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Dietary supplements and bioactive compounds for managing Parkinson's Disease

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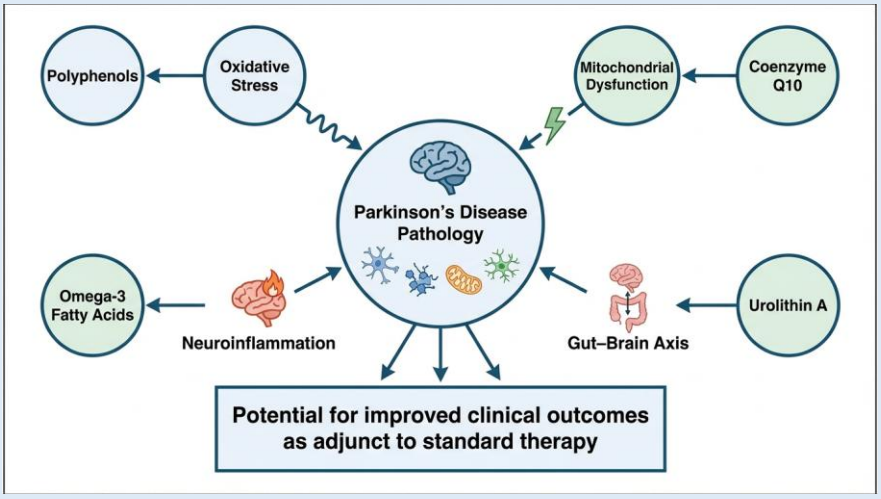
ABSTRACT

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by dopaminergic neuronal loss and multisystem pathology involving oxidative stress, mitochondrial impairment, neuroinflammation, proteostasis disruption with α-synuclein aggregation, and gut–brain axis dysfunction. Levodopa remains the most effective symptomatic therapy, yet it does not directly target upstream pathogenic processes and may be limited by long-term complications, motivating interest in adjunct strategies that support multiple disease-relevant pathways. This review integrates mechanistic, preclinical, and clinical evidence on dietary supplements, functional food–derived nutrients, and bioactive compounds that may complement standard pharmacotherapy in PD. A structured search of major scientific databases was conducted to identify studies relevant to PD pathology, with findings synthesized qualitatively using a pathway-based framework that includes proteostasis and α-synuclein biology, mitochondrial bioenergetics and mitophagy, oxidative stress responses, neuroinflammatory signaling, neurotrophic support, and gut–brain communication. Across compound classes, polyphenols, omega-3 fatty acids, mitophagy-associated metabolites, and neurotrophic modulators show consistent mechanistic relevance in experimental models, while human data is still emerging and heterogeneous across study designs, formulations, and outcome measures. Overall, the evidence supports nutraceuticals and functional food–derived bioactives as potential adjuncts—not replacements—to established PD therapies, with translational progress dependent on improved standardization of formulations, bioavailability considerations, and long-term trials using clinically interpretable endpoints.

Novelty of the Study: This review synthesizes dietary supplements, functional food–derived nutrients, and bioactive compounds in Parkinson's disease (PD) using a multi-pathway framework aligned with Functional Food Science (FFS), linking mechanistic plausibility to translational biomarkers and clinically relevant outcomes. To our knowledge, this is the first structured analysis integrating PD pathology with the FFC functional food development model, including bioactive compound identification, biomarker mapping, and adjunct therapeutic potential.

Keywords: Parkinson's disease; nutraceuticals; bioactive compounds; functional foods; oxidative stress; mitochondrial dysfunction; neuroinflammation; α-synuclein; proteostasis; mitophagy; gut–brain axis; adjunct therapy



Graphical Abstract: Dietary supplements and bioactive compounds for managing Parkinson's Disease

INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative disorder defined by the loss of dopaminergic neurons in the substantia nigra pars compacta and the accumulation of α-synuclein–rich Lewy pathology. Clinical features commonly include resting tremor, bradykinesia, rigidity, postural instability, and a broad spectrum of non-motor symptoms. Symptoms often become clinically evident only after substantial dopaminergic neuronal loss has occurred, and disease risk reflects a complex interplay of genetic susceptibility and environmental exposures [1–2]. Current standard treatment relies heavily on dopaminergic replacement strategies. Levodopa, a dopamine precursor, remains the most effective symptomatic therapy because it can cross the blood–brain barrier and increase central dopamine availability [3–4]. However, levodopa primarily addresses symptoms and does not directly resolve multiple upstream biological processes implicated in neurodegeneration.

In parallel with pharmacologic management, increasing attention has been directed toward functional foods, dietary supplements, and bioactive compounds—food-derived constituents that can modulate cellular pathways relevant to neurodegeneration. Many of these compounds interact with mechanisms implicated in PD progression, including oxidative stress, mitochondrial dysfunction and impaired mitophagy, chronic

neuroinflammation, and disruptions in proteostasis associated with α-synuclein aggregation. Because PD is multifactorial, multi-target nutritional bioactives are best discussed as supportive adjuncts to standard therapy rather than stand-alone interventions. The strength of evidence varies widely across compound classes, study models, and formulations, making careful synthesis necessary to distinguish mechanistic plausibility from clinical efficacy.

