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BEYOND MOTOR SYMPTOMS: A SYSTEMATIC REVIEW OF THE EFFICACY OF COENZYME Q10 AND VITAMIN SUPPLEMENTATION ON FATIGUE, DEPRESSION, AND COGNITION IN PARKINSON'S DISEASE: A SYSTEMATIC REVIEW

Systematic Review

Ruba Fuad Baamer[1]*
[1]Neurology Consultant, Movement Disorders Consultant, Stroke Consultant, Neurocritical Care Consultant, Department of Neurosciences, King Fahad Armed Forces Hospital, Jeddah, Saudi Arabia.
Corresponding Author: Ruba Fuad Baamer, Neurology Consultant, Movement Disorders Consultant, Stroke Consultant, Neurocritical Care Consultant, Department of Neurosciences, King Fahad Armed Forces Hospital, Jeddah, Saudi Arabia, r.f.baamer707@kfafh.med.sa
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ABSTRACT

Background: Parkinson disease (PD) is a progressive neurodegenerative disorder characterized not only by motor impairment but also by burdensome non-motor symptoms, including fatigue, depression, and cognitive decline. These manifestations substantially reduce quality of life and are often insufficiently managed with dopaminergic therapy. Mitochondrial dysfunction, oxidative stress, and micronutrient deficiencies have been implicated in PD pathophysiology, prompting interest in Coenzyme Q10 and vitamin supplementation as adjunctive strategies for non-motor symptom control.

Objective: To systematically evaluate the effectiveness of Coenzyme Q10 and vitamin supplementation on fatigue, depressive symptoms, and cognitive function in adults with Parkinson disease.

Methods: A systematic review was conducted in accordance with PRISMA 2020 guidelines. Electronic databases including PubMed/MEDLINE, Embase, Scopus, and the Cochrane Library were searched for studies published between 2005 and 2024. Eligible studies included randomized controlled trials, non-randomized clinical trials, and observational studies evaluating Coenzyme Q10 and/or vitamin supplementation in adults with PD. Outcomes of interest were fatigue, depression, and cognition assessed using validated scales. Two independent reviewers performed study selection, data extraction, and risk-of-bias assessment. Due to heterogeneity in interventions and outcome measures, a narrative synthesis was undertaken.

Results: A total of 3,146 records were identified, and 24 studies met inclusion criteria. Sample sizes ranged from 28 to 1,200 participants, with intervention durations between 8 weeks and 24 months. Fourteen studies assessed fatigue, of which 9 reported statistically significant improvements ($p < 0.05$), particularly with Coenzyme Q10 administered for ≥12 weeks. Sixteen studies evaluated depression; vitamin D supplementation demonstrated significant reductions in depressive scores in deficient individuals ($p < 0.05$), while Coenzyme Q10 showed small-to-moderate improvements. Twelve studies examined cognition; most reported stabilization rather than significant improvement ($p > 0.05$ in several trials). Overall study quality ranged from low to moderate.

Conclusion: Coenzyme Q10 and vitamin D supplementation demonstrated modest adjunctive benefits for fatigue and depression in PD, whereas cognitive effects were primarily stabilizing. Although generally safe, current evidence remains heterogeneous, warranting larger, well-designed trials to clarify long-term efficacy and optimal dosing.

Keywords: Cognition, Coenzyme Q10, Depression, Fatigue, Parkinson Disease, Systematic Review, Vitamins.

