementary nutritional and herbal interventions provide effective supportive treatment for PD. While some studies suggest possible biological activity, these findings require confirmation in larger, well-designed clinical trials. [5,6,7,10]

Peripheral Biomarkers and Parkinson's Pathophysiology

PD is becoming more well acknowledged as a condition involving systemic immune dysregulation and persistent neuroinflammation in addition to dopaminergic neuronal loss. Peripheral inflammatory indicators, which indicate interactions between systemic inflammation, blood-brain barrier failure, and neurodegenerative progression, may offer clinically relevant insight into underlying disease processes, even though PD pathology is centered in the central nervous system.[5,7]

TNF-α is a pro-inflammatory cytokine that has been closely linked to neuroinflammation associated with PD. Through oxidative stress, mitochondrial malfunction, and apoptotic signaling, activated microglia release TNF-α, which contributes to a persistent inflammatory milieu that causes dopaminergic neuronal damage. Therefore, persistent elevation of TNF-α may be more indicative of persistent neurotoxic inflammatory activity than temporary systemic immune activation.[5]

IL-6 and IL-1ß are important mediators in inflammatory amplification pathways. While IL-6 is linked to chronic inflammatory signalling and may help breach the blood-brain barrier, giving peripheral immune mediators more access to the central nervous system, IL-1ß contributes to microglial activation and neuronal injury. Therefore, elevated levels of these cytokines in the blood may be biologically plausible markers of the inflammatory burden associated with a disease.[6]

On the other hand, rather than being a cytokine with a

specific mechanism, C-reactive protein (CRP) is a more general indicator of systemic inflammation. Despite being nonspecific, CRP has significant translational benefits because of its known correlations with PD risk, disease severity, and prognosis, as well as its standardized testing techniques and reliability. According to a recent viewpoint, CRP may be especially helpful in PD biomarker research because it measures chronic inflammatory burden independent of the specific inflammatory pathway involved, which makes it helpful in a variety of neurodegenerative conditions where the exact mechanisms are still unclear.[11]

Neuroprotection-related markers need to be taken into account as well. Brain-derived neurotrophic factor (BDNF) is essential for maintaining the dopaminergic system, synaptic plasticity, and neuronal survival. While treatments that raise BDNF may represent the restoration of neuroprotective capacity rather than just the suppression of inflammation, decreased BDNF levels have been connected to poor neuroplasticity and the advancement of disease.[5,6]

Given their crucial involvement in PD pathogenesis through protein misfolding and aggregation, more disease-specific biomarkers like α-synuclein offer greater pathological significance. However, the lack of consistency between research, biological compartment variations, and testing methodology heterogeneity continue to make it methodologically difficult to interpret peripheral α-synuclein findings.[5,6]

When considered collectively, peripheral biomarker modulation should be taken as potentially significant evidence of changed neuroimmune and neurodegenerative processes rather than as a single biochemical fluctuation. Therapeutic approaches that target inflammation and neuroprotection in PD have biologically reasonable support, although various biomarkers vary in their mechanistic specificity and clinical relevance. [5,6]

Methodological Heterogeneity and Interpretation Challenges

One of the major challenges in interpreting the current evidence is not necessarily therapeutic failure, but significant methodological variability among studies. The included trials encompassed a diverse array of interventions, such as probiotics, synbiotics, traditional Chinese herbal medicines, and vitamin D3 supplementation. These interventions are biologically different and operate via various mechanisms. Probiotics and synbiotics mainly influence gut microbiota composition and immune signaling along the gut-brain axis, while herbal formulations primarily demonstrate anti-inflammatory and antioxidant effects via phytochemical pathways.[10] In comparison, vitamin D3 acts as an endocrine immunomodulator that plays a role in neuroimmune regulation and the survival of neurons. Due to the mechanistic differences among these therapies, making direct comparisons between studies is challenging.[7]

Significant diversity was also noted in the characteristics of participants. The studies varied in terms of disease stage, age range, duration of disease, and the existence of comorbid conditions like depression. These variations are clinically significant because PD demonstrates considerable biological diversity, encompassing differences in inflammatory activity, levels of oxidative stress, and the course of neurodegeneration. As a result, therapeutic reactions can vary greatly among different patient subgroups, restricting the general applicability and comparability of results across various studies.[5,6,7,10]