Current Research Landscape: Recent literature reflects growing interest in nutraceutical-based strategies for PD, spanning mechanistic in vitro work, animal models, observational studies, and a limited number of clinical trials [5–8]. Although several compounds demonstrate neuroprotective potential in experimental systems, findings remain heterogeneous due to differences in study design, dosing, bioavailability, intervention duration, and outcome selection [5–7]. Many existing reviews emphasize isolated compounds or single mechanisms, highlighting the need for an integrated synthesis that maps candidate interventions onto convergent PD-relevant pathways and clarifies their translational relevance within adjunct care frameworks [5–6, 9–10].

Methodology of Literature Selection: This narrative review was developed through a structured evaluation of published literature examining dietary supplements, functional food–derived nutrients, and bioactive compounds relevant to Parkinson's disease. Emphasis was placed on integrating mechanistic, preclinical, and clinical evidence to support a translational discussion of nutraceutical-based adjunct approaches.

Literature Search Strategy: A structured literature search was conducted using PubMed, Scopus, Web of Science, Google Scholar, and the Functional Foods in Health and Disease Journal (FFHDJ) archive. Searches used combinations of the following terms: Parkinson's disease, nutraceuticals, dietary supplements, bioactive compounds, functional foods, polyphenols, mitochondrial dysfunction, oxidative stress, neuroinflammation, α-synuclein aggregation, proteostasis, mitophagy, and gut–brain axis. Reference lists of relevant review articles were also screened to identify additional studies.

Inclusion and Exclusion Criteria: Studies were included if they met one or more of the following criteria:

1. Investigated dietary supplements, bioactive compounds, or functional food–derived molecules relevant to Parkinson's disease.
2. Reported mechanistic insights related to dopaminergic neuroprotection, oxidative stress, mitochondrial function, neuroinflammation, proteostasis, or gut–brain axis modulation; or
3. Consisted of in vitro studies, in vivo animal models, observational studies, or human clinical trials.

Studies were excluded if they lacked relevance to Parkinson's disease pathology, focused exclusively on unrelated neurological disorders, or provided insufficient methodological detail. Non–peer-reviewed sources were considered only when they offered novel mechanistic insights and were clearly identified as such.

Data Extraction and Analytical Framework: From each included study, data were extracted on compound classification, proposed mechanism(s) of action, experimental model, dosage or dietary source, reported effects on motor and non-motor outcomes, and safety considerations when available. Findings were synthesized qualitatively rather than pooled quantitatively. Evidence was organized using a pathway-based framework centered on proteostasis and α-synuclein aggregation, mitochondrial bioenergetics and mitophagy, oxidative stress responses,

neuroinflammation, neurotrophic support, and gut–brain axis regulation.

Bioactive Compounds, Functional Food Groups, and Sources: Parkinson's disease involves multiple interacting pathways, which makes a food-based, multi-target framework particularly relevant. In this review, candidate interventions were organized around functional food groups (FFGs) and the food-derived bioactive compounds most associated with PD-relevant mechanisms, including oxidative stress regulation, mitochondrial bioenergetics and mitophagy, neuroinflammatory signaling, proteostasis and α-synuclein handling, neurotrophic support, and gut–brain communication. Table 1 summarizes major functional foods and their key bioactives, highlighting primary dietary sources and representative supporting evidence. Importantly, the table emphasizes foods and food patterns first; where supplement or formulation studies are cited, they are presented as translational evidence rather than as substitutes for dietary intake.

Table 1. Dietary supplements and bioactive compounds relevant to parkinson's disease: mechanisms of action, dietary sources, and supporting evidence.

