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**Review Article**

# Phytochemicals in Neurodegenerative Diseases: Natural Neuroprotectants

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## ABSTRACT

Neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD) pose significant challenges due to their progressive nature and lack of effective treatments. Phytochemicals, bioactive compounds derived from plants, have gained increasing attention for their neuroprotective properties, including antioxidant, anti-inflammatory, and anti-apoptotic effects. This review explores the role of key phytochemicals such as curcumin, resveratrol, quercetin, epigallocatechin gallate (EGCG), and ginsenosides in modulating cellular pathways associated with neurodegeneration. Despite their promising therapeutic potential, limitations such as poor bioavailability, low brain penetration, and variations in extract standardization hinder their clinical translation. Advances in nanotechnology-based drug delivery systems, improved extraction methods, and targeted clinical trials are crucial for optimizing their efficacy. Integrating phytochemicals with conventional neuroprotective strategies may offer novel, multi-targeted approaches for managing neurodegenerative disorders. Future research should focus on overcoming pharmacokinetic barriers and developing standardized formulations to enhance their therapeutic viability.

## INTRODUCTION

Neurodegenerative diseases (NDs) encompass a range of disorders characterized by the progressive loss of structure and function of neurons, ultimately leading to neuronal death. These diseases significantly affect cognitive, motor, and sensory functions, imposing a substantial burden on patients, families, and healthcare systems worldwide. Among the most prevalent NDs are Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS). The etiologies of NDs are multifactorial, involving

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genetic predispositions, environmental factors, mitochondrial dysfunction, oxidative stress, and abnormal protein aggregation (1-3). AD is the most common cause of dementia, marked by the accumulation of amyloid-beta plaques and tau tangles, leading to synaptic dysfunction and neuronal loss (4,5). PD primarily affects motor control due to dopaminergic neuron degeneration in the substantia nigra, associated with Lewy body formation composed of alpha-synuclein aggregates (6,7). HD is a genetic disorder resulting from CAG trinucleotide repeat expansions in the huntingtin gene, causing widespread neurodegeneration, particularly in the striatum (8). ALS involves the degeneration of motor neurons, leading to muscle weakness and respiratory failure (9). Pathophysiological mechanisms shared across NDs include oxidative stress, neuroinflammation, mitochondrial dysfunction, and excitotoxicity (10-12). Oxidative stress results from an imbalance between reactive oxygen species (ROS) production and antioxidant defenses, causing cellular damage. Neuroinflammation, driven by activated microglia and astrocytes, exacerbates neuronal injury. Mitochondrial dysfunction impairs ATP production, while excitotoxicity involves excessive glutamate release, leading to calcium overload and neuronal death (13). Current therapeutic strategies for NDs are primarily symptomatic, offering limited efficacy in halting disease progression. Consequently, there is an increasing interest in exploring alternative treatments, including phytochemicals derived from plants, known for their antioxidant, anti-inflammatory, and neuroprotective properties (14-16). Phytochemicals such as curcumin, resveratrol, and quercetin have demonstrated the ability to modulate key pathological processes in NDs. Curcumin exhibits antioxidant activity by scavenging ROS and enhancing endogenous antioxidant enzymes (17). Resveratrol activates sirtuin pathways, promoting mitochondrial biogenesis and reducing neuroinflammation (18). Quercetin offers neuroprotection through the inhibition of oxidative stress and inflammatory cytokines (19). Epidemiological studies suggest that diets rich in phytochemicals correlate with reduced risk of NDs, highlighting the potential of natural neuroprotectants in preventive and therapeutic contexts (20,21). Despite promising preclinical findings, clinical translation remains challenging due to issues like poor bioavailability and limited blood-brain barrier permeability (22). Advances in nanotechnology and drug delivery systems are being explored to enhance the efficacy of phytochemical-based therapies (23,24).

### A. Importance of Phytochemicals in Neuroprotection

Phytochemicals, plant-bioactive compounds, are central to neuroprotection by countering the intrinsic mechanisms of neurodegenerative disorders like Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD). These conditions involve oxidative stress, neuroinflammation, mitochondrial impairment, and protein aggregation as key processes that synergistically result in progressive neuronal injury. Phytochemicals manifest their neuroprotective actions via their multifunctional mechanisms such as antioxidant activity, regulation of inflammatory processes, inhibition of apoptosis, and augmentation of neurotrophic factors (25. Resveratrol, curcumin, quercetin, and epigallocatechin gallate have been studied thoroughly for their free radical-scavenging activity and induction of endogenous antioxidant enzymes (26). In addition, phytochemicals regulate major signaling pathways, such as the nuclear factor erythroid 2–related factor 2 (Nrf2) pathway, that activate cellular defense mechanisms (27). Interestingly, polyphenolic compounds have been shown to suppress amyloid-beta aggregation, a characteristic of AD, and

alleviate neuroinflammation by inhibiting pro-inflammatory cytokines (28) The neurotrophic action of some phytochemicals, which increase brain-derived neurotrophic factor (BDNF) levels, also lends support to their function in stimulating neuronal survival and plasticity(29)

