

β -Sitosterol and Stigmasterol-Mediated Nrf2/Keap1 Signaling in Parkinson's Disease: Mechanisms and Therapeutic Potential

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Abstract

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by selective degeneration of substantia nigra pars compacta dopaminergic neurons, involving interconnected oxidative stress, mitochondrial dysfunction, α -synuclein proteostasis failure, neuroinflammation, iron dysregulation and impaired cellular quality control. The Kelch-like ECH-associated protein 1 (Keap1)/nuclear factor erythroid 2-related factor 2 (Nrf2)/antioxidant response element (ARE) axis is a central endogenous defense system that regulates glutathione synthesis, NADPH generation, xenobiotic detoxification, heme metabolism and inflammatory responses. β -Sitosterol and stigmasterol are structurally related phytosterols with emerging neuroprotective and anti-inflammatory properties. Recent experimental evidence is particularly notable for stigmasterol, which in MPP⁺- and MPTP-induced PD models enhanced Nrf2 nuclear translocation, increased antioxidant proteins, reduced reactive oxygen species and lipid peroxidation, preserved tyrosine hydroxylase-positive neurons and improved motor performance. β -Sitosterol shows supportive evidence from neuronal oxidative-stress and Nrf2/HO-1 studies, although direct PD-specific validation remains limited. This review critically examines sterol-mediated Nrf2/Keap1 regulation, mitochondrial homeostasis, neuroinflammation, α -synuclein proteostasis, pharmacokinetic barriers, blood-brain-barrier delivery, nanocarrier strategies, safety and translational biomarkers.

Keywords: β -Sitosterol; Stigmasterol; Parkinson's disease; Nrf2/Keap1; Oxidative stress

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1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder and is increasingly recognized as a systemic network disorder rather than a condition caused solely by dopamine deficiency. Global epidemiological analyses indicate a rapidly expanding disease burden, driven by population ageing, longer survival and changing exposure to environmental and metabolic risk factors [1-4]. Clinically, bradykinesia, rigidity, resting tremor and postural dysfunction coexist with non-motor manifestations such as constipation, sleep disturbance, depression, autonomic dysfunction and cognitive impairment. Neuropathologically, the cardinal lesion is progressive loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc), accompanied in many patients by Lewy pathology containing misfolded and aggregated α -synuclein [5-8]. Levodopa and other dopaminergic therapies remain highly effective for symptomatic control, but they do not comprehensively correct the molecular processes that drive neuronal loss. Consequently, disease-modifying strategies directed toward mitochondrial failure, redox imbalance, neuroinflammation and proteostasis remain a major research priority [9-12].

Oxidative stress occupies a central position within this network. Dopaminergic neurons are intrinsically vulnerable because dopamine can undergo auto-oxidation and enzymatic metabolism to reactive intermediates, while mitochondrial complex-I impairment increases electron leakage and superoxide generation. High iron content in the substantia nigra further favors Fenton chemistry, whereas relatively low glutathione availability and extensive axonal arborization increase the metabolic burden of these neurons [13-17]. Lipid peroxidation generates electrophilic products such as 4-hydroxynonenal that can modify proteins and amplify mitochondrial and inflammatory dysfunction. Thus, the therapeutic objective is not simply to scavenge radicals after they have formed, but to restore the cellular stress-adaptation systems that continuously maintain redox homeostasis.

Nrf2 is the major transcriptional regulator of this adaptive response. Under basal conditions, Keap1 acts as a redox-sensitive substrate adaptor for a CUL3-RBX1 E3 ubiquitin ligase complex and promotes constitutive Nrf2 ubiquitination and proteasomal turnover. Oxidative or electrophilic stress modifies critical Keap1 sensor cysteines and alters the geometry of the Keap1-Nrf2 complex, allowing newly synthesized Nrf2 to escape degradation, accumulate and enter the nucleus. Nrf2 then heterodimerizes with small Maf proteins and

binds antioxidant response elements (AREs), inducing genes involved in glutathione biosynthesis, NADPH regeneration, quinone reduction, heme metabolism and detoxification [18-24].

Phytosterols provide an unusual opportunity to interrogate this pathway because their steroidal structures allow interactions with biological membranes, lipid domains and intracellular lipid signaling, while their downstream actions extend into inflammation and oxidative stress. β -Sitosterol and stigmasterol are among the most abundant plant sterols. Their structures differ by the degree of side-chain unsaturation, a seemingly modest change that can influence membrane behavior and biological activity [25-29]. The present review therefore evaluates these compounds as mechanistically related but not interchangeable molecules. Particular emphasis is placed on the distinction between direct evidence and pathway extrapolation: stigmasterol now has direct MPP⁺/MPTP-induced evidence for Keap1/Nrf2 signaling, whereas the evidence for β -sitosterol in PD remains largely indirect or derived from non-PD models [30-34].