Compound / Food	Mechanism of Action (How it helps)	Primary Food Sources	References
Epigallocatechin Gallate (EGCG)	Iron chelator; prevents alpha-synuclein misfolding; inhibits nitric oxide & TNF-α production.	Green tea; matcha; white tea.	[11]
Resveratrol	Activates SIRT1 (longevity gene) & Nrf2; promotes mitochondrial biogenesis; reduces neuroinflammation.	Red grape skins; red wine, peanuts; pistachios; berries.	[11–12]
Curcumin	Crosses BBB to inhibit alpha-synuclein aggregation; activates PI3K/AKT survival pathway; potent anti-inflammatory. Demonstrated neuroprotection in MPTP-treated mice when administered at 60 mg/kg/day for 35 days, attenuating dopaminergic neuronal loss and neuroinflammation.	Turmeric, yellow curry powder (needs black pepper/fat for absorption).	[13]
Sulforaphane	Most potent natural Nrf2 activator; boosts glutathione (brain's master antioxidant); promotes detoxification. In a 6-OHDA mouse model, 5 mg/kg intraperitoneal sulforaphane administered twice weekly for 4 weeks significantly reduced oxidative stress–mediated dopaminergic damage.	Broccoli sprouts (highest), Brussels sprouts, kale, cabbage.	[14]
Omega-3 (DHA/EPA)	Precursor to "resolvins" (resolve inflammation); maintains synaptic membrane fluidity; increases BDNF.	Fatty fish (salmon, mackerel, sardines), algal oil, flaxseeds (ALA).	[15]
Caffeine	Adenosine A2A receptor antagonist; blocks receptors that inhibit dopamine signaling; improves motor deficits. Exhibited A2A receptor–mediated neuroprotection in 6-OHDA models, with functional effects observed at 100–300 μM concentrations and behavioral improvements reported in n = 6–8 experimental groups.	Coffee, espresso, black tea, dark chocolate.	[16]
Natural L-DOPA	Direct dopamine precursor; typically has fewer side effects than synthetic levodopa due to co-factors like CoQ10. In a crossover clinical study of 18 PD patients, Mucuna pruriens delivering 3.5–17.5 mg/kg L-DOPA equivalents produced sustained motor improvements with fewer dyskinesias compared to standard levodopa.	Mucuna pruriens (Velvet bean), Fava beans (Broad beans - especially pods).	[17]
Dietary Nicotine	Stimulates α7-nicotinic receptors to prevent neuronal apoptosis; may reduce alpha-synuclein clumping. Epidemiological analysis of 486 PD cases	Peppers, Tomatoes, Eggplant, Potatoes (Solanaceae family).	[18]

Compound / Food	Mechanism of Action (How it helps)	Primary Food Sources	References
	and 636 controls showed a 19% reduction in PD risk per daily serving of edible Solanaceae, consistent with low-dose dietary nicotine exposure.		
Astaxanthin	"Super-antioxidant" (crosses BBB); protects mitochondrial membrane; reduces dopaminergic cell loss by modulating NF-κB. In MPTP-treated mice, lactoferrin-modified astaxanthin liposomes administered at 0.665 mg/kg intravenously every other day for 2 weeks significantly restored striatal dopamine levels and mitochondrial integrity.	Sockeye salmon, krill oil, shrimp, red trout, haematococcus pluvialis algae.	[19]
Fisetin	Senolytic agent; clears "zombie" (senescent) cells in the brain; induces autophagy (cellular cleanup) via Atg-3.	Strawberries, apples, persimmons, onions, cucumbers.	[20]
Spermidine	Induces autophagy (self-eating of damaged cells) independent of mTOR; promotes degradation of protein aggregates.	Aged cheese (cheddar/parmesan), mushrooms, soy products, wheat germ.	[21]
Urolithin A	Stimulates mitophagy (recycling of defective mitochondria); dampens NLRP3 inflammasome activation.	Gut metabolite formed after eating Pomegranates, walnuts, raspberries.	[22]
Pterostilbene	Methylated version of resveratrol (better bioavailability); potent SIRT1 activator; inhibits MAO-B enzyme (similar to Selegiline).	Blueberries, almonds, grape leaves, vaccinium berries.	[23]
Magnesium L-Threonate	Magnesium L-threonate enhances brain magnesium availability and supports synaptic function. In MPTP-treated mice (30 mg/kg/day for 7 days), chronic oral magnesium L-threonate (0.8–1.6 mM) reduced dopaminergic neuron loss and motor deficits more effectively than magnesium sulfate.	Supplement form (L-threonate); Mg rich foods: Pumpkin seeds, spinach, almonds.	[24]
Vitamin D3	Regulates GDNF (Glial cell-derived neurotrophic factor) synthesis; reduces autoimmunity (T-reg expansion). Clinical data indicate that higher serum vitamin D levels correlate with reduced PD severity, and supplementation up to 10,000 IU/day for 16 weeks has been evaluated in pilot PD cohorts (n ≈ 50).	Sunlight, fatty fish, egg yolks, fortified foods.	[25]
Lycopene	Protects against MPTP-induced dopamine depletion; reduces oxidative stress and apoptosis.	Cooked tomatoes, watermelon, pink grapefruit, papaya.	[26]
Cinnamaldehyde	Upregulates Parkin and DJ-1 (genes linked to PD); promotes autophagy of protein aggregates.	Ceylon Cinnamon (avoid Cassia in high doses due to coumarin).	[27]
Crocin & Safranal	Prevents alpha-synuclein fibrillation; protects dopaminergic cells from rotenone toxicity.	Saffron threads (Crocus sativus).	[28]
6-Shogaol	Suppresses neuroinflammation via TLR pathway; regulates gut-brain axis to prevent spread of pathology.	Dried Ginger (Shogaols are formed when ginger is dried or cooked).	[29]
Carnosic Acid	Activates PI3K pro-survival pathway; protects neurons from excitotoxicity.	Rosemary, Sage.	[30]
Oleuropein	Promotes autophagy; destabilizes alpha-synuclein fibrils into non-toxic forms.	Extra Virgin Olive Oil (high quality, peppery taste indicates content).	[31]
Hericenones / Erinacines	Stimulates synthesis of Nerve Growth Factor (NGF); promotes remyelination.	Lion's Mane Mushroom (Hericium erinaceus).	[32]
Bacosides	Bacosides, the active saponins in Bacopa monnieri (Brahmi), exert neuroprotective effects by restoring dopamine levels, reducing oxidative stress, and inhibiting MAO-B activity, with animal studies showing	Bacopa monnieri (Brahmi).	[33]