**B. Recent Advancements in Research**

Recent advancements in research on phytochemicals in neurodegenerative diseases have focused on elucidating molecular mechanisms, improving bioavailability, and exploring novel delivery systems. Nanotechnology has emerged as a promising approach to enhance the bioavailability and targeted delivery of phytochemicals, overcoming limitations such as poor solubility and rapid metabolism(30) Nanoformulations of curcumin and resveratrol, for instance, have shown improved blood-brain barrier permeability and enhanced neuroprotective efficacy (31) Recent clinical trials have explored the therapeutic potential of phytochemicals, with some demonstrating cognitive improvement in patients with mild cognitive impairment and early-stage AD(32) Advances in understanding the gut-brain axis have also highlighted the role of phytochemicals in modulating gut microbiota, thereby influencing neuroinflammation and cognitive functions(33. The exploration of combination therapies, where phytochemicals are used alongside conventional drugs, has shown potential in enhancing therapeutic outcomes and reducing drug-associated side effects (34) Multi-target approaches that address oxidative stress, inflammation, and protein misfolding simultaneously are being prioritized in ongoing research efforts (35) Despite significant progress, further research is required to establish optimal dosages, long-term safety profiles, and effective therapeutic combinations.

**Major Classes of Phytochemicals with Neuroprotective Potential**

***A. Polyphenols***

Polyphenols, a diverse class of plant-derived compounds, have gained substantial attention for their neuroprotective properties, particularly in the context of neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD). Their neuroprotective potential is attributed to their antioxidant, anti-inflammatory, anti-apoptotic properties, and their ability to modulate cell signaling pathways(36)

- **Recent Discoveries in Flavonoids and Phenolic Acids**

Flavonoids, the most abundant subclass of polyphenols, include flavones, flavanols, and anthocyanins, known for their potent antioxidant capacity and ability to cross the blood-brain barrier (BBB)(37) Recent studies reveal that quercetin and epigallocatechin gallate (EGCG) can attenuate amyloid-beta (Aβ) aggregation and tau hyperphosphorylation, key pathological features of AD (38) Flavonoids also modulate the nuclear factor erythroid 2–related factor 2 (Nrf2) pathway, enhancing endogenous antioxidant responses (39) Phenolic acids like caffeic and ferulic acid have demonstrated neuroprotective effects through inhibition of neuroinflammation and promotion of neurogenesis (40) Recent clinical studies report cognitive improvements in elderly populations following diets rich in flavonoid-containing foods (41)

- **Emerging Research on Stilbenes and Lignans**

Stilbenes, particularly resveratrol, have garnered interest due to their ability to activate sirtuin 1 (SIRT1), a protein that promotes neuronal survival

and mitochondrial function(42) Resveratrol has been shown to reduce oxidative stress, modulate neuroinflammatory responses, and improve cognitive function in both preclinical and clinical settings(43). Lignans, another subclass of polyphenols found in seeds and whole grains, have demonstrated potential in reducing neuroinflammation and enhancing neurotrophic factors such as brain-derived neurotrophic factor (BDNF)(44)

**B. Alkaloids**

Alkaloids, a diverse group of naturally occurring nitrogen-containing compounds, have attracted considerable interest for their neuroprotective properties. These phytochemicals are abundant in various plants and exhibit a wide range of pharmacological activities, including antioxidant, anti-inflammatory, and anti-apoptotic effects, which are crucial in combating neurodegenerative diseases (NDDs) such as Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD) [45-47]. Among the numerous classes of alkaloids, isoquinoline, indole, and tropane alkaloids have demonstrated significant neuroprotective potential.