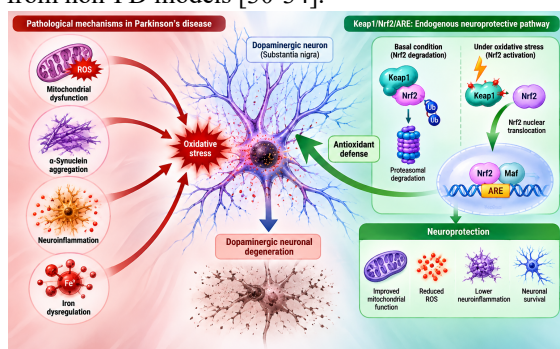


Fig 1: Interconnected Pathological Mechanisms of Parkinson's Disease and the Keap1/Nrf2/ARE Defense System

2. Parkinson's Disease Pathobiology Relevant to Nrf2 Modulation

2.1 Dopamine oxidation, iron and redox pressure

Dopamine metabolism generates hydrogen peroxide through monoamine oxidase reactions, while spontaneous oxidation produces dopamine quinones and aminochrome. These electrophilic species can react with protein thiols, alter mitochondrial enzymes and promote abnormal protein modification. Iron accumulation in the SNpc can intensify peroxide-dependent hydroxyl-radical formation. At the same time, mitochondrial complex-I dysfunction increases superoxide production and compromises ATP generation [13-17,35]. This creates a self-amplifying loop: mitochondrial ROS oxidize proteins and lipids; damaged mitochondria produce more ROS; oxidative modification impairs proteostasis; and inflammation further increases metabolic and redox stress. An intervention that strengthens endogenous antioxidant transcription therefore has theoretical advantages over a molecule that acts only as a stoichiometric radical scavenger.

2.2 Mitochondrial dysfunction and quality control

Mitochondria integrate ATP production, calcium buffering, apoptosis and innate immune signaling. Genetic evidence has established that PINK1 and Parkin-dependent mitophagy is crucial for neuronal mitochondrial quality control [36-39]. PINK1 accumulates on depolarized mitochondria and phosphorylates ubiquitin and Parkin, promoting ubiquitination of outer-mitochondrial-membrane proteins and recruitment of autophagic machinery. Failure of this pathway allows damaged mitochondria to persist, increasing ROS and inflammatory signaling. Nrf2 can complement mitophagy by increasing cellular reducing capacity, supporting NADPH-dependent antioxidant systems and facilitating survival during transient mitochondrial stress [40-43].

2.3 α -Synuclein, proteostasis and lysosomal stress

α -Synuclein is not simply an aggregation marker; its oligomeric forms can perturb membranes, mitochondria, vesicular trafficking and lysosomal degradation. Oxidation, nitration and lipid interactions can modify α -synuclein conformation, while impaired autophagy can increase the pool of toxic species [44-47]. Nrf2 signaling intersects with proteostasis through p62/SQSTM1, autophagy and stress-responsive transcription. Consequently, pharmacological Nrf2 modulation could potentially reduce the cellular conditions that favor α -synuclein toxicity, although direct clearance of pathological α -synuclein by β -sitosterol or stigmasterol has not yet been convincingly demonstrated.

2.4 Neuroinflammation and the NLRP3 axis

Microglia respond to neuronal debris, aggregated proteins, mitochondrial danger signals and oxidized lipids. Chronic activation produces TNF- α , IL-1 β , IL-6, nitric oxide and ROS, which can feed back into dopaminergic neuronal injury [48-53]. The NLRP3 inflammasome provides a mechanistic bridge between mitochondrial stress and inflammatory amplification. Mitochondrial ROS, potassium efflux and lysosomal disruption promote inflammasome activation, leading to caspase-1-mediated maturation of IL-1 β and IL-18. Nrf2 can counter this process by reducing the oxidative inputs that promote inflammasome activation and by antagonizing NF- κ B-associated inflammatory transcription [54-57].

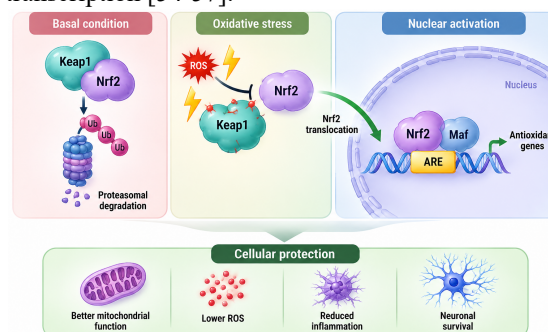


Fig 2: Molecular Regulation of the Keap1/Nrf2/ARE Signaling Axis in Oxidative Stress

Table 1. Molecular mechanisms of the Keap1/Nrf2/ARE axis relevant to Parkinson’s disease.