Compound / Food	Mechanism of Action (How it helps)	Primary Food Sources	References
	improved motor function and preservation of dopaminergic neurons in Parkinsonian models.		
Withanolides	Improves mitochondrial function; ameliorates climbing deficits in PD models; reduces cortisol.	Ashwagandha (Withania somnifera) root.	[29]
Creatine	Creatine acts as a neuronal energy buffer by increasing phosphocreatine availability and stabilizing mitochondrial permeability. One study showed creatine treatment protected against morphological deterioration by increasing overall process length per neuron by ~60% and branching points per neuron by ~80% in cultured dopaminergic neurons exposed to MPP+ in vitro.	Red meat, herring, supplement (Creatine Monohydrate).	[35]
Coenzyme Q10 (CoQ10)	Electron acceptor in mitochondrial Complex I (often defective in PD); potent antioxidant.	Organ meats (heart/liver), beef, sardines, broccoli.	[36]
Anthocyanins	Crosses BBB to localize in hippocampus/striatum; rescues mitochondrial Complex I activity.	Blueberries, blackberries, blackcurrants, purple corn/potatoes.	[37]
Ginsenoside Rg1	Ginsenoside Rg1 activates the BDNF–TrkB signaling pathway in animal models, increasing hippocampal BDNF and phosphorylated TrkB expression (e.g., p-TrkB levels were significantly upregulated versus control, $P < 0.05$) and improving synaptic plasticity and memory performance in transgenic mice treated with 1–10 mg/kg Rg1 for 1 month.	Panax Ginseng (Asian Ginseng).	[38]
Quercetin	Mitochondria-targeted antioxidant; protects against 6-OHDA toxicity; reduces microglial activation.	Onions, capers, apples (skin), berries.	[39]
Vitamin B12 & Folate	Reduces Homocysteine (neurotoxin elevated in PD/Levodopa use); supports methylation.	B12: Meat, eggs, nutritional yeast. Folate: Leafy greens, lentils.	[40]
Fermented Papaya	Enhances endogenous antioxidant defenses (increases GSH and BAP); reduces oxidative DNA and protein damage (reduces 8-OHdG and 3-nitrotyrosine); may indirectly modulate gut–brain axis via improved redox balance rather than microbiome composition.	Fermented Carica papaya preparation (typically ~9 g/day oral supplement).	[41]

Supplementary Table 1. Detailed study parameters for newly cited bioactive compounds in parkinson's disease models and review.

Compound/ Intervention	Key Study Design & Model	Dosage / Concentration	Administration Route & Duration	Sample Size / Group Size	Main Outcomes / Effect Size	Pathway Relevance	Reference
Curcumin	Systematic review of preclinical and some clinical studies (various toxin-based models, e.g., MPTP, 6-OHDA, rotenone)	Varied across studies; commonly 50–200 mg/kg in animal models; human trials often 500–2000 mg/day (with piperine or nano-formulations)	Oral (gavage in animals); oral capsules in humans	Animal groups typically n = 6–12 per group; human trials n = 20–100+	Neuroprotection via ↓ α-syn aggregation, ↑ PI3K/AKT; motor improvement in many models (e.g., rotarod latency ↑ 30–60%)	Proteostasis, neuroinflammation, oxidative stress, PI3K/AKT survival	[75]

Compound/ Intervention	Key Study Design & Model	Dosage / Concentration	Administration Route & Duration	Sample Size / Group Size	Main Outcomes / Effect Size	Pathway Relevance	Reference
Astaxanthin (lactoferrin-modified liposomes)	MPTP-induced PD mouse model	0.665 mg/kg astaxanthin (liposomal form)	Intravenous	n = 6–8 per group (control, MPTP, MPTP + treatment)	Restored striatal dopamine levels (~80–90% recovery vs. MPTP alone); improved mitochondrial integrity; ↓ NF-κB, ↓ oxidative markers	Mitochondrial bioenergetics, oxidative stress, neuroinflammation	[79]
Oleuropein aglycone	Multiple PD models: in vitro (fibril formation assays), cellular (dopaminergic lines), and in vivo (MPTP or rotenone rodents)	In vitro: 1–50 µM; in vivo: 10–50 mg/kg	Not specified (likely oral/i.p. in vivo)	In vivo groups typically n = 8–12; in vitro replicates n = 3–6	Inhibited α-syn fibril formation (ThT fluorescence ↓ >50% at 10 µM); reduced dopaminergic loss; promoted non-toxic conformers	Proteostasis, α-synuclein aggregation, autophagy	[81]
Probiotics, prebiotics, or synbiotics	Systematic review & meta-analysis of RCTs in PD patients (various strains/formulations)	Varied, e.g., multi-strain probiotics 10^9–10^{10} CFU/day; prebiotics 5–10 g/day	Oral (capsules, sachets, fermented foods)	Trials n = 20–120 participants per arm; meta-analysis pooled n ≈ 300–500 across studies	Improved UPDRS scores (SMD –0.45 to –0.78 in some domains); better non-motor symptoms; gut microbiota shifts	Gut–brain axis, neuroinflammation, microbiota modulation	[83]