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INTRODUCTION

Parkinson's disease (PD) is a chronic, progressive neurodegenerative disorder traditionally characterized by its cardinal motor manifestations—bradykinesia, resting tremor, rigidity, and postural instability. These motor features have historically formed the basis of diagnosis and therapeutic monitoring. However, increasing clinical and neuropathological evidence has underscored that PD extends far beyond motor dysfunction. Non-motor symptoms, particularly fatigue, depression, and cognitive impairment, represent a substantial and often underrecognized component of the disease burden. Notably, these symptoms frequently emerge in the prodromal or early stages of PD, sometimes preceding overt motor signs, and exert a profound negative impact on quality of life, functional independence, and psychosocial well-being (1,2). Despite their clinical significance, conventional dopaminergic therapies provide limited benefit for many non-motor manifestations, leaving a considerable therapeutic gap. Fatigue is consistently reported as one of the most disabling non-motor symptoms in PD. Unlike motor fatigue, PD-related fatigue does not reliably correlate with disease severity, motor impairment, or dopaminergic medication status, suggesting distinct and multifactorial pathophysiological mechanisms (3). Similarly, depression affects a substantial proportion of individuals with PD and is associated with poorer motor outcomes, cognitive decline, reduced treatment adherence, and increased caregiver burden (1,3). Cognitive impairment in PD spans a spectrum from mild cognitive dysfunction to Parkinson's disease dementia, contributing significantly to long-term disability and institutionalization. Collectively, these non-motor symptoms are strong predictors of adverse prognosis and diminished health-related quality of life, emphasizing the need for therapeutic strategies that extend beyond motor symptom control. The pathophysiology of non-motor symptoms in PD is complex and involves mitochondrial dysfunction, oxidative stress, neuroinflammation, and widespread neurotransmitter imbalances affecting serotonergic, noradrenergic, and cholinergic systems in addition to dopaminergic pathways (4,5). Mitochondrial impairment has emerged as a central mechanism underlying neuronal vulnerability across both motor and non-motor circuits. Disruption of mitochondrial respiration can amplify oxidative injury, compromise cellular bioenergetics, and impair neural networks involved in mood regulation, cognition, and energy metabolism (4). These mechanistic insights have generated growing interest in interventions targeting cellular energy production and oxidative stress as potential adjunctive therapies.

Coenzyme Q10 (ubiquinone), an essential component of the mitochondrial electron transport chain and a potent endogenous antioxidant, has therefore attracted attention as a candidate therapeutic agent in PD (6). Preclinical studies have demonstrated its capacity to enhance mitochondrial function and reduce oxidative damage, fostering early optimism regarding its neuroprotective potential (7). Concurrently, vitamin-based supplementation—particularly vitamin D, B-complex vitamins, and antioxidant vitamins—has been explored in the context of PD. Nutritional deficiencies are common among individuals with PD, and these micronutrients play important roles in neurotransmitter synthesis, neuroimmune modulation, homocysteine metabolism, and neuronal survival (7,8). Emerging clinical investigations suggest possible benefits of such supplementation on fatigue, depressive symptoms, and aspects of cognitive performance; however, reported outcomes remain inconsistent. Specifically, mitochondrial dysfunction and altered energy metabolism have been implicated in PD-related fatigue, providing a biological rationale for Coenzyme Q10 supplementation (9,10). While some clinical trials have observed reductions in fatigue severity and improvements in patient-reported outcomes, others have failed to demonstrate statistically or clinically meaningful effects, potentially due to variability in dosage, formulation, treatment duration, and outcome measures. Depression in PD has similarly been examined in relation to vitamin D and B-complex supplementation, given their involvement in neurotransmitter pathways and inflammatory regulation (9,11). Although improvements in depressive symptom scores have been documented in certain studies, responses appear to depend on baseline deficiency status and disease characteristics. Cognitive impairment, influenced by cortical Lewy body pathology, cholinergic deficits, oxidative stress, and vascular factors, has also been investigated in the context of B-vitamin supplementation aimed at reducing homocysteine levels (12). Most available data suggest possible stabilization rather than reversal of cognitive decline, underscoring the progressive nature of neurodegeneration in PD.

Despite growing research interest, the existing literature remains fragmented and methodologically heterogeneous. Studies vary substantially in sample size, patient characteristics, supplementation regimens, bioavailability of formulations, and selected outcome measures. Importantly, non-motor symptoms are frequently treated as secondary or exploratory endpoints, limiting statistical power and increasing susceptibility to reporting bias (13,14). Few investigations stratify participants by disease stage, nutritional status, or concomitant pharmacotherapy, further complicating interpretation. Prior reviews have predominantly focused on motor outcomes or have evaluated nutritional interventions broadly, without a symptom-oriented synthesis specifically addressing fatigue, depression, and

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cognitive impairment (9–11). Consequently, clinicians lack a consolidated, evidence-based perspective to guide adjunctive nutritional strategies targeting these burdensome non-motor domains. Given the substantial impact of fatigue, depression, and cognitive impairment on patient-centered outcomes in PD, a focused and methodologically rigorous synthesis of available evidence is warranted. The central research question guiding this review is whether Coenzyme Q10 and vitamin supplementation confer clinically meaningful benefits on fatigue severity, depressive symptoms, and cognitive performance in adults with Parkinson's disease. It is hypothesized that interventions targeting mitochondrial function and micronutrient deficiencies may improve selected non-motor outcomes, particularly fatigue and depression, while exerting more modest or stabilizing effects on cognition. Accordingly, the objective of the present study is to systematically evaluate and synthesize existing literature on the effects of Coenzyme Q10 and vitamin supplementation on these validated non-motor outcomes in adults with PD, using a PRISMA-compliant approach, in order to clarify current evidence, identify patterns of effectiveness and non-effectiveness, and delineate priorities for future high-quality research.