Molecular component	Normal biological function	Alteration in PD	Relevance to β-sitosterol/stigmasterol
Keap1	Cytoplasmic Nrf2 sensor/adaptor ; promotes Nrf2 ubiquitination and proteasomal degradation under basal conditions	Oxidative/electrophilic stress can modify Keap1 cysteine residues, reducing Nrf2 degradation	Phytosterol-associated redox modulation may influence Keap1-dependent Nrf2 stabilization
Nrf2 (NFE2L2)	Master transcriptional regulator of antioxidant and cytopro	Impaired Nrf2 activity can reduce cellular resistance to oxidative and	Stigmasterol has experimental evidence for enhanced Nrf2 nuclear translocation; β-

	protective genes	mitochondrial stress	β-sitosterol evidence remains more indirect
ARE	DNA regulatory element controlling transcription of Nrf2-responsive genes	Reduced transcriptional antioxidant capacity may increase susceptibility to oxidative injury	Represents the downstream transcriptional endpoint for phytosterol-mediated Nrf2 activation
HO-1	Heme degradation and cytoprotective enzyme ; contributes to cellular stress adaptation	Dysregulated oxidative/inflammatory signaling can alter HO-1 responses	Increased HO-1 is reported in Nrf2-associated phytosterol responses
NQO1	Quinone detoxification and redox	Reduced antioxidant defense may enhance quinone-mediated	Potential downstream biomarker of Nrf2 activation

	stabilization	oxidative injury	
GCLC/ GCLM	Catalyzes glutathione synthesis	Reduced glutathione availability increases oxidative vulnerability	Potential mechanism through which Nrf2 activation can restore redox buffering
SOD1/ SOD2	Detoxification of superoxide radicals	Mitochondrial oxidative stress can increase superoxide burden	Stigmasterol-associated increases in antioxidant proteins support a broader cytoprotective response
NADPH-generating enzymes	Maintain reducing equivalents required for antioxidant	Metabolic/redox imbalance can compromise antioxidant capacity	Nrf2 activation may improve cellular reducing capacity

	dant regeneration		
BACH1	Transcriptional repressor opposing Nrf2-dependent antioxidant gene expression	Altered Nrf2–BACH1 balance may influence antioxidant transcription	Represents an important unexplored regulatory layer for phytosterol-mediated Nrf2 signaling
Keap1–Nrf2–ARE axis	Coordinates antioxidant, detoxification and stress-adaptation programs	Dysfunction may contribute to oxidative neuronal vulnerability	Central mechanistic hypothesis connecting phytosterols with neuroprotection

3. Molecular Architecture and Pharmacology of the Keap1/Nrf2/ARE System

3.1 Canonical Keap1-Nrf2 regulation

Nrf2 contains several regulatory domains, with the Neh2 region carrying the ETGE and DLG motifs that engage the Kelch domain of Keap1. Keap1 simultaneously acts as a sensor and an adaptor for CUL3-dependent ubiquitination. Under non-stressed conditions, Nrf2 turnover is rapid. Oxidative and electrophilic signals modify sensor cysteines in Keap1 and reduce productive ubiquitination, allowing Nrf2 to accumulate [18–24,58]. Nuclear Nrf2 associates with small Maf proteins and binds ARE sequences in promoters or enhancers of cytoprotective genes. Important targets

include HMOX1, NQO1, GCLC, GCLM, GSTs, TXNRD1, SLC7A11 and multiple NADPH-producing enzymes [19–24].

3.2 Canonical and non-canonical activation

Nrf2 activation is broader than direct Keap1 oxidation. Autophagy dysfunction can increase p62/SQSTM1, which competes with Nrf2 for Keap1 binding and can promote Nrf2 stabilization. Other regulators include p21, DPP3 and metabolic signals [23,24,58,59]. This matters for phytosterol research because a change in Nrf2 abundance alone does not establish the precise mechanism. A rigorous study should distinguish increased Nrf2 transcription from increased protein stability, altered nuclear import,

Keap1 sequestration, altered cysteine sensing or downstream transcriptional activation.

3.3 Nrf2 as a metabolic and inflammatory regulator

The Nrf2 program is not restricted to classical antioxidant enzymes. It influences glutamine utilization, pentose-phosphate pathway activity, NADPH production, iron handling and lipid metabolism. The Nrf2-NF- κ B relationship is bidirectional, creating a functional link between redox control and inflammation [40,54-57]. Excessive or chronic Nrf2 activity can also produce reductive stress or alter metabolism, demonstrating why “more Nrf2” is not automatically equivalent to better biology. In PD, the objective should therefore be context-appropriate restoration of redox resilience rather than indiscriminate pathway activation.

3.4 Nrf2-BACH1 balance

BACH1 is a transcriptional repressor that can oppose Nrf2-dependent antioxidant gene expression. Studies in neurodegeneration have highlighted the importance of the Nrf2-BACH1 equilibrium, particularly for genes such as HO-1 [60-63]. This concept is highly relevant to sterol development. If β -sitosterol or stigmasterol increases Nrf2 but does not alter nuclear BACH1 or ARE occupancy, the functional transcriptional response may be smaller than expected. Future mechanistic studies should therefore measure nuclear Nrf2, BACH1, Nrf2/BACH1 ratio, chromatin occupancy and multiple downstream gene products rather than relying on a single western-blot endpoint.