Proteostasis-Targeting Nutraceuticals Modulating α-Synuclein Aggregation in Parkinson's Disease: Misfolding and aggregation of α-synuclein into toxic oligomers and fibrils are central pathological features of Parkinson's disease that contribute to dopaminergic neuronal vulnerability and loss [42]. Within a functional foods framework, several diet-associated bioactives have been studied for their ability to support proteostasis by influencing α-synuclein aggregation dynamics, promoting cellular clearance pathways (including autophagy), and reducing upstream oxidative and inflammatory pressure that can worsen protein misfolding [42].

Epigallocatechin gallate (EGCG), a major green tea polyphenol, has been reported to remodel mature α-synuclein fibrils into smaller aggregates with reduced toxicity, while also contributing to redox and inflammatory regulation in experimental systems [43–45]. Curcumin, commonly obtained from turmeric-containing foods, has been shown to interfere with α-synuclein aggregation and to activate pro-survival signaling pathways in PD models, supporting neuronal viability under toxin stress [46–47]. Olive-derived polyphenols such as oleuropein may stabilize monomeric α-synuclein, interfere with fibril formation, and support autophagy-linked clearance of misfolded proteins [48]. Saffron constituents (crocin and safranal) have been evaluated for anti-aggregation effects and dopaminergic protection in toxin-based models. Additional food-derived compounds, including cinnamaldehyde and polyamines such as spermidine, have been explored for their relationship to autophagic and proteostasis pathways, including mTOR-independent mechanisms and aggregate turnover [49–51]. Urolithin A, a gut-derived metabolite formed from ellagitannin-rich foods, has also been studied for mitophagy-related quality control that can indirectly reduce proteotoxic stress under PD-like conditions [52–53]. Together, these food-associated bioactives converge on proteostasis and cellular quality-control networks that are mechanistically relevant to PD [42].

Mitochondrial Dysfunction and Energy Metabolism: Mitochondrial dysfunction in Parkinson's disease includes defects in electron transport (commonly described at Complex I), impaired oxidative phosphorylation, reduced ATP production, and elevated oxidative stress in dopaminergic neurons. Within nutrition-focused strategies, several food-derived mitochondrial cofactors and metabolites have been investigated for their ability to support bioenergetic resilience and mitochondrial quality control. Coenzyme Q10 (ubiquinone), present in certain foods and commonly used as a supplement, functions as an electron carrier transferring electrons from Complexes I and II to Complex III and has been investigated for its potential to support mitochondrial function in PD contexts [36].

Creatine, obtained from dietary sources and supplement forms, contributes to cellular energy buffering via the phosphocreatine system and has been evaluated in experimental PD systems for bioenergetic stabilization [54]. Beyond energy support, increasing attention has been directed toward mitophagy-linked food metabolites such as urolithin A and spermidine, which have been studied for their ability to promote mitochondrial quality control through removal of dysfunctional mitochondria in PD models [53].

Magnesium L-threonate has been shown to effectively elevate cerebrospinal fluid magnesium levels and attenuate motor deficits and dopamine neuron loss in PD mouse models, supporting the role of magnesium in neuroprotection. Collectively, these compounds address distinct but complementary mechanisms of mitochondrial impairment in PD, ranging from electron transport efficiency and energy buffering to the clearance of dysfunctional organelles [24].

Neuroinflammation and Microglial Activation: Chronic neuroinflammation and sustained microglial activation are commonly implicated in dopaminergic neurodegeneration, including signaling patterns associated with NF-κB activation and pro-inflammatory cytokine production (e.g., TNF-α, IL-1β) [55]. In a functional foods framework, anti-inflammatory dietary patterns and bioactive-rich foods are often discussed as modulators of inflammatory tone and oxidative burden, rather than as single-target interventions. Omega-3 polyunsaturated fatty acids (from fatty fish and other dietary sources) have been studied for their role in inflammatory mediator balance and neurotrophic signaling, including effects linked to neuroinflammatory regulation [56]. Carotenoids and flavonoids found in seafoods, fruits, vegetables, and plant foods—including astaxanthin and quercetin—have been evaluated in experimental systems for their relationship to inflammatory signaling pathways, including NF-κB-related mechanisms under oxidative stress conditions [57–58]. Caffeine-containing foods and beverages (coffee, tea, cocoa) have also been investigated in PD models, largely through adenosine A2A receptor–linked pathways with downstream implications for neuroinflammatory activity in the striatum [59]. Overall, these findings support the rationale that dietary bioactives may influence inflammatory signaling in PD-relevant models, while translational interpretation depends on formulation, dosing, and study design.

