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"BERRY-DERIVED POLYPHENOLS IN PARKINSON'S DISEASE: NEUROPROTECTIVE MECHANISMS WITH SPECIAL EMPHASIS ON *VACCINIUM OXYCOCCOS*"

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Abstract: Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by the selective degeneration of dopaminergic neurons in the substantia nigra pars compacta, leading to motor and non-motor dysfunction. Oxidative stress, neuroinflammation, mitochondrial dysfunction, and aberrant protein aggregation involving alpha-synuclein are recognized as central pathophysiological drivers of PD. Berry-derived polyphenols, particularly anthocyanins, proanthocyanidins, quercetin, and phenolic acids, have attracted significant scientific interest for their multi-target neuroprotective potential. Among berry species, *Vaccinium oxycoccos* L. (European small cranberry) is distinguished by its exceptionally rich polyphenolic profile, encompassing cyanidin and peonidin glycosides, A-type and B-type proanthocyanidins, quercetin glycosides, chlorogenic acid, and ursolic acid. Preclinical evidence from rotenone-induced and other experimental PD models demonstrates that Vaccinium-derived bioactives reduce alpha-synuclein accumulation, restore antioxidant enzyme activity, suppress pro-inflammatory cytokines including TNF-alpha and IL-6, modulate the Keap1/Nrf2/ARE and NF-kappaB signalling cascades, and protect dopaminergic neurons from apoptotic cell death. This review comprehensively discusses the phytochemical composition of *V. oxycoccos*, the molecular pathophysiology of PD, and the mechanistic basis of polyphenol-mediated neuroprotection. The potential of *V. oxycoccos* as a source of therapeutic agents, including novel phytosome based delivery systems to enhance bioavailability, is examined. Current limitations, including the absence of species-specific clinical trials, are acknowledged, and future research directions are proposed.

Keywords: ***Vaccinium oxycoccos*; Parkinson's disease; Neuroprotection; Anthocyanins; Polyphenols; Oxidative stress; Neuroinflammation; Phytosomes**

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1. INTRODUCTION

Parkinson's disease (PD) is the second most prevalent neurodegenerative disorder globally, affecting more than ten million individuals and representing a mounting burden on healthcare systems worldwide [1,2]. Clinically, PD manifests as bradykinesia, resting tremor, muscular rigidity, and postural instability, collectively arising from the progressive and selective degeneration of dopaminergic neurons within the substantia nigra pars compacta (SNpc) and subsequent depletion of striatal dopamine [3]. Beyond these cardinal motor features, non-motor manifestations including cognitive impairment, autonomic dysfunction, sleep disturbances, and depression substantially diminish quality of life [4]. The pathological hallmarks of PD include the intraneuronal accumulation of Lewy bodies and Lewy neurites, which are predominantly composed of misfolded alpha-synuclein aggregates, alongside widespread mitochondrial dysfunction, neuroinflammatory activation, and oxidative damage [5].

Despite extensive research, disease-modifying pharmacotherapy for PD remains elusive. Current standard-of-care agents, principally levodopa-carbidopa, dopamine agonists, and monoamine oxidase-B inhibitors, provide symptomatic relief but do not arrest the underlying neurodegenerative process [6]. Long-term levodopa therapy is further complicated by motor fluctuations and dyskinesias, creating an urgent clinical need for neuroprotective strategies targeting the primary mechanisms of dopaminergic cell death [7].

In this context, polyphenolic phytochemicals derived from dietary berries have emerged as promising candidates for neuroprotection. Anthocyanins, proanthocyanidins, flavonols, and phenolic acids, abundant in Vaccinium species, modulate oxidative stress, neuroinflammatory signalling, mitochondrial function, and protein aggregation through pleiotropic molecular mechanisms [8,9]. *Vaccinium oxycoccos* L., the European small cranberry, is among the most phytochemically diverse Vaccinium species, accumulating exceptionally high concentrations of cyanidin and peonidin glycosides, A-type proanthocyanidins, quercetin glycosides, chlorogenic acid, and triterpenoids such as ursolic acid [10,11]. While substantial literature exists on the neuroprotective properties of V. macrocarpon (American cranberry) and other Vaccinium species, *V. oxycoccos* remains comparatively understudied, despite its superior or comparable phytochemical richness [12].

This review systematically consolidates current knowledge on the phytochemical composition of *V. oxycoccos*, the molecular pathophysiology of PD, and the mechanistic basis through which berry-derived polyphenols, with particular emphasis on bioactives

characteristic of *V. oxycoccos*, exert neuroprotective effects. Emerging therapeutic strategies including phytosome formulations to overcome bioavailability limitations are also discussed, alongside critical appraisal of existing evidence and future research directions.

2. LITERATURE SEARCH METHODOLOGY

The present review was prepared through a comprehensive literature search conducted using electronic databases including PubMed, Scopus, Web of Science, Google Scholar, and ScienceDirect. Relevant studies published between 2000 and 2025 were identified using combinations of the keywords "Parkinson's disease", "*Vaccinium oxycoccos*", "cranberry", "polyphenols", "anthocyanins", "proanthocyanidins", "quercetin", "chlorogenic acid", "neuroprotection", "oxidative stress", "neuroinflammation", "mitochondrial dysfunction", "alpha-synuclein", "Nrf2", "NF-κB", and "phytosomes".

Peer-reviewed original research articles, review articles, experimental studies, and clinical investigations published in English were considered for inclusion. Studies focusing on the phytochemical composition of Vaccinium species, molecular mechanisms involved in Parkinson's disease pathogenesis, and the neuroprotective effects of berry-derived polyphenols were prioritized. Duplicate records, conference abstracts without full-text availability, and studies lacking relevance to the review objectives were excluded.