4. β -Sitosterol: Molecular Evidence, Neuroprotection and Nrf2 Relevance

4.1 Structural and pharmacological characteristics

β -Sitosterol is a plant sterol structurally related to cholesterol, with a tetracyclic steroid nucleus, a 3 β -hydroxyl group and a C24-ethyl side chain. Its molecular weight is approximately 414.7 g/mol and its high lipophilicity contributes to very low aqueous solubility. Reviews published during 2015-2026 describe antioxidant, anti-inflammatory, immunomodulatory, metabolic and membrane-associated actions [25-29,64-66]. These properties make β -sitosterol attractive for diseases in which lipid membranes, oxidative damage and inflammatory signaling intersect, but they also create pharmacokinetic challenges for oral and CNS delivery.

4.2 Experimental neuroprotective evidence

A 2019 study using vanadium-induced neurotoxicity in mice showed that β -sitosterol improved motor coordination and attenuated memory impairment and demyelination while correcting oxidative-stress-associated biochemical abnormalities [67]. The model is not PD, but its findings are relevant because vanadium toxicity produces ROS

generation, lipid peroxidation and antioxidant depletion. The study supports the proposition that β -sitosterol can modify neuronal oxidative injury rather than merely altering circulating lipids. However, the absence of a PD-specific Nrf2 loss-of-function experiment means that the mechanism cannot be equated with direct Nrf2 activation in nigrostriatal neurons.

4.3 Nrf2/HO-1 evidence outside PD

The strongest direct Nrf2 evidence for β -sitosterol comes from non-PD inflammatory models. In 2020, β -sitosterol-loaded solid lipid nanoparticles significantly improved redox and inflammatory parameters in complete Freund's adjuvant-induced arthritis and increased Nrf2 and HO-1 expression while suppressing NF- κ B signaling [68]. The study reported $p < 0.001$ for several pharmacodynamic endpoints and demonstrated changes in MDA, SOD, GSH and catalase. The optimized nanoparticle formulation had a nanoscale particle size, illustrating that formulation can improve the practical pharmacology of a highly lipophilic sterol. These results establish biological compatibility between β -sitosterol and Nrf2/HO-1 signaling but should not be presented as direct evidence of anti-PD efficacy.

5. Stigmasterol: Direct Evidence for Keap1/Nrf2-Mediated Neuroprotection

5.1 Structural basis and neuronal activity

Stigmasterol is closely related to β -sitosterol but contains an additional Δ^{22} double bond in the side chain. Its molecular weight is approximately 412.7 g/mol. In a 2021 human SH-SY5Y neuronal-cell study, stigmasterol protected cells against H₂O₂-induced oxidative injury and increased SIRT1, FoxO3a, catalase and Bcl-2 while reducing oxidative stress and apoptosis [69, 70]. The study used 400 μ M H₂O₂ for 24 hours and showed preservation of cell viability and mitochondrial membrane potential with stigmasterol pretreatment. These findings established a neuroprotective phenotype before direct PD-specific Nrf2 evidence became available.

5.2 Direct MPP⁺ and MPTP evidence

The most important recent evidence comes from a 2026 Journal of Translational Medicine study, published online in late 2025, that investigated stigmasterol in MPP⁺-treated neuronal cells and MPTP-induced PD mice [71]. The investigators used behavioral testing, immunohistochemistry, immunofluorescence, western blotting and biochemical assays. Stigmasterol promoted Nrf2 nuclear translocation and increased antioxidant proteins, reduced ROS and lipid peroxidation, improved SOD, catalase and GSH-related defenses, increased HO-1, SOD1 and SOD2, preserved tyrosine hydroxylase expression and reduced dopaminergic neuronal loss. Motor impairment was also improved in the MPTP model. These convergent endpoints are important because they

connect molecular target engagement to cellular protection and then to an organism-level phenotype [72].

5.3 Causality and Nrf2 inhibition

A major strength of the stigmasterol study was the use of the Nrf2 inhibitor ML385. If a compound merely increases Nrf2 as a secondary consequence of reduced injury, inhibition of Nrf2 should not necessarily abolish protection. In contrast, attenuation of stigmasterol-associated protection by Nrf2 inhibition provides evidence that the pathway is mechanistically relevant [72]. This is a substantially stronger claim than simply reporting an increase in total Nrf2 protein. Nevertheless, pharmacological inhibitors have off-target limitations; definitive confirmation would require NFE2L2 genetic knockdown or knockout and ideally rescue experiments.