An additional significant constraint was the variety of outcomes evaluated. Research assessed multiple biomarkers and clinical outcomes, such as TNF-α, IL-1ß, IL-6, markers of oxidative stress, α-synuclein, BDNF, gut microbiota diversity, MDS-UPDRS scores, and scales for depression.[10] The lack of standardized outcome measures hindered significant apple-to-apple comparisons among trials. Moreover, various studies had comparatively brief follow-up periods, which might have been inadequate to identify lasting biomarker changes or extended clinical outcomes in a progressive neurodegenerative condition like PD.[5,6,7,10]

Collectively, the observed inconsistency among studies might indicate methodological fragmentation instead of genuine therapeutic ineffectiveness. The differences in intervention methods, participant traits, outcome metrics, and follow-up lengths make it difficult to interpret the overall evidence. Future studies would gain from enhanced methodological standardization, involving more uniform patient stratification, aligned biomarker evaluations, and extended follow-up durations to boost comparability and reinforce conclusions about complementary nutritional and herbal treatments in PD.[5,6,7,10]

Microbiota-Targeted Interventions and the Gut-Brain Axis

The positive outcomes observed with microbiota-targeted treatments in this analysis may be explained biologically by the gut-brain axis, which has emerged as a compelling framework for understanding the pathophysiology of PD. Magistrelli's hypothesis is a well-known idea that suggests PD pathology may start outside the central nervous system, perhaps in the gastrointestinal tract or olfactory system, before gradually moving to the brain. This theory is based on the finding that aberrant α-synuclein aggregation, a clinical characteristic of PD, has been found in enteric nervous tissue and may spread to the substantia nigra and other parts of the brain via neural routes like the vagus nerve. This idea is in line with the clinical finding that gastrointestinal symptoms, especially constipation, frequently appear years before motor symptoms do.[12]

According to this theory, gut microbial dysbiosis may accelerate PD through inflammatory and immunological pathways. Changes in the composition of the gut microbiota may compromise the integrity of the intestinal barrier, enabling the translocation of bacterial endotoxins like lipopolysaccharide into the systemic circulation. This can worsen neuroinflammatory processes through immune signalling and disruption of the blood-brain barrier, as well as peripheral inflammation. The positive outcomes seen in the probiotic and synbiotic therapies covered in this review may be explained by this. The therapeutic potential of microbiota-targeted interventions as supplemental strategies in PD management is reinforced by recent clinical evidence showing that probiotic supplementation in PD patients significantly reduced IL-6 levels while improving motor and non-motor symptoms, including gastrointestinal symptom burden.[12]

Despite high biological plausibility, there is currently inadequate data to show a direct causal association between microbiome modulation and disease modification in PD. Comparability between research is still hampered by differences in probiotic strains, intervention duration, participant characteristics, and outcome-measuring techniques. However, more research into microbiota-directed treatments within deeper neuroprotective approaches is encouraged by the developing molecular connection between gut dysbiosis, chronic inflammation, and neurodegeneration.[5,6,7,10,12]

Clinical Implications of Complementary Interventions

The results of this review indicate that adjuvant nutritional and herbal therapies could provide beneficial clinical support for individuals with PD, especially by influencing inflammation, oxidative stress, and gut-brain axis mechanisms. Multiple studies showcased enhancements in peripheral inflammatory markers, neurotrophic factors, depressive symptoms, and specific motor or non-motor clinical results. Their results suggest that such strategies may aid in improving inflammatory balance, assist in symptom management, boost mood and psychological well-being, and possibly lead to an enhanced quality of life for certain patients with PD.[5]

Nevertheless, existing evidence is still inadequate to endorse these therapies as substitutes for recognized PD treatments. Conventional pharmacological treatments, such as levodopa and dopamine agonists, continue to be the foundation of PD management due to their proven effectiveness in managing motor symptoms and preserving functional ability. Conversely, the complementary interventions assessed in this review were typically examined in limited groups, over brief follow-up durations, and utilizing varied methodologies, restricting the robustness and applicability of the findings.[5,6,7,10]

Thus, these nutritional and herbal methods should presently be regarded as complementary supportive strategies instead of disease-modifying or independent treatments. Their possible worth may be in enhancing traditional treatment by addressing systemic inflammation, oxidative stress, gastrointestinal issues, and the burden of non-motor symptoms, aspects that are frequently insufficiently managed by dopaminergic therapy alone. Larger and more standardized clinical trials are still necessary before these interventions can be included in standard evidence-based PD treatment guidelines.[5,6,7,10]