The selected literature was critically evaluated and organized into thematic sections covering the phytochemistry of *Vaccinium oxycoccos*, Parkinson's disease pathophysiology, molecular mechanisms of neuroprotection, preclinical and clinical evidence, bioavailability challenges, and future therapeutic perspectives.

BOTANICAL AND PHYTOCHEMICAL PROFILE OF VACCINIUM OXYCOCCOS L.

2.1 BOTANICAL CHARACTERISTICS

Vaccinium oxycoccos L., commonly designated the European small cranberry, is a low-growing evergreen subshrub belonging to the family Ericaceae. The species is circumboreal in distribution, inhabiting oligotrophic peatlands, bogs, and wetland habitats across northern Europe, northern Asia, Greenland, Canada, Alaska, and the northeastern United States [13,14]. Morphologically, the plant features slender reddish-brown creeping stems reaching up to 1 m in length, small alternate ovate leaves measuring 3–10 mm in length with characteristic enrolled margins and glaucous undersides, and solitary pink reflexed flowers borne on slender red peduncles [15]. Fruit ripening occurs between September and October, producing globose red berries of 6–12 mm diameter with intense anthocyanin pigmentation. The species thrives in acidic soils with pH 3.5–5.5, reflecting adaptation to nutrient-poor environments, and exhibits considerable morphological and phytochemical variability across geographic populations [16].

2.2 POLYPHENOLIC COMPOSITION

The fruits of *V. oxycoccos* accumulate one of the richest polyphenolic profiles among Vaccinium species, with total polyphenol content varying markedly between geographic populations and ripening stages [10,17]. Anthocyanins constitute the predominant polyphenolic class, with concentrations ranging from 698 to 8352 µg per gram fresh weight. The dominant anthocyanins are cyanidin-3-galactoside, cyanidin-3-arabinoside, peonidin-3-galactoside, and peonidin-3-arabinoside, with minor contributions from cyanidin-3-glucoside and peonidin-3-glucoside [10]. These pigments are responsible for the characteristic deep red coloration of the fruit and exhibit potent free radical-scavenging activity attributable to their hydroxylated B-ring structures and extended conjugated systems [18].

Proanthocyanidins (PACs) are present at concentrations of 919–3038 µg epicatechin equivalents per gram and comprise both A-type and B-type oligomeric dimers and trimers of catechin and epicatechin [10]. The A-type PACs are particularly distinctive in Vaccinium fruits and confer notable anti-adhesive, antioxidant, and neuroprotective properties. Flavonols are detected at 518–2811 µg per gram, with quercetin-3-galactoside (hyperoside) and myricetin-3-galactoside as dominant forms, alongside quercetin-3-arabinoside, quercetin-3-rhamnoside, kaempferol derivatives, and isorhamnetin [17,19]. Quercetin and its glycosides are particularly relevant to neuroprotection, given their established capacity to cross the blood-brain barrier and modulate neuroinflammatory and apoptotic signalling pathways [20].

Phenolic acids contribute approximately 389 mg per 100 g fresh weight and include chlorogenic acid (17–1224 µg/g), benzoic acid (99.6–214.6 mg/100 g), p-coumaric acid, caffeic acid, ferulic acid, and gallic acid [10]. Chlorogenic acid is of particular interest for neurodegeneration research given its capacity to inhibit monoamine oxidase-B and modulate dopamine metabolism [21]. Triterpenoids, principally ursolic acid (76%) and oleanolic acid (17%), occur at 4060–6542 µg/g and exhibit anti-inflammatory, neuroprotective, and mitochondria-stabilizing effects relevant to PD pathology [22]. The organic acid fraction, comprising citric, malic, quinic, and ascorbic acids, contributes antioxidant capacity and may enhance polyphenol bioavailability through pH modulation [10].

Table 1: Major phytochemical classes of Vaccinium oxycoccos L. and their neuroprotective relevance

Phytochemical Class	Key Compounds	Concentration (FW basis)	Neuroprotective Relevance
Anthocyanins	Cyanidin-3-galactoside, Peonidin-3-arabinoside, Cyanidin-3-arabinoside	698–8352 µg/g	BBB penetration, ROS scavenging, anti-apoptotic signalling, alpha-synuclein inhibition
Proanthocyanidins (PACs)	A-type and B-type dimers/trimers of catechin and epicatechin	919–3038 µg ECE/g	Anti-neuroinflammatory, mitochondrial protection, NF-κB inhibition
Flavonols	Quercetin-3-galactoside, Myricetin-3-galactoside, Quercetin-3-arabinoside	518–2811 µg/g	MAO-B inhibition, Nrf2 activation, anti-inflammatory, BDNF upregulation
Phenolic acids	Chlorogenic acid, Benzoic acid, Caffeic acid, Ferulic acid	~389 mg/100 g	MAO-B inhibition, dopamine metabolism modulation, antioxidant
Triterpenoids	Ursolic acid (76%), Oleanolic acid (17%)	4060–6542 µg/g	NF-κB/NLRP3 suppression, mitochondrial stabilisation, anti-apoptotic
Organic acids	Citric acid, Ascorbic acid, Quinic acid, Malic acid	10–25% dry matter	Antioxidant defence, polyphenol bioavailability enhancement

BBB: blood-brain barrier; ROS: reactive oxygen species; ECE: epicatechin equivalents; MAO-B: monoamine oxidase-B; FW: fresh weight.