Oxidative Stress and Antioxidant Defense: Oxidative stress is a central feature of PD pathology, reflecting reactive oxygen species (ROS) accumulation and insufficient endogenous antioxidant capacity. Many food-derived bioactives have been explored for their ability to support antioxidant defenses and redox-responsive signaling pathways in experimental PD systems, including toxin-based models such as 6-OHDA and MPTP [60]. Sulforaphane, associated with cruciferous vegetables (particularly sprouts), has been studied for its activation of the Nrf2/ARE pathway and

downstream induction of antioxidant enzymes (e.g., HO-1 and glutathione-linked systems), supporting dopaminergic protection in PD models [61]. Pigment-rich plant foods containing anthocyanins and lycopene (berries and deeply colored fruits/vegetables; tomato-based foods) have also been evaluated for direct and indirect antioxidant effects, including redox-sensitive signaling modulation under PD-like stress [60-62]. Carnosic acid, associated with culinary herbs such as rosemary and sage, has been described as a pro-electrophilic compound that can activate Nrf2-related antioxidant responses under oxidative conditions, contributing to neuroprotection in experimental contexts [63]. These observations are consistent with a functional foods approach in which habitual intake of bioactive-rich foods may support redox balance, with clinical relevance dependent on long-term dietary feasibility and human outcomes.

Dopaminergic Neuronal Survival and Neurotrophic Support: Neurotrophic signaling contributes to neuronal survival and synaptic maintenance, and reduced neurotrophic support is frequently discussed as a vulnerability factor in neurodegeneration. Nutrition-related compounds have been investigated for their potential relationship to neurotrophic factor expression and pro-survival signaling in PD-relevant models. Vitamin D status has been studied in relation to PD symptom severity and neurotrophic pathways, including regulation of GDNF expression and immunomodulatory signaling [64]. Botanical bioactives such as ginsenosides (from Panax ginseng) have been evaluated in animal models for effects on BDNF-related signaling and downstream resilience pathways [65]. Compounds associated with edible mushrooms—particularly *Hericium erinaceus* (lion's mane)—including hericenones and erinacines, have been studied for NGF-associated mechanisms and neurite-supportive effects in experimental work [32]. These findings support a food-based rationale for targeting neurotrophic resilience as one component of a multi-pathway dietary strategy.

Gut–Brain Axis and Microbiota Modulation: Gut dysbiosis and intestinal inflammation are increasingly discussed in PD pathogenesis, including hypotheses linking gut inflammation, barrier disruption, and α-synuclein-related processes with downstream CNS effects via gut–brain communication pathways [29]. In a functional foods framework, this supports interest in dietary components that influence gut inflammation, microbial metabolism, and microbiota-derived metabolites. 6-Shogaol, enriched in dried or cooked ginger preparations, has been studied in PD-like models for its relationship to intestinal inflammatory signaling, barrier integrity, and downstream α-synuclein-related outcomes across gut and brain tissues [29]. Urolithin A, formed through microbial metabolism of ellagitannin-rich foods (e.g., pomegranate and walnuts), has been evaluated for mitophagy-associated mechanisms and inflammasome-linked inflammatory modulation in microglial and PD model systems [29]. Collectively, these findings support the concept that diet can influence PD-relevant pathways through microbial transformation of food bioactives and longer-term modulation of gut inflammatory tone, although translation remains dependent on human dietary studies and individualized microbiome variability.

Novelty and Emerging Research Trends: Recent work increasingly frames dietary supplements and food-derived bioactives as adjunct strategies that may influence multiple interconnected mechanisms relevant to Parkinson's disease rather than isolated endpoints. Compared with earlier single-compound antioxidant approaches, more recent studies emphasize polyphenols, lipid mediators, and microbiota-derived metabolites that concurrently map to oxidative stress

regulation, neuroinflammation, mitochondrial quality control, and proteostasis-related pathways. This multi-pathway emphasis aligns with PD biology and supports integrative, diet-informed frameworks. A second emerging focus is improving real-world feasibility of nutrition-based interventions. Challenges related to bioavailability, stability, and inter-individual variability have contributed to interest in food-matrix effects, fermentation strategies, and dietary patterns that support sustained intake over time. From a functional foods perspective, these approaches prioritize chronic practicality, dietary source clarity, and safety considerations alongside mechanistic plausibility, which is essential for translation into PD populations.

Bridging Parkinson's Disease to Functional Food Science: Functional food science (FFS), as advanced by the Functional Food Center (FFC), provides a standardized framework for translating nutrition research into functional food products (FFPs) with defined bioactive compounds, measurable biomarkers, and evidence-based claims [66–67-70]. This framework is particularly relevant to Parkinson's disease (PD) because PD is multifactorial and involves interacting mechanisms—oxidative stress, mitochondrial dysfunction, neuroinflammation, impaired proteostasis with α-synuclein pathology, and gut–brain axis disruption—rather than a single target that can be addressed by one intervention [66-70]. As a result, the FFC approach aligns well with multi-pathway, food-first strategies that emphasize dietary sources and functional food groups, while positioning nutraceuticals as supportive adjuncts rather than replacements for pharmacotherapy [67-70].