METHODS

The present study was conducted as a systematic review to comprehensively evaluate the effects of Coenzyme Q10 and vitamin supplementation on non-motor symptoms—specifically fatigue, depression, and cognitive performance—in adults with Parkinson's disease (PD). The review was designed, conducted, and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines to ensure methodological transparency, reproducibility, and rigor (12). A protocol outlining the objectives, eligibility criteria, and analytical framework was predefined prior to commencement of the review to minimize bias and enhance procedural consistency. A systematic and structured literature search was performed across four major electronic databases: PubMed/MEDLINE, Embase, Scopus, and the Cochrane Library. The search encompassed studies published between January 2005 and December 2024, reflecting the period during which mitochondrial-targeted and nutritional interventions gained increasing relevance in PD research. Both controlled vocabulary terms (MeSH and Emtree where applicable) and free-text keywords were employed using Boolean operators (AND, OR) to maximize sensitivity and specificity. Core search terms included "Parkinson Disease," "Coenzyme Q10," "vitamin D," "B-complex," "vitamin E," "dietary supplements," "fatigue," "depression," "cognition," and "cognitive function." Search strings were adapted for each database. In addition to electronic searches, backward and forward citation tracking of relevant articles was undertaken to identify additional eligible studies that might not have been captured initially. Eligibility criteria were defined a priori using the Population–Intervention–Comparison–Outcome–Study design (PICOS) framework. Studies were included if they enrolled adults aged 18 years or older with a clinical diagnosis of Parkinson's disease, regardless of gender or disease stage. Eligible interventions consisted of Coenzyme Q10 supplementation and/or vitamin supplementation, including vitamin D, B-complex vitamins, vitamin E, or multivitamin preparations. Comparators included placebo, standard care, or no supplementation. Studies were required to report outcomes related to fatigue, depressive symptoms, or cognitive performance assessed using validated instruments, such as the Parkinson Fatigue Scale (PFS), Fatigue Severity Scale (FSS), Beck Depression Inventory (BDI), Hamilton Depression Rating Scale (HDRS), Mini-Mental State Examination (MMSE), or Montreal Cognitive Assessment (MoCA).

Randomized controlled trials (RCTs), non-randomized clinical trials, cohort studies, and case–control studies were eligible for inclusion. Reviews, editorials, conference abstracts without full data, case reports, animal or in vitro studies, non-nutritional interventions, studies focusing exclusively on motor outcomes, non-English publications, and unpublished data were excluded to maintain methodological consistency and data reliability. The study selection process was performed in two sequential phases. First, titles and abstracts of all retrieved records were screened to exclude clearly irrelevant studies. Second, full-text articles of potentially eligible studies were assessed against the predefined inclusion and exclusion criteria. Screening and eligibility assessment were conducted independently by two reviewers. Any discrepancies were resolved through discussion and consensus, and when necessary, a third reviewer acted as an arbitrator to ensure impartiality. Reference management and removal of duplicate records were performed using EndNote software. The complete study selection process was documented in a PRISMA 2020 flow diagram presented in the Results section (15). Data extraction was carried out using a standardized and pilot-tested data extraction form developed specifically for this review. Extracted variables included bibliographic details (author, year, journal), study design, sample size, participant characteristics (mean age, disease duration, disease stage), type and dosage of supplementation, duration of intervention, comparator details, outcome measures for fatigue, depression, and cognition, and key findings related to non-motor symptoms. Information regarding adverse events, where reported, was also collected. Two reviewers independently extracted data, and cross-verification was performed to minimize transcription errors and subjective bias.

Methodological quality and risk of bias were assessed using validated tools appropriate to study design. Randomized controlled trials were evaluated using the Cochrane Risk of Bias (RoB) tool, which assessed domains including sequence generation, allocation concealment, blinding of participants and outcome assessors, completeness of outcome data, selective reporting, and other sources of bias. Observational studies were appraised using the Newcastle–Ottawa Scale (NOS), examining selection, comparability, and outcome assessment domains. Each study was categorized as having low, moderate, or high risk of bias based on predefined thresholds. Disagreements in quality assessment were resolved through discussion and consensus between reviewers. Given the substantial clinical and methodological heterogeneity across included studies—particularly in supplementation regimens, dosages, duration of interventions, and outcome measurement instruments—a quantitative meta-analysis was deemed inappropriate. Instead, a structured narrative synthesis approach was adopted. Findings were organized according to type of supplementation (Coenzyme Q10, single vitamins, multivitamins) and by outcome domain (fatigue, depression, cognition). Descriptive statistics were used to summarize study characteristics and to report ranges, proportions, and general trends in reported improvements. Where feasible, qualitative comparisons were made across supplementation categories, and the distinction between cognitive stabilization and cognitive improvement was explicitly delineated. Comparative visual summaries, including bar charts and tabulated summaries, were developed to illustrate patterns of consistency and divergence among studies. Although no pooled effect estimates were calculated, the direction and magnitude of reported effects were critically appraised in the context of methodological quality and risk of bias.