3. PATHOPHYSIOLOGY OF PARKINSON'S DISEASE: MOLECULAR TARGETS FOR POLYPHENOLIC INTERVENTION

3.1 Oxidative Stress and Dopaminergic Vulnerability

The substantia nigra pars compacta is intrinsically vulnerable to oxidative damage due to several converging factors: high basal rates of dopamine oxidative metabolism generating reactive oxygen species (ROS), relatively low endogenous antioxidant enzyme expression including superoxide dismutase and glutathione peroxidase, elevated iron content catalysing Fenton-type hydroxyl radical generation, and high mitochondrial density with attendant electron transport chain-derived superoxide production [23,24]. In PD, this oxidative burden is substantially amplified. Post-mortem nigral tissue from PD patients demonstrates markedly elevated markers of oxidative damage including 4-hydroxynonenal, 8-hydroxy-2-deoxyguanosine, and protein carbonyls, alongside profound depletion of reduced glutathione [25].

Dopamine metabolism itself constitutes a pro-oxidant process. Monoamine oxidase-B (MAO-B)-catalysed dopamine catabolism generates hydrogen peroxide as a byproduct, which, in the presence of iron, undergoes Fenton reactions to produce the highly reactive hydroxyl radical. Additionally, spontaneous dopamine auto-oxidation produces dopamine quinones that covalently modify proteins and contribute to alpha-synuclein oligomerization [26]. The Keap1/Nrf2/ARE (nuclear factor erythroid 2-related factor 2 / antioxidant response element) pathway represents a master regulator of antioxidant and cytoprotective gene expression, including NAD(P)H quinone oxidoreductase-1, heme oxygenase-1, and glutamate-cysteine ligase. Dysregulation of Nrf2 activity is documented in PD, representing a critical pharmacological target [27].

3.2 Neuroinflammation and Microglial Activation

Sustained microglial activation and astrogliosis are cardinal features of PD pathology, contributing to dopaminergic neurodegeneration through release of pro-inflammatory cytokines, nitric oxide, and additional reactive oxygen and nitrogen species [28]. Activated microglia in the PD substantia nigra overexpress inducible nitric oxide synthase, cyclooxygenase-2, and NADPH oxidase, amplifying oxidative and inflammatory tissue damage in a self-perpetuating cycle [29]. Nuclear factor-kappa B (NF-κB) is the central transcriptional regulator of microglial inflammatory gene expression, coordinating the production of TNF-alpha, IL-1beta, IL-6, and chemokines that propagate neuroinflammatory signalling [30].

The NLRP3 inflammasome pathway represents an additional inflammatory amplification mechanism of relevance to PD. Alpha-synuclein aggregates serve as danger-associated molecular patterns that activate NLRP3 in microglia, triggering caspase-1-dependent maturation and secretion of IL-1beta and IL-18, further promoting neuroinflammation and pyroptotic cell death [31].

Toll-like receptor 4 (TLR4) also mediates microglial sensing of alpha-synuclein oligomers and activates downstream NF-κB and MAPK signalling cascades [32].

3.3 Mitochondrial Dysfunction

Mitochondrial dysfunction occupies a central position in PD pathogenesis, evidenced by Complex I deficiency in nigral neurons, impaired mitophagy, altered mitochondrial dynamics, and disruption of the electron transport chain resulting in enhanced superoxide generation [33]. The pesticide rotenone and neurotoxin MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), both established experimental models of PD, exert their dopaminergic toxicity through selective Complex I inhibition [34]. Mitochondrial dysfunction triggers cytochrome c release, activating the intrinsic apoptotic cascade via caspase-9 and caspase-3 activation, ultimately mediating dopaminergic cell death [35]. Therapeutic strategies targeting mitochondrial biogenesis through PGC-1alpha activation or stabilization of mitochondrial membrane potential represent important neuroprotective approaches [36].

3.4 Alpha-Synuclein Aggregation and Proteostasis

The misfolding and aggregation of alpha-synuclein from native monomers through soluble oligomers to insoluble fibrillar Lewy body inclusions constitutes the defining proteinopathy of PD [37]. Soluble alpha-synuclein oligomers are recognized as the primary neurotoxic species, disrupting membrane integrity, impairing synaptic vesicle trafficking, inducing mitochondrial dysfunction, and perpetuating neuroinflammation [38]. Oxidative post-translational modifications including nitration, phosphorylation at Ser129, and dopamine-induced quinone adduct formation accelerate alpha-synuclein misfolding and aggregation in the nigral microenvironment [39]. Therapeutic strategies directed at preventing alpha-synuclein aggregation, enhancing autophagic and proteasomal clearance, and reducing the intracellular oxidative milieu that promotes misfolding are under active investigation [40].

Del Rio D, Rodriguez-Mateos A, Spencer JPE, Tognolini M, Borges G, Crozier A. Dietary (Poly)phenolics in Human Health: Structures, Bioavailability, and Evidence of Protective Effects Against Chronic Diseases. Antioxid Redox Signal. 2013;18(14):1818–1892. doi:10.1089/ars.2012.4581.

4. BERRY-DERIVED POLYPHENOLS AND NEUROPROTECTION: MECHANISTIC OVERVIEW

4.1 Blood-Brain Barrier Penetration

A prerequisite for direct neuroprotective activity is the capacity of polyphenols to cross the blood-brain barrier (BBB). Anthocyanins, particularly cyanidin and delphinidin glycosides, have been detected in brain tissue following oral administration in rodent models, confirming BBB penetration [41]. The lipophilicity imparted by methylation and the compact molecular size of certain aglycones facilitate passive transcellular transport, while active transport mechanisms involving organic anion-transporting polypeptides have also been implicated [42]. Quercetin and its metabolites, including isorhamnetin and tamarixetin, similarly penetrate the BBB and accumulate in hippocampal, striatal, and cortical regions at pharmacologically relevant concentrations following dietary supplementation [43]. Ferulic acid and caffeic acid, phenolic acid constituents are well-established BBB-permeable compounds that exert direct antioxidant and neuroprotective effects within the central nervous system [44].