Functional food definition and biomarker-centered claims in a PD context: A core FFC principle is that a food is "functional" only when its bioactive compound(s) deliver a documented health benefit in defined, effective, and safe amounts, supported by biomarkers and clinical evidence [66–67]. For PD, this matters because many proposed dietary bioactives show strong mechanistic plausibility in experimental systems, but clinical translation varies due to heterogeneity in formulations, dosing, study design, and outcome selection [69–70]. Organizing PD nutrition evidence around the functional food chain—bioactive compound → mechanistic pathway → biomarker change → clinically interpretable outcome—reduces overgeneralization and helps separate mechanistic potential from clinical strength [66-69–70].

Translational pathway: how PD bioactives become functional food products: FFC-affiliated papers describe stepwise methods for developing functional food products, including identifying the goal and the relevant bioactive compound(s), selecting appropriate biomarkers, demonstrating efficacy and safety, and ensuring that claims are regulated and transparent [67-75-79]. In PD, this translational structure is useful because it forces alignment between (1) a PD-relevant mechanism (e.g., redox balance or inflammatory signaling), (2) the biomarker(s) that plausibly represent that mechanism, and (3) an outcome that is meaningful for patients (motor and non-motor domains) [66–67-69]. This approach naturally supports a "food-first" tone because it asks not only whether a compound can act on a pathway, but also whether the intervention can be delivered through a realistic food matrix, consumed chronically, and evaluated with interpretable endpoints [67–68-70].

Dosage and timing: applying "Quantum" and "Tempus" concepts to PD nutrition: FFC authors propose that dosage and time of consumption are central translational variables for functional foods. The "quantum theory"

framing emphasizes determining a critical effective amount of a bioactive compound needed to produce a meaningful biological effect, while also considering safety above that threshold [77]. The "tempus theory" highlights that timing of intake can influence functional outcomes and should be considered during product development and evaluation [78]. These concepts are relevant to PD because many bioactives have variable absorption and metabolism, and PD symptom patterns (sleep, gastrointestinal function, and medication schedules) can influence when intake is practical and potentially impactful [77–78].

Scientific Innovation: The scientific innovation lies in bridging PD's multifactorial biology—oxidative stress, mitochondrial dysfunction, neuroinflammation, proteostasis disruption, and gut–brain axis dysregulation—with Functional Food Science (FFS) methodology, enabling a biomarker-centered, bioactive-driven, stepwise translational pathway. In alignment with the Functional Food Center's 17-step functional food development model, this review links candidate bioactives to the core elements required for translation, including functional goal definition, mechanism-to-biomarker mapping, and the practical requirements for evidence-based product development (standardized composition, feasibility of delivery, and clinically interpretable endpoints). Additionally, applying "Quantum" (dose) and "Tempus" (timing) concepts to PD nutrition introduces a structured framework for identifying defined, effective, and safe intake ranges and for evaluating when and how adjunct nutritional strategies can be realistically implemented (e.g., dosing duration, adherence constraints, and compatibility with PD symptom progression and medication routines) to support functional food product development.

Practical Implications: This work supports a food-first adjunct strategy in PD, positioning nutraceuticals and functional food–derived bioactives as complementary to—not replacements for—pharmacotherapy, while emphasizing feasibility, adherence, safety, and real-world dietary delivery. By organizing the literature according to FFS principles consistent with the 17-step model, the review helps clarify what evidence is sufficient for translation versus what remains preliminary, guiding future PD nutrition trials toward standardized formulations, biomarker-linked endpoints, and clinically meaningful outcomes. This structured approach may also facilitate responsible, regulatory-compliant communication of benefits and accelerate development of functional food products with reproducible composition and defensible claims.

Hypothesis: The figure visually summarizes our hypothesis that dietary supplements and bioactive food compounds function as adjunct strategies in Parkinson's Disease by modulating several interconnected pathogenic pathways. These include reducing oxidative stress, improving mitochondrial function, decreasing neuroinflammation, supporting proteostasis and preventing α-synuclein aggregation, promoting dopaminergic neuron survival, and balancing the gut–brain axis. The diagram shows how specific dietary bioactives map onto these mechanisms, leading to relevant biomarker changes and potentially improved clinical outcomes, all within a practical functional food science framework.