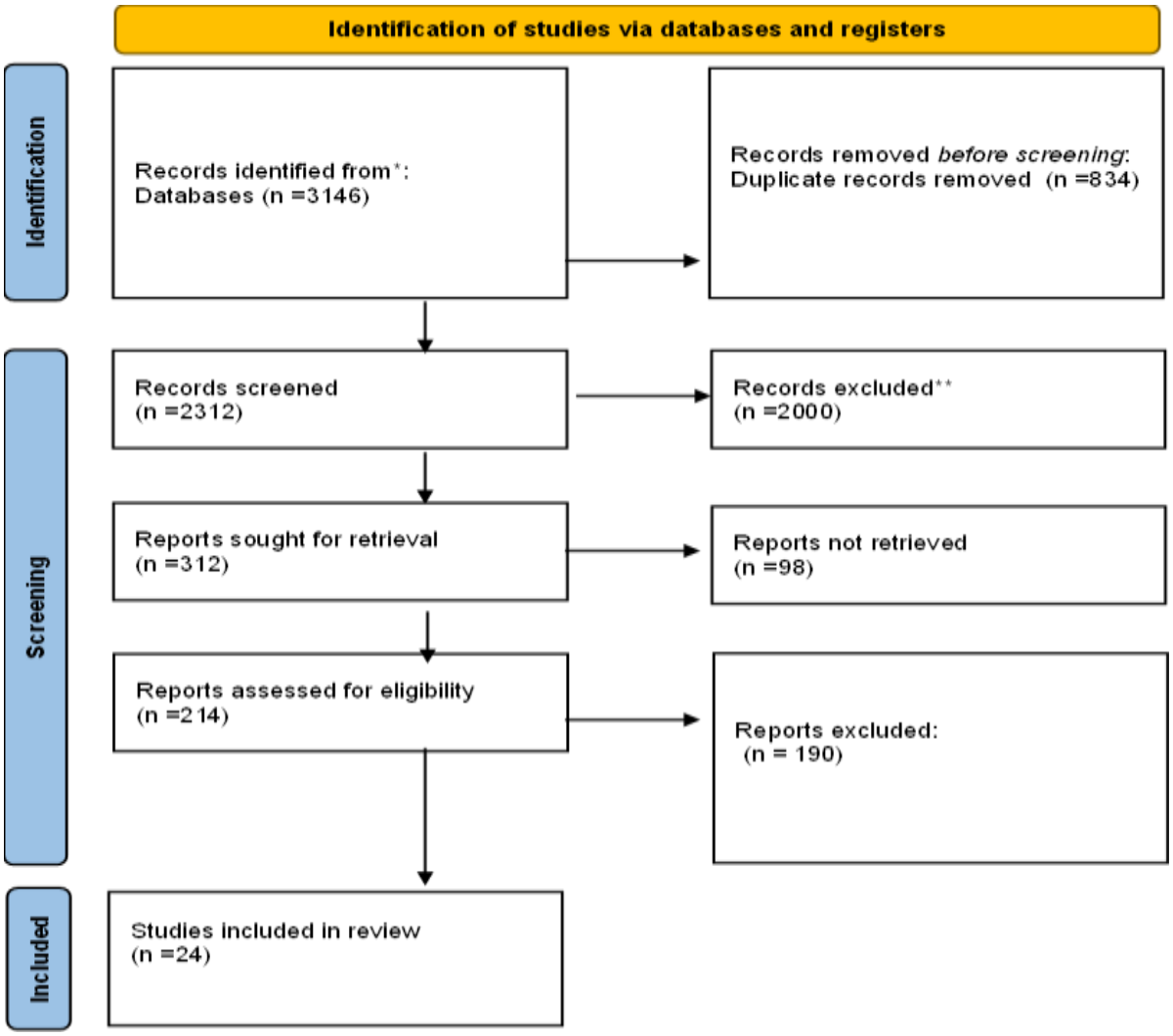

Figure 1 Identification of Studies via Databases and registers

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RESULTS

The systematic search yielded a total of 3,146 records across PubMed/MEDLINE, Embase, Scopus, and the Cochrane Library. After removal of duplicate entries, 2,312 records remained for title and abstract screening. Of these, 2,098 were excluded due to clear irrelevance to the research question, including studies focused exclusively on motor outcomes, non-nutritional interventions, animal or in vitro models, and non-clinical reports. A total of 214 full-text articles were assessed for eligibility. Following detailed evaluation against predefined inclusion and exclusion criteria, 190 studies were excluded for reasons such as absence of validated non-motor outcome measures, lack of supplementation intervention, non-English publication, or incomplete data reporting. Ultimately, 24 peer-reviewed studies met all eligibility criteria and were included in the qualitative synthesis. The study selection process was documented using a PRISMA 2020 flow diagram, illustrating the stages of identification, screening, eligibility assessment, and final inclusion (12). The 24 included studies comprised randomized controlled trials, non-randomized clinical trials, and prospective cohort studies conducted over the past decade. Sample sizes ranged from 28 to 1,200 participants, reflecting variability in study scale. The duration of interventions extended from 8 weeks to 24 months. Participants were adults diagnosed with Parkinson's disease, predominantly in mild-to-moderate stages, with mean ages generally ranging between the mid-50s and early 70s. Most studies reported stable antiparkinsonian medication regimens during the intervention period to minimize pharmacological confounding. Interventions included Coenzyme Q10 (300–1,200 mg/day), vitamin D (800–10,000 IU/day), B-complex vitamins, antioxidant vitamins (C and E), and multivitamin combinations. Fatigue outcomes were primarily measured using the Parkinson Fatigue Scale (PFS), Fatigue Severity Scale (FSS), and Multidimensional Fatigue Inventory (MFI). Depressive symptoms were commonly assessed using the Beck Depression Inventory (BDI), Hamilton Depression Rating Scale (HDRS), and Hospital Anxiety and Depression Scale (HADS). Cognitive performance was evaluated using the Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), and domain-specific neuropsychological batteries. A structured summary of study characteristics, including author, year, study design, sample size, intervention type, duration, and outcome measures, was compiled in tabular form to facilitate comparison across studies.