4.2 Antioxidant and Nrf2 Pathway Activation

Polyphenols activate the Keap1/Nrf2/ARE pathway through direct modification of reactive cysteine residues on the Keap1 sensor protein, releasing Nrf2 for nuclear translocation and transcriptional activation of antioxidant and cytoprotective genes [45]. In experimental PD models, anthocyanin-rich berry extracts significantly elevate nigral and striatal activities of superoxide dismutase, catalase, glutathione peroxidase, and glutathione reductase, while restoring depleted reduced glutathione levels [46]. Quercetin has been demonstrated to activate Nrf2 in dopaminergic SH-SY5Y cells and primary midbrain cultures, inducing heme oxygenase-1 and NAD(P)H quinone oxidoreductase-1 expression and conferring protection against 6-hydroxydopamine (6-OHDA)-induced cytotoxicity [47]. Chlorogenic acid, a major phenolic acid in *V. oxycoccos*, may activates Nrf2/HO-1 signalling in neuronal cells subjected to oxidative insult and attenuates rotenone-induced Complex I inhibition in mitochondrial preparations [48].

4.3 Inhibition of NF-κB Neuroinflammatory Signalling

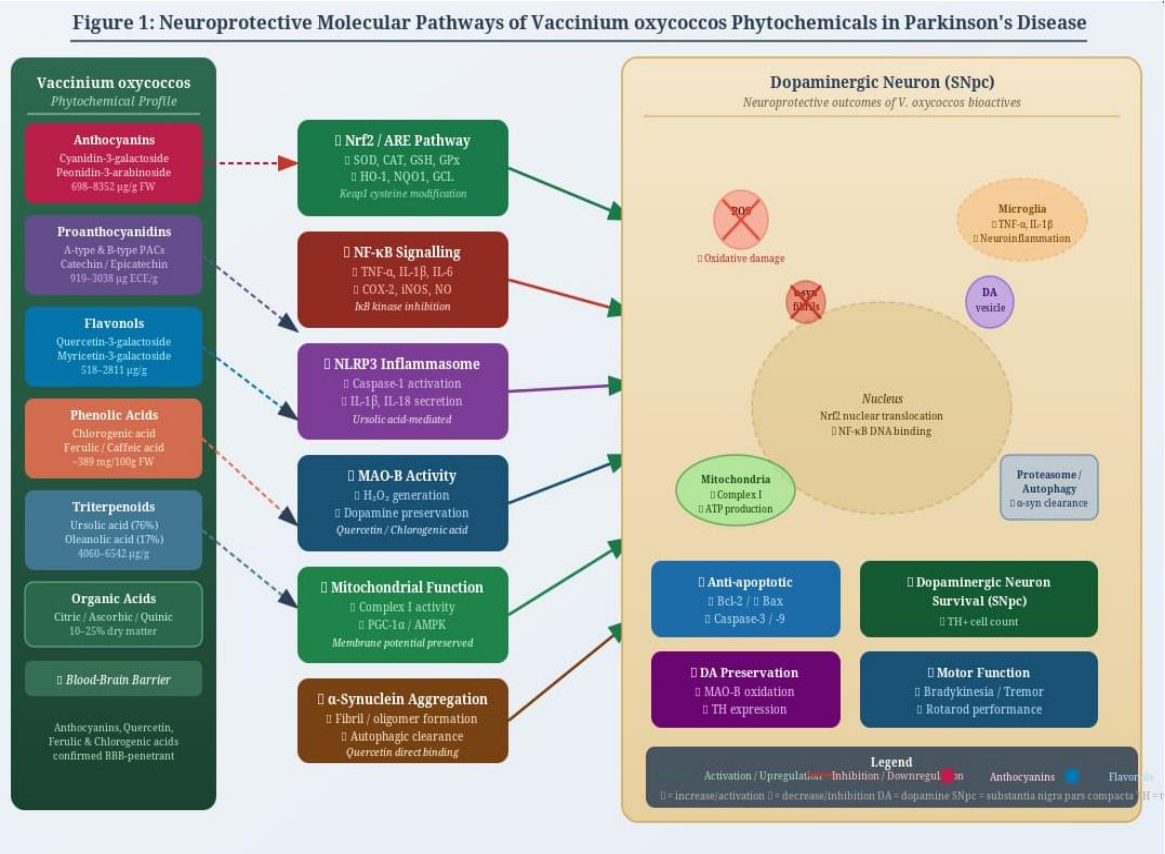
Polyphenolic compounds suppress microglial NF-κB activation through multiple converging mechanisms, including inhibition of IκB kinase complex activity, prevention of IκB-alpha phosphorylation and proteasomal degradation, direct interference with NF-κB DNA binding, and upstream suppression of TLR4 and NLRP3 signalling [49,50]. In lipopolysaccharide-stimulated BV-2 microglial cells, anthocyanin-rich fractions significantly reduce production of TNF-alpha, IL-1beta, IL-6, nitric oxide, and prostaglandin E2, recapitulating the anti-inflammatory profile of pharmacological NF-κB inhibitors [51]. Quercetin specifically suppresses COX-2 mRNA expression and TNF-alpha-mediated NF-κB activation, attenuating neuroinflammation in both in vitro and in vivo PD models [52]. Ursolic acid has demonstrated inhibitory effects on NLRP3 inflammasome activation and IL-1β secretion in inflammatory models, suggesting potential relevance in neuroinflammatory pathways associated with Parkinson's disease[53].