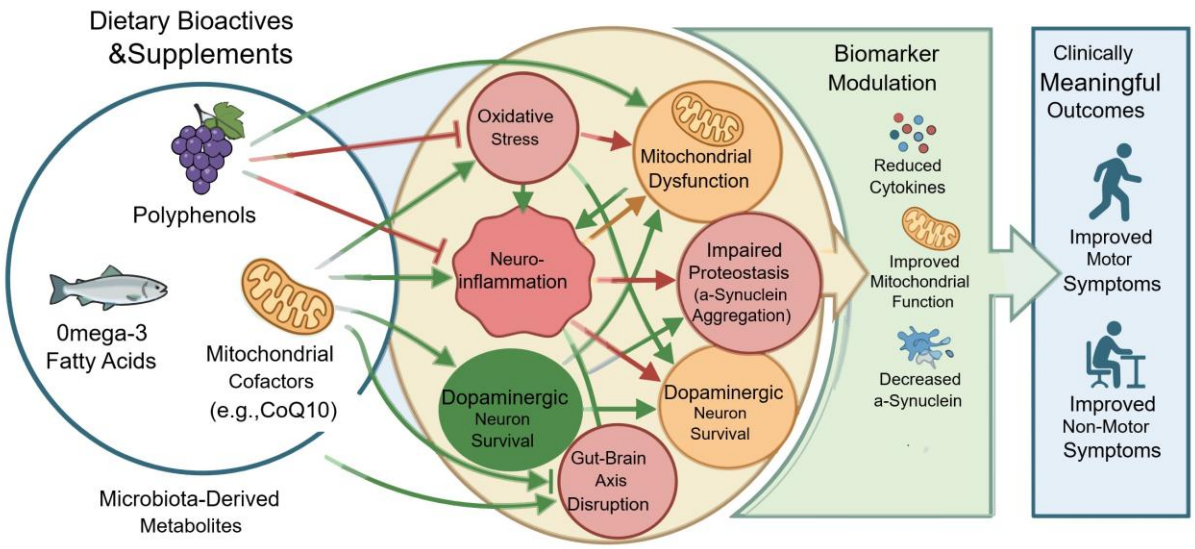


Figure 1. Hypothesis: Dietary supplements and bioactive compounds for managing Parkinson's Disease

CONCLUSION

Current evidence supports a mechanistic rationale for functional foods, dietary supplements, and food-derived bioactive compounds as adjunct strategies in Parkinson's disease (PD), given that PD pathology reflects interacting processes including oxidative stress, mitochondrial impairment, neuroinflammation, disrupted proteostasis/α-synuclein aggregation, and gut–brain axis dysregulation. Across the reviewed literature, the most consistent support remains mechanistic and preclinical: many bioactives modulate PD-relevant endpoints in toxin-based and genetic models, particularly markers related to redox balance, mitochondrial quality control, inflammatory signaling, and aggregate handling. Multi-target compound classes—such as polyphenols, omega-3 fatty acids, mitochondrial cofactors/energy-supporting nutrients, and microbiota-derived metabolites—appear conceptually aligned with PD's multi-pathway biology. However, the human evidence base remains limited and heterogeneous due to differences in formulations, dosing approaches, intervention duration, disease stage, baseline nutritional status, and outcome selection (motor and non-motor domains). These factors reduce cross-study comparability and prevent uniform efficacy claims. From a functional foods standpoint, translation depends on aligning mechanistic plausibility with dietary feasibility, long-term adherence, and clinically interpretable outcomes. Additional constraints include variable absorption and metabolism, uncertain CNS exposure for many compounds, lack of standardized preparations, and meaningful inter-individual variability driven by diet patterns, microbiome composition, and comorbidity burden. Safety and interaction considerations are also central in real-world PD populations, particularly in the context of polypharmacy. Future progress will likely depend less on expanding the list of candidate compounds and more on strengthening translational structure: standardized preparations with verified composition, dietary-relevant dose ranges, biomarker-linked trials that connect pathway targets to patient-relevant outcomes, and stratified designs that account for disease stage, genotype, baseline nutrition, and microbiome-dependent metabolism. Overall, the literature supports a multi-pathway adjunct framework grounded in functional foods and food-derived bioactives, while emphasizing that clinically defensible guidance requires better-standardized interventions and higher-quality long-term human studies. This review advances prior work by integrating PD's multifactorial pathology within the Functional Food Science (FFS)

framework, mapping candidate bioactives to convergent pathways and biomarker domains to better define adjunct therapeutic potential and support practical product development and clinical translation.

Abbreviations: PD, Parkinson's disease; SNpc, substantia nigra pars compacta; BBB, blood–brain barrier; FFGs, functional food groups; ROS, reactive oxygen species; NF-κB, nuclear factor kappa-B; TNF-α, tumor necrosis factor-alpha; IL-1β, interleukin-1 beta; iNOS, inducible nitric oxide synthase; Nrf2, nuclear factor erythroid 2–related factor 2; ARE, antioxidant response element; HO-1, heme oxygenase-1; SIRT1, sirtuin 1; PI3K, phosphoinositide 3-kinase; Akt, protein kinase B; mTOR, mechanistic target of rapamycin; BDNF, brain-derived neurotrophic factor; GDNF, glial cell-derived neurotrophic factor; TrkB, tropomyosin receptor kinase B; NGF, nerve growth factor; MAO-B, monoamine oxidase-B; ATP, adenosine triphosphate; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; A2A, adenosine A2A receptor; α-syn, alpha-synuclein; 6-OHDA, 6-hydroxydopamine; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; NLRP3, NOD-like receptor family pyrin domain-containing 3.

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