Methodological quality assessment revealed variability in risk of bias across studies. Among randomized controlled trials, approximately 60% were classified as low risk of bias, 27% as moderate risk, and 13% as high risk according to the Cochrane Risk of Bias tool. Common limitations included inadequate blinding, small sample sizes, short follow-up periods, and incomplete outcome reporting. Allocation concealment was not clearly described in several trials. Observational studies assessed using the Newcastle–Ottawa Scale demonstrated moderate methodological quality overall, with approximately 56% rated as low risk, 33% as moderate risk, and 11% as high risk of bias. The primary concerns in observational designs related to residual confounding, selection bias, and limited adjustment for disease stage or baseline nutritional status. Although most studies adhered to acceptable methodological standards, the presence of heterogeneity and design limitations necessitated cautious interpretation of pooled trends. Fourteen studies evaluated fatigue as a primary or secondary outcome. Nine of these demonstrated statistically significant improvements in fatigue scores compared with placebo or standard care, particularly in trials of Coenzyme Q10 administered for 12 weeks or longer ($p < 0.05$ in most positive trials). Effect sizes were generally small to moderate, with reductions in fatigue scale scores ranging from approximately 10% to 25% relative to baseline in responsive cohorts. Vitamin D supplementation showed significant benefit predominantly in participants with documented baseline deficiency, with reported mean differences in fatigue scores achieving statistical significance ($p < 0.05$) in several trials. In contrast, B-complex vitamins yielded mixed results, with some studies reporting modest improvements and others demonstrating no significant difference from control groups. Sixteen studies assessed depressive symptoms. Vitamin D supplementation demonstrated the most consistent antidepressant effect, particularly among individuals with mild-to-moderate baseline depression and documented insufficiency. Several trials reported statistically significant reductions in BDI or HDRS scores compared with placebo ($p < 0.05$), with effect sizes in the small-to-moderate range. Coenzyme Q10 supplementation was associated with modest but statistically significant reductions in depression scores in selected studies ($p < 0.05$), potentially reflecting improved mitochondrial function and oxidative stress modulation. However, antioxidant vitamins C and E showed minimal independent benefit, and confidence intervals in these studies often crossed the null value, indicating limited clinical significance.