4.4 Modulation of Alpha-Synuclein Aggregation

Berry-derived polyphenols interfere with alpha-synuclein aggregation at multiple stages. Epicatechin and its gallate esters remodel toxic alpha-synuclein oligomers into non-toxic off-pathway aggregates and reduce their membrane-disrupting activity [54]. Quercetin directly binds alpha-synuclein monomers through hydrophobic and hydrogen-bonding interactions, stabilizing the native unfolded conformation and inhibiting beta-sheet-rich fibril formation [55]. Anthocyanins including cyanidin-3-glucoside have been shown to reduce total alpha-synuclein protein levels in rotenone-treated rat brain, consistent with enhanced autophagic clearance or reduced expression [43]. Furthermore, polyphenol-mediated reduction of oxidative stress decreases dopamine quinone formation, thereby limiting covalent modification of alpha-synuclein that accelerates its pathological misfolding [56].

4.5 Mitochondrial Protection and Anti-Apoptotic Effects

Polyphenols exert direct mitochondria-stabilizing effects relevant to dopaminergic neuron survival. Quercetin preserves mitochondrial membrane potential, prevents cytochrome c release, and inhibits caspase-3 and caspase-9 activation in rotenone- and 6-OHDA-treated neuronal cells [57]. Anthocyanins regulate the Bcl-2 family apoptotic pathway, upregulating anti-apoptotic Bcl-2 and Bcl-xL while suppressing pro-apoptotic Bax expression [58]. AMPK (AMP-activated protein kinase) activation by polyphenols induces PGC-1alpha-mediated mitochondrial biogenesis and upregulates mitophagy through the AMPK/ULK1/PINK1/Parkin pathway, restoring mitochondrial quality control in dopaminergic neurons [59]. Ferulic acid protects against MPTP induced mitochondrial dysfunction in mice, normalizing Complex I activity and reducing striatal dopamine depletion [60].



4.6 MAO-B Inhibition and Dopamine Preservation

Monoamine oxidase-B (MAO-B) catalyses the oxidative deamination of dopamine, generating hydrogen peroxide and contributing to oxidative nigral damage. Pharmacological MAO-B inhibition constitutes an established therapeutic strategy in PD, forming the basis of selegiline and rasagiline therapy [61]. Several polyphenolic constituents exhibit MAO-B inhibitory activity. Quercetin and its glycosides competitively inhibit MAO-B with IC50 values in the low micromolar range, comparable to rasagiline in certain in vitro assays [62]. Chlorogenic acid inhibits MAO-B through reversible binding at the active site and attenuates dopamine metabolism-driven oxidative stress in neuronal preparations [63]. This dual activity antioxidant capacity combined with MAO-B inhibition represents a particularly relevant mechanistic profile for potential PD-modifying effects.

Table 2: Summary of neuroprotective mechanisms of key Vaccinium oxycoccos phytochemicals in Parkinson's disease-relevant models

Compound	Mechanism	Model/Evidence	Key Reference
Anthocyanins (cyanidin, peonidin glycosides)	Nrf2 activation; ROS scavenging; Bax/Bcl-2 modulation; alpha-synuclein reduction	Rotenone rat model; 6-OHDA cell model	[43,46,58]
Quercetin glycosides	MAO-B inhibition; NF-κB suppression; Nrf2/HO-1 induction; caspase inhibition; alpha-synuclein aggregation inhibition	SH-SY5Y cells; MPTP mouse; 6-OHDA rat	[47,52,55,57,62]
Proanthocyanidins (A-type)	NF-κB/NLRP3 inhibition; microglial activation suppression; mitochondrial stabilisation	LPS microglia; rotenone model	[49,50,51]
Chlorogenic acid	MAO-B inhibition; Nrf2/HO-1 activation; Complex I protection; dopamine metabolism modulation	Rotenone mitochondrial prep; neuronal cells	[21,48,63]
Ursolic acid	NLRP3 inflammasome inhibition; NF-κB suppression; anti-apoptotic; mitochondrial protection	LPS macrophage/microglia; in vivo neuroinflammation	[22,53]
Ferulic acid	MAO-B inhibition; Complex I activity restoration; antioxidant; anti-apoptotic	MPTP mouse model	[44,60]

MAO-B: monoamine oxidase-B; ROS: reactive oxygen species; HO-1: heme oxygenase-1; NLRP3: NOD-like receptor protein 3; LPS: lipopolysaccharide.

5. PRECLINICAL EVIDENCE FOR VACCINIUM SPECIES IN PARKINSON'S DISEASE MODELS

5.1 Rotenone-Induced Models

The most direct preclinical evidence linking Vaccinium-derived polyphenols to PD neuroprotection derives from rotenone-induced experimental models. In a rat model of rotenone-induced PD, cranberry juice treatment significantly attenuated the progressive motor deficits, reduced alpha-synuclein protein accumulation in the substantia nigra, decreased pro-apoptotic Bax and cleaved caspase-9 expression, normalized cytochrome c release, and improved striatal dopamine levels [64]. These findings provide direct evidence that Vaccinium bioactives protect dopaminergic neurons against Complex I inhibitor-induced neurodegeneration, acting at multiple convergent apoptotic and proteinopathy targets simultaneously.

Mechanistically, the neuroprotective effect of cranberry juice in the rotenone model was accompanied by restoration of antioxidant enzyme activities including superoxide dismutase and catalase in striatal tissue, consistent with Nrf2 pathway activation [64]. The preservation of motor function, assessed by rotarod performance and open-field activity, correlated with the degree of dopaminergic neuron survival, confirming functional relevance of the biochemical protection [64]. These data support the proposition that *V. oxycoccos*, given its superior or equivalent content of the relevant bioactive compounds, would demonstrate comparable neuroprotective efficacy in such models.