5.4 Keap1 as a potential molecular interaction site

Computational studies have proposed direct stigmasterol interactions with Keap1 and other proteins involved in oxidative and inflammatory signaling [73]. Reported docking energies should be interpreted as computational scores, not experimental binding constants. Direct Keap1 engagement remains to be validated using surface plasmon resonance, microscale thermophoresis, isothermal titration calorimetry or structural approaches. Establishing whether stigmasterol acts through covalent Keap1 modification, non-covalent disruption of Keap1-Nrf2 binding, indirect redox signaling or another upstream mechanism would substantially advance the field.

5.5 SIRT1/FoxO3a convergence

The SIRT1/FoxO3a pathway provides a second mechanistic layer. SIRT1 deacetylates transcription factors and proteins involved in stress resistance, while FoxO3a regulates catalase and other antioxidant genes. Stigmasterol increased SIRT1 and FoxO3a signaling in neuronal cells [71]. Nrf2 and FoxO pathways can therefore be conceptualized as parallel stress-adaptation systems that may converge on mitochondrial and antioxidant resilience. Future studies should determine whether combined SIRT1 and Nrf2 blockade eliminates stigmasterol-mediated protection, which would reveal whether the pathways are redundant, additive or hierarchically organized.

6. Integrated Mechanistic Model: Redox, Mitochondria, Inflammation and Proteostasis

6.1 From sterol exposure to Nrf2 transcription

A coherent model begins with cellular exposure to β -sitosterol or stigmasterol, followed by membrane partitioning, intracellular trafficking and interaction with signaling proteins. For stigmasterol, direct PD evidence supports increased Nrf2 nuclear localization [72]. The downstream sequence can be represented as: sterol exposure $\rightarrow$ altered Keap1-Nrf2 regulation $\rightarrow$ Nrf2 stabilization/nuclear

translocation $\rightarrow$ sMaf-dependent ARE binding $\rightarrow$ transcription of HMOX1, NQO1, GCLC/GCLM, TXNRD1 and related genes $\rightarrow$ increased glutathione and reducing capacity. For β -sitosterol, this sequence is plausible but remains to be demonstrated specifically in dopaminergic PD models [68,69].

6.2 Mitochondrial protection and mitophagy

Improved glutathione and NADPH availability can reduce mitochondrial oxidative pressure, preserve membrane potential and limit opening of permeability-transition pathways. Lower ROS may also reduce damage to mitochondrial DNA, respiratory-chain proteins and cardiolipin. Because PINK1/Parkin-mediated mitophagy removes severely damaged mitochondria, a combined sterol-Nrf2 effect could shift the mitochondrial population toward healthier organelles [36-43]. This hypothesis should be tested by measuring oxygen-consumption rate, spare respiratory capacity, ATP, complex-I activity, mitochondrial superoxide, PINK1 stabilization, Parkin recruitment and mitophagic flux rather than using membrane-potential staining alone.

6.3 Neuroinflammation and inflammasome suppression

Nrf2 activation can reduce the oxidative triggers that sustain NF- κ B and NLRP3 signaling. Consequently, phytosterol-mediated redox adaptation could decrease microglial TNF- α , IL-1 β and IL-18 output. β -Sitosterol nanoparticle studies already demonstrate suppression of inflammatory signaling together with Nrf2/HO-1 induction in peripheral inflammatory tissue [68]. Whether the same relationship exists in microglia exposed to α -synuclein or MPP⁺ requires direct experimentation. A particularly informative experiment would compare wild-type and Nrf2-deficient microglia while measuring NLRP3 assembly, ASC speck formation and caspase-1 activity.

6.4 α -Synuclein and proteostasis

Reducing oxidative stress may decrease oxidative modification of α -synuclein, while improved autophagic function could facilitate clearance of damaged proteins. The p62-Keap1-Nrf2 axis provides a mechanistic bridge between autophagy and antioxidant transcription [23,24,58]. However, there is presently insufficient evidence to claim that either sterol directly removes Lewy-body-like α -synuclein aggregates. Future work should use preformed-fibril seeding models, α -synuclein reporter systems and quantitative aggregation assays to determine whether Nrf2-dependent sterol treatment changes pathological propagation.

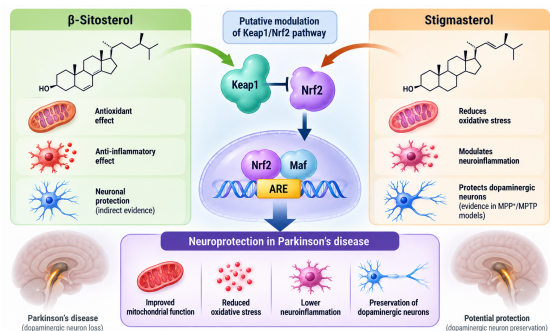


Table 2. Experimental evidence and proposed mechanisms of β -sitosterol and stigmasterol in neuroprotection