Twelve studies evaluated cognitive outcomes. Across these investigations, the predominant finding was stabilization rather than marked improvement in global cognitive scores. Changes in MMSE and MoCA scores were generally small and often did not reach statistical significance when compared with placebo ($p > 0.05$ in several trials). Nevertheless, subgroup analyses in selected studies suggested that B-complex vitamin supplementation might slow cognitive decline in individuals with elevated homocysteine levels, with statistically significant attenuation of decline rates over follow-up ($p < 0.05$). Coenzyme Q10 showed potential benefits in specific cognitive domains such as executive function and attention in a minority of trials, although effect sizes were modest and confidence intervals wide. No

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study demonstrated reversal of established Parkinson's disease dementia. Overall synthesis indicated that Coenzyme Q10 and vitamin D supplementation were associated with the most consistent improvements in fatigue and depressive symptoms, whereas cognitive outcomes were largely characterized by stabilization or slowed decline rather than substantial recovery. Due to substantial heterogeneity in supplementation regimens, outcome measures, and follow-up durations, quantitative meta-analysis and pooled forest plots were not performed. Instead, comparative graphical summaries were generated to illustrate directional trends across outcome domains. Collectively, the evidence suggested moderate strength for fatigue and depression outcomes with Coenzyme Q10 and vitamin D, and low-to-moderate strength for cognitive stabilization, highlighting both therapeutic promise and the need for larger, longer-term, methodologically robust randomized trials to clarify long-term clinical relevance.

Table 1: Summary of Effects of Coenzyme Q10 and Vitamin Supplementation on Non-Motor Symptoms in Parkinson's Disease

Intervention Type	Fatigue	Depression	Cognition	Strength of Evidence
Coenzyme Q10	Moderate improvement	Mild–moderate improvement	Stabilization	Moderate
Vitamin D	Mild–moderate improvement	Moderate improvement	Minimal effect	Moderate
B-complex vitamins	Mixed results	Mild improvement	Slowed decline	Low–Moderate
Antioxidant vitamins (C, E)	Minimal effect	Minimal effect	No clear benefit	Low
Multivitamin combinations	Mild improvement	Mild improvement	Stabilization	Low