5.2 6-Hydroxydopamine Models

The 6-hydroxydopamine (6-OHDA) model, in which the neurotoxin selectively ablates dopaminergic neurons through oxidative damage and apoptotic mechanisms, has been widely employed to assess berry polyphenol neuroprotection. Quercetin supplementation prior to 6-OHDA injection in rats significantly attenuated striatal dopamine depletion, reduced nigral oxidative stress markers, and improved rotational behaviour [65]. Anthocyanin-rich extracts from blueberry *(V. corymbosum)* and other Vaccinium species reduce 6-OHDA-induced apoptosis in SH-SY5Y dopaminergic cells through Bcl-2 upregulation, caspase-3 suppression, and mitochondrial membrane potential preservation [66]. Given the shared anthocyanin profile between *V. corymbosum* and *V. oxycoccos*, extrapolation of these findings is scientifically justified and consistent with structure-activity relationships.

5.3 MPTP Models

In the MPTP mouse model of PD, which selectively destroys dopaminergic neurons through mitochondrial Complex I inhibition following MAO-B catalysed conversion to the active toxin MPP+, several berry-derived polyphenols have demonstrated

neuroprotective efficacy. Oral ferulic acid supplementation in MPTP-treated mice restored striatal dopamine and its metabolites, normalized tyrosine hydroxylase immunoreactivity in the substantia nigra, and improved motor performance[60]. Chlorogenic acid has been reported to modulate dopaminergic neurotransmission and exert antioxidant neuroprotective effects in experimental Parkinsonian models[63]. The relevance of these findings to *V. oxycoccos* is substantial given the high chlorogenic acid and ferulic acid contents of the fruit.

5.4 Quinolinic Acid-Induced Cognitive Impairment Model

In a quinolinic acid-induced model of cognitive impairment involving oxidative and excitotoxic striatal damage, cranberry supplementation significantly improved spatial memory and motor performance, restored glutathione levels, reduced lipid peroxidation products, enhanced mitochondrial respiratory chain function, and attenuated neuroinflammation in hippocampal and striatal regions [67]. These findings suggest that cranberry bioactives protect against multiple mechanisms of striatal and basal ganglia neurodegeneration beyond purely dopaminergic pathways, potentially conferring broader neuroprotective efficacy relevant to the full spectrum of PD-related pathology.

5.5 In Vitro Evidence in Dopaminergic Cell Models

Extensive in vitro evidence in human SH-SY5Y neuroblastoma cells and primary dopaminergic neuron cultures supports the mechanistic framework described above. Cyanidin-3-glucoside and peonidin-3-glucoside, anthocyanins present in *V. oxycoccos*, protect SH-SY5Y cells against hydrogen peroxide and rotenone-induced cytotoxicity at concentrations achievable through dietary intake [68]. Quercetin at nanomolar to low micromolar concentrations activates the Nrf2/HO-1 axis, suppresses NF-κB-dependent inflammatory gene expression, inhibits alpha-synuclein fibril formation, and reduces caspase-3-mediated apoptosis in dopaminergic cell models [47,57]. PAC fractions from cranberry suppress LPS-activated microglial release of TNF-alpha, IL-6, and nitric oxide, attenuating the pro-inflammatory microenvironment contributing to bystander dopaminergic neurodegeneration [51].

6. CLINICAL EVIDENCE FOR BERRY POLYPHENOLS IN NEURODEGENERATION

Direct clinical evidence specifically relating *V. oxycoccos* to PD neuroprotection is currently absent, reflecting the early stage of translation from preclinical findings. However, relevant clinical data from broader Vaccinium species and polyphenol interventions provide an important evidentiary framework. In a well-designed 12-week randomized placebo-controlled trial in healthy older adults, daily consumption of freeze-dried cranberry powder equivalent to approximately one cup of fresh cranberries significantly improved visual episodic memory performance and increased regional cerebral blood flow in memory-associated cortical regions as assessed by functional magnetic resonance imaging [69]. These cognitive benefits were attributed to anthocyanin-mediated enhancement of cerebral perfusion and endothelial nitric oxide synthesis.

Blueberry *(V. corymbosum and V. angustifolium)* supplementation trials in older adults with mild cognitive impairment and early dementia have demonstrated improvements in memory, executive function, and psychomotor speed over periods of 12–16 weeks [70]. Meta-analyses of berry supplementation trials report consistent improvements in cognitive performance domains associated with prefrontal and hippocampal function, supporting the translational relevance of preclinical neuroprotection data [71]. Anthocyanin bioavailability studies confirm that oral consumption of berry products results in detectable plasma and urinary anthocyanin metabolites, including protocatechuic acid and phloroglucinol aldehyde, at concentrations associated with cellular antioxidant and anti-inflammatory activity [72].

While not specific to *V. oxycoccos*, this trial provides direct clinical support for the anti-neuroinflammatory activity of a major phytochemical constituent of the plant in PD patients. The absence of species-specific *V. oxycoccos* clinical trials represents a significant gap in the evidence base and constitutes a priority area for future research.

7. SPECIAL EMPHASIS ON *VACCINIUM OXYCOCCOS*: COMPARATIVE ADVANTAGES AND UNIQUE FEATURES

7.1 Phytochemical Superiority and Unique Profile

V. oxycoccos demonstrates several phytochemical characteristics that may confer advantages over more studied Vaccinium species for neuroprotective applications. Comparative metabolomic analyses have identified unique metabolites in *V. oxycoccos* not present in V. macrocarpon, alongside higher relative concentrations of certain anthocyanin species and triterpenoids [12,73]. The high ursolic acid content of *V. oxycoccos* (76% of the triterpenoid fraction) is particularly noteworthy given the compound's documented NLRP3 inflammasome-inhibiting and NF-κB-suppressing activities, mechanisms increasingly recognized as central to PD neuroinflammation [22,53]. The A-type proanthocyanidin profile of *V. oxycoccos*, while primarily studied in the context of anti-adhesion activity, confers antioxidant and anti-neuroinflammatory properties through mechanisms distinct from B-type PACs [10,74].