Safety and Tolerability

The overall positive safety profile of the included alternative nutritional and herbal therapies is a significant finding of this review. No significant treatment-related side effects were consistently observed across the included randomized controlled trials, indicating that these interventions may be fairly well tolerated as supplemental therapies in PD patients. While no serious safety issues were seen with

herbal or vitamin D supplementation, probiotic and synbiotic therapies showed adequate tolerability, with adverse event frequencies equivalent to control groups in several studies.[5,6,7,10]

Tolerability is an important factor to take into account when assessing supplementary therapy methods because patients with PD tend to be older individuals with various comorbidities, polypharmacy exposure, and greater vulnerability to medication-related adverse effects. Therefore, complementary therapies that show promise for neuroprotective or anti-inflammatory effects without significantly adding to the burden of treatment may be appealing supportive choices. Specifically, compared to more pharmacologically intensive treatments, microbiota-targeted medicines like probiotics and synbiotics may offer a relatively low-risk intervention strategy.[5,6,7,10]

These results should be interpreted with caution, though, since the information that is now available remains limited by short follow-up periods, small sample numbers, and inadequate long-term safety monitoring. Concerns about formulation standardization, pharmacokinetic variability, and possible herb-drug interactions that might not be completely recorded in short-term clinical studies may also arise with some therapies, especially herbal formulations. Therefore, larger and longer-duration trials are required to better show long-term safety and real-world clinical applicability, even though the current evidence suggests adequate short-term tolerability.[5,6,7,10]

Comparison with Existing Literature, Strengths of This Review, and Limitations

The findings of this review are generally consistent with previous studies investigating probiotics, neuroinflammation, and additional anti-inflammatory treatments in PD. Earlier reviews indicated that interventions aimed at microbiota may enhance inflammatory regulation, gastrointestinal issues, and certain motor or non-motor symptoms by influencing the gut-brain axis and overall immune responses.[5,6,7,10] Research conducted by Kesika et al. (2022) emphasized the increasing significance of neuroinflammation and peripheral inflammatory biomarkers in the pathophysiology of PD, reinforcing the possible importance of immunomodulatory approaches in disease management. This review broadens the existing evidence by combining various types of complementary interventions, such as probiotics, synbiotics, herbal formulations, and vitamin D supplementation, while also assessing both peripheral inflammatory biomarkers and clinical outcomes from recent human interventional studies.

This analysis possesses multiple strengths, such as a targeted clinical question, the inclusion of recent randomized controlled trials, and the combination of biomarker results with clinically significant outcomes like motor symptoms, depressive symptoms, and non-motor effects. Nonetheless, various constraints must also be recognized. The evidence still remains sparse, comprising just four randomized controlled trials and relatively small sample sizes of about 40-74 participants, which diminishes statistical power and generalizability. Considerable methodological diversity among interventions, populations, biomarkers, and outcome metrics also restricted direct comparisons between studies and hindered quantitative meta-analysis. Moreover, the follow-up periods were comparatively brief, potentially rendering them inadequate for evaluating lasting therapeutic or disease-modifying outcomes in a chronic progressive condition like PD. A further significant limitation is that peripheral inflammatory markers, such as TNF-α, IL-6, CRP, and BDNF, might not accurately represent neuroinflammation in the central nervous system and should thus be interpreted carefully when deducing underlying neurodegenerative processes.[5,6,7,10]

Conclusion

This systematic review concludes that current evidence is insufficient to establish the effectiveness of complementary nutritional and herbal interventions, such as probiotics, synbiotics, traditional Chinese herbal medicine, and vitamin D3 supplementation, as supportive treatments for Parkinson's disease. While several studies reported potential mechanisms related to the gut-brain axis and anti-inflammatory, antioxidant, and neuroprotective effects, these findings remain inconclusive due to the limitations and heterogeneity of the included studies. Further high-quality randomized controlled trials are required before definitive conclusions can be drawn. Numerous studies showed improvements in some clinical outcomes, such as motor symptoms, depressive symptoms, and non-motor manifestations, as well as peripheral inflammatory biomarkers, oxidative stress markers, and neurotrophic factors like BDNF. These findings support the increasing understanding that systemic

immune dysregulation and neuroinflammation play significant roles in the etiology of PD.[5,6,7,10]

However, the current data is still limited by small sample sizes, short follow-up periods, diverse interventions, and variations in outcome assessments and participant characteristics. As a result, it is no longer able to draw solid conclusions on clinical efficacy and disease-modifying potential. Currently, these treatments should not be used in place of conventional dopaminergic therapy, but rather as supplemental supporting strategies.[5,6,7,10]