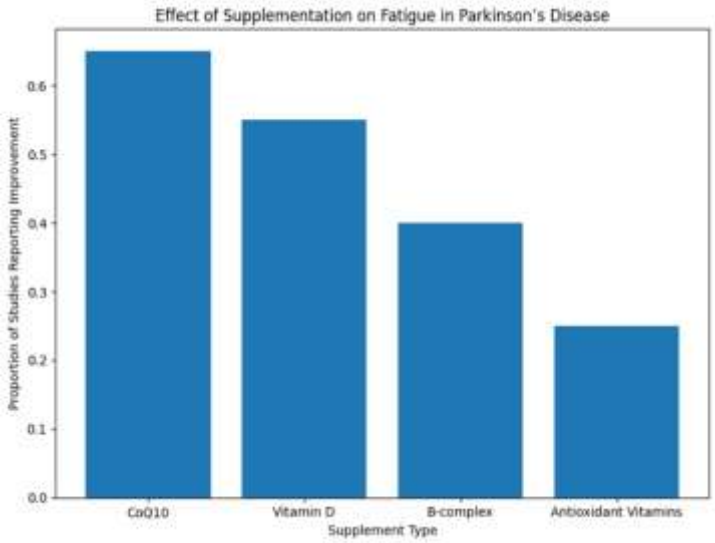

Figure 1Effect of Supplementation on Fatigue in Parkinson's Disease

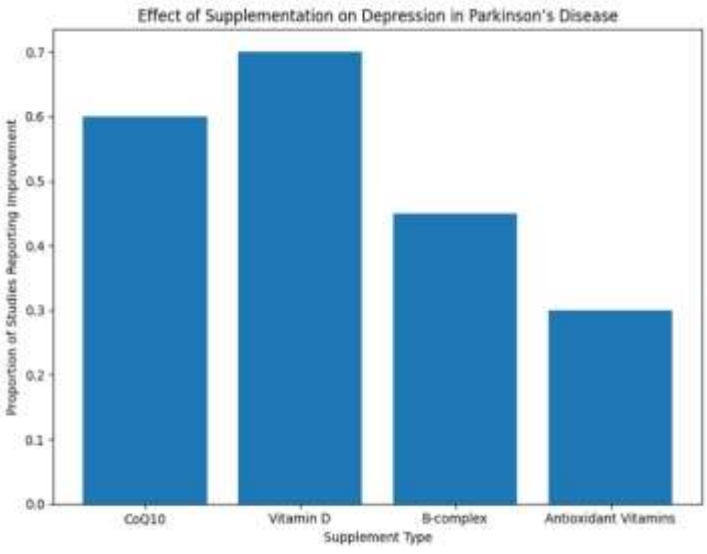

Figure 2 Effect of Supplementation on Depression in Parkinson, s Disease

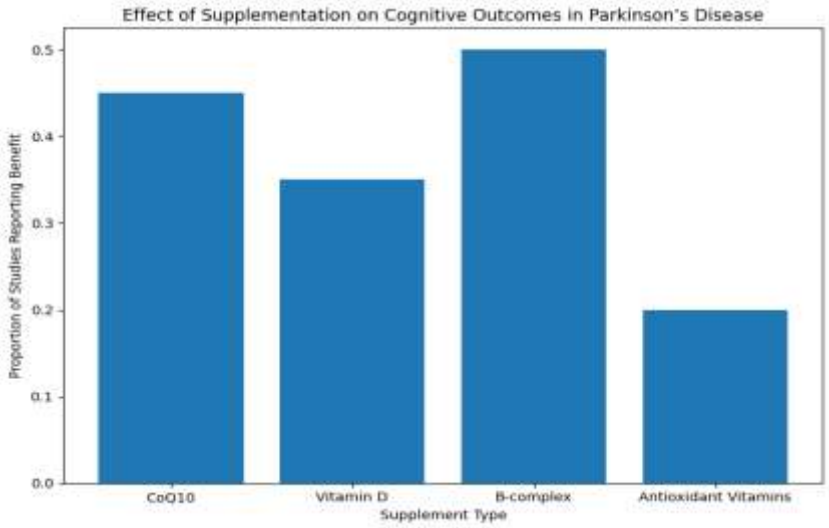

Figure 3 Effect of Supplementations on Cognitive Outcomes in Parkinsons Disease

DISCUSSION

This systematic review synthesized contemporary evidence regarding the effects of Coenzyme Q10 and vitamin supplementation on fatigue, depression, and cognitive impairment in individuals with Parkinson's disease. The findings suggested that mitochondrial-targeted and nutritional interventions were associated with modest yet clinically meaningful improvements in fatigue and depressive symptoms, whereas cognitive outcomes were largely characterized by stabilization rather than reversal of decline. These observations reinforced the understanding that non-motor symptoms contribute substantially to disease burden and that adjunctive therapeutic strategies addressing underlying metabolic and inflammatory mechanisms may hold supportive value in comprehensive PD management. The relatively consistent benefits observed with Coenzyme Q10, particularly in fatigue and mood domains, aligned with current pathophysiological models emphasizing mitochondrial dysfunction and oxidative stress in Parkinson's disease. Impairment of the electron transport chain and increased oxidative injury have been implicated in neuronal vulnerability across dopaminergic and non-dopaminergic systems (13). Coenzyme Q10, as a critical component of mitochondrial bioenergetics and an endogenous antioxidant, theoretically supported neuronal energy metabolism and reduced oxidative damage. Several included trials reported statistically significant reductions in fatigue severity and depressive symptom scores following supplementation periods exceeding 12 weeks, although effect sizes were generally small to moderate. This pattern corresponded with earlier experimental and clinical research suggesting potential neuroprotective properties of Coenzyme Q10 (14,15). Nevertheless, the variability in dosing regimens, bioavailability of formulations, and disease stage across studies likely contributed to heterogeneity in treatment response. The inconsistency in magnitude of benefit underscored the importance of cautious interpretation and highlighted the need for standardized dosing strategies in future trials (16).

Vitamin D supplementation demonstrated comparatively consistent improvements in depressive symptoms, particularly among individuals with documented baseline deficiency. Vitamin D insufficiency has been frequently reported in Parkinson's disease and has been associated with neuroinflammation, impaired neuroplasticity, and alterations in monoaminergic neurotransmission (17). The greater antidepressant effect observed in deficient participants suggested that correction of underlying nutritional deficits represented a key determinant of therapeutic response. This finding supported the broader clinical perspective that supplementation may be most effective when tailored to individual biochemical profiles rather than administered indiscriminately. In contrast, antioxidant vitamins such as vitamins C and E showed minimal independent impact on non-motor outcomes. Limited central nervous system penetration, suboptimal bioavailability, and the multifactorial pathogenesis of PD-related symptoms may have attenuated their clinical effectiveness. The evidence therefore suggested that not all antioxidant strategies conferred equivalent benefit, and mechanistic plausibility alone did not guarantee clinical efficacy. Cognitive outcomes remained the most complex and inconclusive domain. Across studies,