Phytosterol	Experimental model	Exposure/dose	Principal findings	Nrf2/related pathway evidence	Current evidence interpretation
β -Sitosterol	Vanadium-induced neurotoxicity model	Study-specific exposure	Improved behavioral/neurobiological parameters and reduced oxidative injury	Associated with Nrf2/HO-1-related antioxidant response	Supportive mechanistic evidence, but indirect for PD
	β -Sitosterol-loaded solid lipid nanoparticles	Study-specific dose	Improved antioxidant and anti-inflammatory responses	Nrf2/HO-1-associated effects reported	Supports pharmacological plausibility and delivery

Fig 3: Comparative Molecular Mechanisms of β -Sitosterol and Stigmasterol-Mediated Neuroprotection

	cles; inflammatory injury model				ery potential
	Neuronal oxidative stress systems	Model-dependent	Reduced oxidative injury and improved cellular defense	Nrf2-related mechanisms proposed/reported in non-PD settings	Requires direct PD-specific validation
	H ₂ O ₂ -induced neuronal oxidative -	1 μ M	Reduced oxidative injury and neuronal death; improved antioxidant	Related to SIRT1/FoxO3a and antioxidant	Strong mechanistic neuroprotective but

Stigmas-terol	stres-s model		ant/cyto-protective response	signal-ing	not a PD model
	MP P ⁺ -treated neuronal model	Study-specific concentration	Reduced ROS/lipid peroxidation and preserved dopaminergic neuronal features	Increased Nrf2 nuclear translocation and antioxidant proteins	Direct preclinical PD evidence
	MP TP-induced mouse PD model	50 and 100 mg/kg	Reduced dopaminergic neuronal loss and improved motor phenotype	Keap1/Nrf2 pathway activation; effects weakened by Nrf2	Strongest current evidence for stigmasterol

				inhibition	
	MP P ⁺ /MP TP + Nrf2 inhibition	ML385 intervention	Pharmacological inhibition weakened protective effects	Supports Nrf2 involvement	Evidence for pathway dependence, but genetic validation remains necessary
Both phyto-sterols	Proposed translational mechanisms	—	Potential effects on oxidative stress, mitochondrial dysfunction and inflammation	Nrf2/ARE-centered hypohypohesis	Requires direct comparative studies

7. Pharmacokinetics, Blood-Brain Barrier and Nanoformulation

7.1 Exposure is a critical translational variable
A mechanistically active compound is not a therapeutic candidate unless sufficient free drug reaches the relevant target tissue. Both sterols are highly lipophilic and poorly water soluble. Dietary absorption depends on micellar solubilization, intestinal transport and esterification, while hepatic metabolism and biliary secretion can reduce systemic exposure [64-66,74]. Plasma total concentration also overestimates pharmacologically

available drug because only the unbound fraction can readily partition into tissues. Consequently, cell-culture concentrations cannot be directly converted into oral doses.
7.2 Blood-brain-barrier considerations
Plant sterols can enter the central nervous system to variable degrees, but transport is influenced by molecular structure, sterol transporters and BBB integrity [75-77]. Stigmasterol-specific experimental literature has suggested CNS accessibility, but quantitative human substantia-nigra exposure remains unknown. A translational

program should measure total and unbound brain concentration, cerebrospinal-fluid concentration, brain/plasma ratio, tissue half-life and metabolites. Demonstrating Nrf2 target engagement in brain tissue is more informative than demonstrating high plasma exposure alone.

7.3 Nanodelivery opportunities

Solid lipid nanoparticles, nanostructured lipid carriers, liposomes, nanoemulsions, micelles and polymeric nanoparticles can increase apparent solubility and modify absorption. β -Sitosterol-loaded solid lipid nanoparticles have already been shown to produce pharmacodynamic effects and Nrf2/HO-1 modulation in an inflammatory animal model [68]. For PD, an optimized carrier should ideally improve systemic stability while enabling BBB passage or intranasal nose-to-brain delivery. Particle size, polydispersity, zeta potential, encapsulation efficiency, release kinetics and long-term physical stability should be reported, followed by brain biodistribution and pharmacodynamic target engagement.

7.4 Safety and formulation-specific risk

The nutritional origin of phytosterols does not eliminate dose-dependent pharmacology. High exposure, oxidized sterols, metabolites and formulation excipients may have distinct biological effects. Importantly, β -sitosterol β -D-glucoside has been used experimentally to produce progressive parkinsonian phenotypes in rodents, illustrating that closely related sterol derivatives can have very different biological consequences [78]. Therefore, future studies should distinguish parent compounds from glycosides and oxidized metabolites and include liver, kidney, hematology, lipid profile, gastrointestinal and neuropathological safety endpoints.

8. Quantitative Evidence, Experimental Priorities and Translational Development

8.1 Quantitative evidence that should be carried forward

The most informative numerical findings currently include the approximately 400 μ M H₂O₂ neuronal-stress paradigm used in the stigmasterol study, where 1 μ M stigmasterol pretreatment preserved neuronal viability and mitochondrial membrane potential [79]. In the direct PD study, stigmasterol was evaluated at 50 and 100 mg/kg during dose exploration, with 50 mg/kg subsequently used for mechanistic efficacy experiments [72]. The β -sitosterol nanoparticle study reported statistically significant effects at $p < 0.001$ across several inflammatory and redox endpoints and demonstrated nanoscale formulation characteristics [80]. These values should be interpreted as model-specific observations rather than human therapeutic targets.