Table: 3 Comparison with Other *Vaccinium* Species in Neuroprotection Context

Parameter	*V. oxycoccos*	*V. macrocarpon*	*V. corymbosum*
Anthocyanin content	698–8352 µg/g FW	Up to 4000 µg/g FW	Up to 4600 µg/g FW
Dominant anthocyanins	Cyanidin and peonidin glycosides	Cyanidin, peonidin glycosides	Delphinidin, malvidin, cyanidin glycosides
Ursolic acid	High (4060–6542 µg/g)	Moderate	Low to absent
A-type PACs	Significant	High (major source)	B-type predominant

Clinical PD evidence	Absent (direct)	Rotenone model (indirect)	MPTP model; MCI trials
Unique metabolites	Yes (metabolomics confirmed)	No	No
BBB-penetrant compounds	Anthocyanins, quercetin, ferulic acid, chlorogenic acid	Anthocyanins, PACs	Anthocyanins, pterostilbene

FW: fresh weight; PACs: proanthocyanidins; BBB: blood-brain barrier; MCI: mild cognitive impairment.

8. EMERGING THERAPEUTIC STRATEGIES: PHYTOSOMES AND ADVANCED DELIVERY SYSTEMS

8.1 Bioavailability Challenges of Berry Polyphenols

A critical limitation of polyphenol-based neuroprotection strategies is the inherently poor systemic bioavailability of most phytochemicals following oral administration. Anthocyanins exhibit rapid gastrointestinal degradation at physiological pH, extensive presystemic metabolism by intestinal microbiota, and limited mucosal permeability, resulting in plasma concentrations substantially lower than those required for pharmacological effects observed in isolated cell systems [75]. Quercetin glycosides require hydrolysis to the aglycone before absorption and undergo extensive phase II metabolic conjugation, producing sulphate and glucuronide conjugates with modified biological activity compared with the parent compound [76]. These pharmacokinetic constraints have prompted development of advanced delivery systems designed to protect polyphenols from premature degradation and enhance their absorption and tissue distribution.

8.2 Phytosome Technology

Phytosomes are a class of phospholipid-polyphenol complexes in which plant bioactives form stoichiometric molecular complexes with phosphatidylcholine through hydrogen bonding interactions between the polar head group and polyphenolic hydroxyl moieties [77]. This complexation confers amphiphilic character on otherwise predominantly hydrophilic polyphenols, substantially enhancing their membrane permeability, gastrointestinal stability, and oral bioavailability. Phytosome formulations of quercetin, silymarin, and curcumin have demonstrated bioavailability enhancements of 1.5 to 4.5-fold compared with unformulated phytochemicals in human pharmacokinetic studies [78].

The phytosome matrix physically protects anthocyanins and PACs from acidic gastric degradation, facilitates lymphatic absorption of lipophilic complexes bypassing first-pass hepatic metabolism, and promotes extended plasma residence times. Preparation typically involves co-dissolution of the extract and soy lecithin in a chloroform:ethanol solvent system followed by rotary evaporation to form a thin film, vacuum drying to eliminate residual solvent, and hydration to produce vesicular phytosome structures [79]. Characterization parameters include vesicle size, zeta potential, entrapment efficiency, and in vitro release kinetics, which collectively determine the pharmacokinetic performance of the formulation [80].

8.3 Relevance to Central Nervous System Delivery

For neuroprotective applications in PD, enhancement of CNS delivery represents the key objective of phytosome formulation. Phosphatidylcholine-based vesicles are inherently compatible with biological membranes, facilitating receptor-mediated and adsorptive endocytosis at the BBB [81]. Furthermore, the surface modification of phytosomes with brain-targeting ligands including transferrin, lactoferrin, or rabies virus glycopeptide represents an active area of research for targeted CNS polyphenol delivery [82]. In vivo studies have confirmed that phytosome encapsulated polyphenols achieve higher brain tissue concentrations than equivalent doses of unformulated extracts, supporting the rationale for this approach in PD treatment strategies [83].

Nanoparticle-based delivery systems including poly(lactic-co-glycolic acid) nanoparticles, solid lipid nanoparticles, and self-nanoemulsifying drug delivery systems represent additional strategies under investigation for *V. oxycoccos* bioactive delivery to the brain. These platforms offer programmable release kinetics, surface functionalization options for active targeting, and compatibility with the lipophilic environment of the BBB endothelium [84]. In addition to improving the stability and bioavailability of polyphenols, phosphatidylcholine may provide complementary antioxidant and membrane-protective effects, potentially enhancing the overall neuroprotective potential of phytosome formulations[85].

9. LIMITATIONS OF CURRENT EVIDENCE AND FUTURE RESEARCH DIRECTIONS

9.1 Current Limitations

The evidence base for *V. oxycoccos* specifically in PD neuroprotection carries important limitations that must be transparently acknowledged. First, no direct clinical trials examining *V. oxycoccos* preparations in PD patients currently exist, and extrapolation from studies employing related Vaccinium species or isolated polyphenols, while scientifically informed by chemical similarity, requires validation with the intact phytochemical matrix of *V. oxycoccos*. Second, the pharmacokinetics of individual *V. oxycoccos* polyphenols following oral administration of the whole extract, and particularly the degree to which anthocyanins, PACs, and quercetin glycosides achieve neuroprotective concentrations in human brain tissue, have not been characterized [86]. Third, the majority of mechanistic evidence derives from in vitro studies at supraphysiological polyphenol concentrations, creating uncertainty about translation to physiologically achievable plasma and brain tissue levels following dietary or supplemental intake [87].