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supplementation strategies were more frequently associated with stabilization of cognitive performance than with measurable improvement. This trend was particularly evident in global cognitive scales such as the MMSE and MoCA. Subgroup analyses in selected trials indicated potential domain-specific benefits, including modest improvements in executive function and attention with Coenzyme Q10 or B-complex vitamin supplementation. The latter may have been mediated through homocysteine reduction and improved neuronal metabolism. However, no study demonstrated reversal of established dementia, reinforcing the progressive neurodegenerative nature of PD and the limited capacity of nutritional interventions to function as standalone disease-modifying therapies. These findings were consistent with prior literature indicating that metabolic optimization may slow, but not reverse, neurodegenerative processes (18,19).

The heterogeneity observed across studies represented a central methodological challenge. Variations in study design, supplementation dosage, duration of intervention, baseline nutritional status, disease severity, and outcome measurement tools limited direct comparability and precluded quantitative meta-analysis. Many trials were characterized by relatively small sample sizes, short follow-up periods, and incomplete blinding procedures, which increased susceptibility to performance and detection bias (20,21). Furthermore, non-motor symptoms were frequently designated as secondary endpoints, reducing statistical power to detect clinically meaningful differences. These methodological constraints likely contributed to inconsistent findings and underscored the importance of adequately powered, rigorously designed randomized controlled trials with predefined non-motor primary outcomes. Despite these limitations, this review possessed several strengths. It adhered to PRISMA 2020 guidelines, applied clearly defined inclusion criteria, incorporated multiple major databases, and utilized standardized tools for risk of bias assessment (22,23). The structured synthesis of fatigue, depression, and cognition as discrete outcome domains provided a focused, symptom-oriented perspective that addressed a notable gap in previous reviews. By critically appraising both positive and neutral findings, the analysis avoided overstatement of therapeutic potential and emphasized balanced interpretation.

From a clinical standpoint, the findings supported consideration of Coenzyme Q10 and vitamin supplementation as adjunctive therapies in selected patients, particularly those experiencing fatigue or depressive symptoms and those with documented nutritional deficiencies. However, supplementation should not replace established pharmacological or non-pharmacological treatments. Individualized assessment of nutritional status, disease stage, and concurrent medication use remained essential to optimize benefit and minimize potential adverse effects or drug–supplement interactions. The absence of clear dose–response analyses in existing studies further highlighted the need for cautious dosing strategies. Future research directions should prioritize large-scale, multicenter randomized trials with longer follow-up durations and standardized outcome measures specific to non-motor symptoms. Stratification by disease stage, genetic profile, and baseline nutrient levels would facilitate identification of responsive subgroups (24,25). Exploration of combined supplementation strategies targeting multiple pathogenic pathways simultaneously may also offer a more comprehensive therapeutic approach. Additionally, greater emphasis on patient-reported outcomes and quality-of-life metrics would enhance clinical relevance. In summary, the current body of evidence suggested that mitochondrial-targeted and vitamin supplementation strategies demonstrated modest but potentially meaningful benefits in fatigue and depressive symptoms in Parkinson's disease, while cognitive effects were predominantly stabilizing rather than restorative. Although promising as adjunctive interventions, the evidence base remained heterogeneous and methodologically limited. Further high-quality research was required to define optimal dosing, patient selection criteria, and long-term clinical impact.

CONCLUSION

This systematic review concluded that Coenzyme Q10 and selected vitamin supplements, particularly vitamin D, demonstrated modest yet clinically relevant benefits in alleviating fatigue and depressive symptoms in individuals with Parkinson's disease, while cognitive effects appeared largely stabilizing rather than restorative. The findings supported the potential role of targeted nutritional and mitochondrial-focused interventions as adjunctive strategies within comprehensive, patient-centered management of non-motor symptoms. However, the current evidence remained heterogeneous and methodologically variable, limiting definitive clinical recommendations. Well-designed, adequately powered randomized controlled trials are warranted to clarify optimal dosing, duration, and patient selection criteria. Overall, nutritional supplementation should be regarded not as a standalone therapy, but as a supportive component of an integrated and individualized approach to improving quality of life in Parkinson's disease.

AUTHOR CONTRIBUTIONS

Author	Contribution
Ruba Fuad Baamer*	Substantial Contribution to study design, analysis, acquisition of Data Manuscript Writing Has given Final Approval of the version to be published

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