8.2 Minimum mechanistic package for β -sitosterol

A rigorous PD study should compare vehicle, toxin, β -sitosterol, stigmasterol, β -sitosterol plus Nrf2 inhibition and stigmasterol plus Nrf2 inhibition. In vitro models should include differentiated SH-SY5Y or LUHMES cells and, ideally, human iPSC-derived dopaminergic neurons. Endpoints should include nuclear Nrf2, Keap1, NQO1, HO-1, GCLC, GCLM, SLC7A11, GSH/GSSG, ROS, 4-HNE, MDA, mitochondrial membrane potential, oxygen consumption, ATP, complex-I activity, TH, dopamine and apoptosis markers. Genetic NFE2L2 knockdown should be used to confirm pathway dependence.

8.3 PD models beyond acute toxins

MPP⁺ and MPTP models are valuable for mitochondrial and dopaminergic injury but reproduce only selected components of human PD. Next-stage studies should include α -synuclein preformed-fibril models, genetic parkinsonism models, PINK1/Parkin deficiency and patient-derived iPSC neurons. The key question is whether phytosterol-Nrf2 modulation can slow progressive pathology rather than simply protect against an acute toxin. Longitudinal behavioral testing, stereological neuron counting and blinded biochemical analysis are essential for translational credibility.

8.4 Biomarker-guided development

Potential pharmacodynamic biomarkers include nuclear Nrf2, HO-1, NQO1, GSH/GSSG ratio, lipid-peroxidation products, inflammatory cytokines and mitochondrial respiration. In clinical development, CSF or blood biomarkers of oxidative stress could be combined with imaging or digital motor phenotyping. The ideal proof-of-mechanism study would demonstrate exposure, target engagement and a biologically coherent downstream response before attempting to demonstrate clinical disease modification.

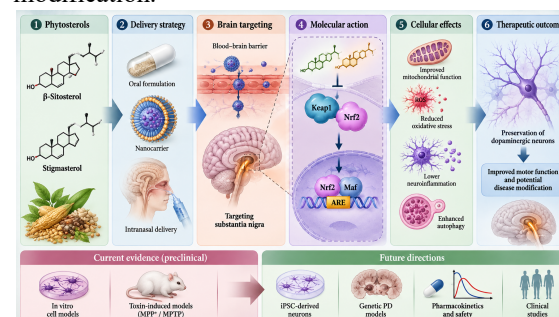


Fig 4: Integrated Therapeutic and Translational Model of Phytosterol-Mediated Nrf2 Activation in Parkinson's Disease

9. Future Perspectives and Conclusion

The next phase of β -sitosterol and stigmasterol research in Parkinson's disease should move beyond descriptive antioxidant pharmacology toward rigorous, target-validated disease biology. A central priority is to establish whether these phytosterols directly modulate the Keap1/Nrf2 axis or influence Nrf2 indirectly through changes in cellular redox status, membrane organization, mitochondrial

signaling, or inflammatory pathways. Direct binding, structural, and biophysical studies should determine whether stigmasterol interacts with Keap1 and whether β -sitosterol exhibits comparable activity. Structure–activity relationship investigations should further examine whether the $\Delta 22$ double bond of stigmasterol contributes to its Nrf2-modulating capacity. Genetic NFE2L2 loss-of-function and rescue experiments will be particularly important for establishing whether neuroprotection is genuinely Nrf2-dependent rather than merely associated with increased Nrf2 expression. The Nrf2–BACH1 regulatory balance should also be incorporated because transcriptional output depends on both activating and repressing mechanisms.

Future studies should place α -synuclein aggregation, propagation, mitochondrial quality control, neuroinflammation, and dopaminergic neuronal survival among primary efficacy endpoints rather than treating them as secondary observations. Experimental designs should increasingly employ human iPSC-derived dopaminergic neurons, α -synuclein preformed-fibril models, genetic Parkinson's disease models, and aged systems to determine whether phytosterol-mediated Nrf2 activation remains effective in disease-relevant biological environments. Cell-type-specific analyses of neurons, astrocytes, and microglia may reveal whether β -sitosterol and stigmasterol exert complementary effects across the neurovascular and neuroimmune compartments.