Fourth, the phytochemical composition of *V. oxycoccos* varies substantially between geographic populations, harvest conditions, and processing methods, complicating standardization of experimental preparations and clinical doses [88]. Fifth, potential pharmacokinetic and pharmacodynamic interactions between the multiple polyphenolic classes co-present in *V. oxycoccos* extract

which may be synergistic, additive, or occasionally antagonistic have not been systematically characterized in neurodegenerative disease models [89]. These limitations collectively underscore the need for carefully designed translational research programmes.

9.2 Future Research Directions

Addressing the identified research gaps requires a multidisciplinary programme spanning phytochemistry, pharmacokinetics, neuroscience, and clinical medicine. Priority areas include: (i) comprehensive pharmacokinetic profiling of *V. oxycoccos* polyphenols, including gut microbiome-derived metabolites, in rodent and non-human primate models, with particular attention to brain tissue distribution; (ii) systematic evaluation of standardized *V. oxycoccos* phytosome formulations in established PD animal models including rotenone, MPTP, and transgenic alpha-synuclein overexpression mice, with neurochemical, behavioural, and histopathological endpoints; (iii) dose-response characterisation of neuroprotective efficacy and establishment of effective doses translatable to human supplementation regimens; (iv) elucidation of synergistic interactions between *V. oxycoccos* phytochemical classes through fractionation and combination studies; and (v) Phase I/II clinical trials in PD patients or high-risk populations with standardized *V. oxycoccos* extract or phytosome formulations, incorporating validated biomarkers of oxidative stress, neuroinflammation, and dopaminergic function [90,91].

Metabolomic profiling of *V. oxycoccos* populations from diverse geographic origins would facilitate identification of elite chemotypes with optimised neuroprotective phytochemical profiles for selective cultivation or directed breeding programmes [92]. Investigation of the role of gut microbiome composition in modulating *V. oxycoccos* polyphenol metabolism and their neuroprotective bioavailability represents a particularly promising frontier, given emerging evidence for bidirectional gut-brain axis communication in PD pathogenesis [93]. Development of validated analytical methods for standardization of *V. oxycoccos* preparations, and establishment of minimum effective polyphenol specifications for neuroprotective formulations, constitute essential prerequisites for regulatory-compliant clinical development [94].

9.3 Research Gaps and Translational Challenges

Despite encouraging preclinical findings, several challenges hinder the translation of *Vaccinium oxycoccos* derived phytochemicals into clinically applicable therapies for Parkinson's disease. First, no clinical trials have directly evaluated standardized *V. oxycoccos* extracts in Parkinson's disease patients. Second, the oral bioavailability of anthocyanins, proanthocyanidins, and other polyphenols remains limited due to poor gastrointestinal stability, extensive metabolism, and restricted brain penetration. Third, considerable variability exists in the phytochemical composition of *V. oxycoccos* fruits due to differences in geographical origin, environmental conditions, harvesting stage, and processing methods, making standardization difficult.

Additionally, most available evidence is derived from in vitro experiments or toxin-induced animal models that may not fully reproduce the complexity of human Parkinson's disease. The optimal therapeutic dose, treatment duration, long-term safety profile, and potential interactions with existing antiparkinsonian medications remain unclear. Future research should focus on standardized extract development, pharmacokinetic characterization, advanced delivery systems such as phytosomes, and well-designed clinical studies to establish the therapeutic relevance of *V. oxycoccos* in Parkinson's disease.

10. CONCLUSION

Berry-derived polyphenols represent a scientifically credible and mechanistically well-characterized class of neuroprotective phytochemicals with direct relevance to the complex multi-target pathophysiology of Parkinson's disease. *Vaccinium oxycoccos* L., the European small cranberry, emerges from this analysis as a particularly promising source of neuroprotective bioactives, distinguished by its exceptionally rich and diverse polyphenolic composition encompassing anthocyanins, A-type proanthocyanidins, quercetin glycosides, chlorogenic acid, ferulic acid, and ursolic acid compounds whose neuroprotective mechanisms individually and synergistically target oxidative stress, neuroinflammation, mitochondrial dysfunction, alpha-synuclein aggregation, and dopaminergic apoptosis.

The mechanistic evidence from experimental PD models supports the proposition that *V. oxycoccos* bioactives activate the Nrf2/ARE antioxidant pathway, suppress NF-kappaB and NLRP3 neuroinflammatory signalling, preserve mitochondrial membrane potential and Complex I function, inhibit MAO-B activity and dopamine quinone-mediated alpha-synuclein modification, and protect dopaminergic neurons from apoptotic cell death through Bcl-2/Bax pathway modulation. These multi target mechanisms, operating concurrently within the degenerating dopaminergic neuron, suggest that polyphenol-based interventions may exert neuroprotection superior to that achievable through single-target pharmacology.

The development of phytosome formulations of *V. oxycoccos* extract represents a rational translational strategy to overcome the inherent bioavailability limitations of berry polyphenols, potentially enabling therapeutic CNS concentrations to be achieved at clinically feasible doses. The absence of species specific clinical data represents the most significant current limitation and the most urgent research priority. Future well designed clinical trials, built upon the robust mechanistic and preclinical foundation reviewed here in, will be essential to establish *V. oxycoccos* as an evidence based neuroprotective intervention for Parkinson's disease prevention or progression modification.

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