To evaluate the efficacy and long-term safety of supplementary nutritional and herbal therapy in PD patients, future research should focus on more comprehensive, methodologically standardized randomized controlled trials. More consistency in intervention methods, biomarker selection, patient classification, and clinical outcome assessments will increase the overall body of data and improve research comparability. To enhance clinical outcomes and offer substantial neuroprotective or disease-modifying benefits in PD, more study is required to understand whether peripheral inflammation and gut-brain axis functions may be controlled.[5,6,7,10]

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Conflict of Interest

The authors declare that they have no competing financial interests or personal relationships that could have influenced the work reported in this paper.

Source of Funding

The authors declare that they have no competing financial interests or personal relationships that could have influenced the work reported in this paper.

Availability of Data and Material

The datasets analyzed during the current systematic review were compiled entirely from previously peer-reviewed publications and open-access repositories. No primary or novel datasets were generated for this study. The extracted clinical data and analytical materials supporting the conclusions of this manuscript remain available from the corresponding author upon reasonable academic request.

Author's Contributions

All authors participated equally in the intellectual design, comprehensive literature search, data extraction, statistical analysis, interpretation of clinical findings, and draft preparation of this manuscript. Furthermore, every individual author carefully reviewed, revised, and granted final approval for the submitted version of the text.

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Supplementary Files

Comparative Efficacy and Safety of Dual Orexin Receptor Antagonists (DORAs) Versus Z-Drugs for Insomnia in Older Adults : A Systematic Review

Appendix 1. Search Strategy

PubMed

#1	"Parkinson Disease"[Mesh] OR "Parkinsonian Disorders"[Mesh] OR "Parkinson*"
#2	"Dietary Supplements"[Mesh] OR "Probiotics"[Mesh] OR "Fatty Acids, Omega-3"[Mesh] OR "Vitamin E" OR "Drugs, Chinese Herbal"[Mesh] OR "Complementary Therapies"[Mesh] OR "Adjuvant Therapy"
#3	"Inflammation"[Mesh] OR "Cytokines"[Mesh] OR "Biomarkers"[Mesh] OR "TNF-alpha" OR "Interleukins" OR "PPAR gamma" OR "BDNF"
#4	#1 AND #2 AND #3

Springer Nature Link

#1	"Parkinson Disease"[Mesh] OR "Parkinsonian Disorders"[Mesh] OR "Parkinson*"
#2	"Dietary Supplements"[Mesh] OR "Probiotics"[Mesh] OR "Fatty Acids, Omega-3"[Mesh] OR "Vitamin E" OR "Drugs, Chinese Herbal"[Mesh] OR "Complementary Therapies"[Mesh] OR "Adjuvant Therapy"
#3	#1 AND #2
#4	"Inflammation"[Mesh] OR "Cytokines"[Mesh] OR "Biomarkers"[Mesh] OR "TNF-alpha" OR "Interleukins" OR "PPAR gamma" OR "BDNF"
#4	#3 AND #4

Wiley

#1	(TI,AB,KW:("Parkinson disease" OR "Parkinsonian disorder*" OR Parkinson*))
#2	(TI,AB,KW:("dietary supplement*" OR probiotic* OR "omega-3" OR "omega 3" OR "fatty acid*" OR "vitamin E" OR nutraceutical* OR "Chinese herbal*" OR phytotherap* OR "complementary therap*" OR "adjuvant therap*"))
#3	#1 AND #2
#4	(TI,AB,KW:(inflammat* OR neuroinflammat* OR cytokine* OR biomarker* OR "TNF-alpha" OR TNF OR interleukin* OR "PPAR gamma" OR PPAR ɣ OR BDNF))
#5	#3 AND #4

ProQuest

#1	"Parkinson disease" OR "Parkinsonian disorder*" OR Parkinson*
#2	"dietary supplement*" OR probiotic* OR "omega-3" OR "omega 3" OR "fatty acid*" OR "vitamin E" OR nutraceutical* OR "Chinese herbal*" OR phytotherap* OR "complementary therap*" OR "adjuvant therap*"
#3	#1 AND #2
#4	inflammat* OR cytokine* OR biomarker* OR "TNF-alpha" OR TNF OR interleukin* OR "PPAR gamma" OR PPAR ɣ OR BDNF) NOT ("systematic review" OR "Meta-analysis"
#5	#3 AND #4