Pharmacokinetic optimization represents another major translational requirement. Brain exposure should be quantified following oral, parenteral, and intranasal administration, with particular attention to free sterol concentrations within the substantia nigra pars compacta. Nanocarrier-based delivery should be evaluated according to pharmacokinetic and pharmacodynamic performance rather than particle characteristics alone. Formulations should also assess sterol oxidation and metabolite formation because oxidized sterols may possess biological activities that differ substantially from the parent molecules. Pharmacokinetic–pharmacodynamic modeling could determine the duration of Nrf2 activation, establish exposure–response relationships, and identify potential tolerance or pathway adaptation during repeated administration. Disease-stage intervention should become another priority. Many experimental studies administer phytosterols before or immediately after neurotoxin exposure, potentially overestimating therapeutic efficacy. More clinically relevant studies should initiate treatment after established dopaminergic injury and determine whether neuronal function, synaptic integrity, α -synuclein pathology, mitochondrial activity, and neuroinflammation can be stabilized or restored. Combination strategies may also be explored because Nrf2 modulation alone is unlikely to replace symptomatic

dopaminergic therapy. Phytosterols could potentially serve as adjunctive disease-modifying candidates alongside established symptomatic treatment or complementary mitochondrial and anti-inflammatory approaches.

Overall, the Keap1/Nrf2 pathway provides a biologically coherent interface connecting oxidative stress, mitochondrial dysfunction, inflammation, and cellular quality control in Parkinson's disease. β -Sitosterol and stigmasterol are attractive molecular scaffolds because their potential pharmacology extends beyond direct radical scavenging toward antioxidant transcription, membrane biology, inflammatory regulation, and mitochondrial stress adaptation. However, their evidence bases remain unequal. β -Sitosterol represents a mechanistically plausible but incompletely validated candidate, whereas stigmasterol currently has stronger direct experimental support for Nrf2-associated neuroprotection in Parkinsonian models. Neither compound should presently be regarded as an established disease-modifying therapy.

The critical scientific opportunity is therefore to determine whether phytosterol-mediated Nrf2 modulation can produce durable, target-dependent neuroprotection in clinically relevant models. Demonstration of direct target engagement, adequate CNS exposure, reproducible pathway activation, preservation of dopaminergic neurons, suppression of α -synuclein pathology, and long-term safety would provide the evidence required for meaningful translational development. Rigorous negative findings should be considered equally informative because failure to achieve brain exposure or disease-relevant target engagement would identify formulation or mechanistic limitations. Ultimately, the progression from molecular target validation through pharmacokinetics, biomarker confirmation, disease-stage efficacy, and safety evaluation will determine whether β -sitosterol and stigmasterol can progress from promising phytosterol hypotheses to credible therapeutic strategies for Parkinson's disease.

LIST OF ABBREVIATIONS

PD: Parkinson's disease; **Nrf2:** nuclear factor erythroid 2-related factor 2; **Keap1:** Kelch-like ECH-associated protein 1; **ARE:** antioxidant response element; **ROS:** reactive oxygen species; **RNS:** reactive nitrogen species; **α -syn:** α -synuclein; **TH:** tyrosine hydroxylase; **MPP⁺:** 1-methyl-4-phenylpyridinium; **MPTP:** 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; **MAO-B:** monoamine oxidase-B; **GSH:** reduced glutathione; **GSSG:** oxidized glutathione; **SOD:** superoxide dismutase; **HO-1:** heme oxygenase-1; **NQO1:** NAD(P)H quinone dehydrogenase 1; **GCLC:** glutamate-cysteine ligase catalytic subunit; **GCLM:** glutamate-cysteine ligase modifier subunit; **GSTs:** glutathione S-transferases; **TXNRD1:** thioredoxin

reductase 1; **SLC7A11**: solute carrier family 7 member 11; **NFE2L2**: nuclear factor erythroid 2-like 2 (gene encoding Nrf2); **BACH1**: BTB and CNC homology 1; **CUL3**: cullin-3; **PINK1**: PTEN-induced kinase 1; **Parkin**: Parkinsonism-associated protein; **NF-κB**: nuclear factor kappa B; **NLRP3**: NOD-, LRR- and pyrin domain-containing protein 3; **ASC**: apoptosis-associated speck-like protein containing a CARD; **SIRT1**: sirtuin 1; **FoxO3a**: forkhead box O3; **MDA**: malondialdehyde; **4-HNE**: 4-hydroxynonenal; **ATP**: adenosine triphosphate; **BBB**: blood-brain barrier; **iPSC**: induced pluripotent stem cell; **PD**: Parkinson's disease; **CNS**: central nervous system; **PK/PD**: pharmacokinetic/pharmacodynamic; **ML385**: Nrf2 inhibitor; **SH-SY5Y**: human neuroblastoma-derived cell line; **LUHMES**: Lund human mesencephalic cells; **CFA**: complete Freund's adjuvant.

ETHICAL APPROVAL

Not applicable.

CONSENT FOR PUBLICATION

Not applicable.

HUMAN AND ANIMAL ETHICAL RIGHT

Not applicable.

CONFLICT OF INTEREST

The authors declared no conflict of interest and no funding was required to conduct these review data.

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AVAILABILITY OF DATA AND MATERIALS

The data supporting this study findings will be available in the cited references.

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AUTHOR CONTRIBUTION

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