- **New Findings on Isoquinoline and Indole Alkaloids**

Isoquinoline alkaloids, characterized by a benzylisoquinoline skeleton, are predominantly found in plants like *Berberis*, *Papaver*, and *Corydalis* species. Berberine, an extensively studied isoquinoline alkaloid, exhibits neuroprotective effects through various mechanisms, including the inhibition of acetylcholinesterase (AChE), reduction of amyloid-beta (Aβ) accumulation, and modulation of mitochondrial function [48-51]. Recent studies have revealed that berberine can attenuate tau hyperphosphorylation, a hallmark of AD pathology, by regulating glycogen synthase kinase-3β (GSK-3β) activity [52]. Similarly, corydalis alkaloids have shown neuroprotective effects through the suppression of neuroinflammation and oxidative stress [53,54]. Indole alkaloids, primarily derived from *Catharanthus roseus*, *Rauwolfia serpentina*, and *Mitragyna speciosa*, have also been explored for their neuroprotective properties. Reserpine, an indole alkaloid from *R. serpentina*, has been investigated for its role in modulating monoaminergic systems, although its clinical use is limited due to adverse effects [55]. In contrast, harmine, another indole alkaloid, has shown promise in promoting neurogenesis and inhibiting monoamine oxidase-A (MAO-A), thereby offering protection against neurodegeneration [56,57]. Notably, recent research indicates that harmine can enhance brain-derived neurotrophic factor (BDNF) levels, facilitating neuronal survival and plasticity [58]. Mitragynine, a major alkaloid from *M. speciosa*, demonstrates anti-inflammatory and antioxidant activities, contributing to its neuroprotective profile [59,60].

- **Potential of Tropane Alkaloids in Neuroprotection**

Tropane alkaloids, predominantly found in plants of the *Solanaceae* family, including *Atropa belladonna*, *Datura stramonium*, and *Hyoscyamus niger*, possess significant neuropharmacological activities. These alkaloids, such as atropine and scopolamine, exert their effects primarily through the modulation of cholinergic neurotransmission [61]. Scopolamine-induced cognitive deficits in animal models have been extensively used to study potential neuroprotective agents, highlighting the relevance of tropane alkaloids in cognitive impairment research [62]. Recent investigations into tropane alkaloids have expanded beyond their traditional anticholinergic roles. Studies have demonstrated that certain tropane derivatives can

reduce oxidative stress and neuroinflammation, two key contributors to NDD progression [63,64]. Furthermore, novel synthetic analogs of tropane alkaloids are being developed to enhance their neuroprotective efficacy while minimizing adverse effects [65]. These findings underscore the therapeutic potential of tropane alkaloids in managing NDDs.

### C. Terpenes

Terpenes, one of the largest classes of phytochemicals, play a significant role in neuroprotection due to their diverse biological activities, including antioxidant, anti-inflammatory, and anti-apoptotic properties. These compounds are categorized based on the number of isoprene units they contain, with monoterpenes (C10), sesquiterpenes (C15), and triterpenes (C30) being the most studied for their neuroprotective potential.

### Latest Research on Monoterpenes and Sesquiterpenes

- ***Monoterpenes***

Monoterpenes, which include compounds such as limonene, linalool, and α-pinene, have demonstrated significant neuroprotective properties. Recent research has focused on their potential against neurodegenerative diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD). Limonene, a major component of citrus essential oils, has shown anti-inflammatory and antioxidant properties that help mitigate neurotoxicity induced by amyloid-beta (Aβ) in AD models (66). Linalool, a floral-scented monoterpene, has been found to inhibit neuroinflammation by suppressing microglial activation and reducing oxidative stress in various neurodegenerative models (67). Additionally, α-pinene, found in pine and rosemary, has demonstrated cognitive enhancement effects through cholinergic modulation and antioxidant action (68). Recent studies suggest that monoterpenes exert neuroprotection through the activation of nuclear factor erythroid 2–related factor 2 (Nrf2) and inhibition of nuclear factor-kappa B (NF-κB), key regulators of oxidative stress and inflammation (69). Moreover, limonene and linalool have been shown to modulate neurotransmitter systems, such as gamma-aminobutyric acid (GABA) and dopamine pathways, which play a crucial role in neurodegenerative disorders (70).

- **Sesquiterpenes**

Sesquiterpenes, including β-caryophyllene, farnesene, and ar-turmerone, have gained attention for their neuroprotective effects. β-Caryophyllene, a dietary sesquiterpene found in black pepper and cannabis, has been reported to act as a selective agonist of the cannabinoid receptor type 2 (CB2R), reducing neuroinflammation and oxidative stress in AD and PD models (71). Studies have shown that β-caryophyllene enhances autophagy and reduces Aβ accumulation, suggesting its therapeutic potential in AD (72). Ar-turmerone, derived from turmeric, has demonstrated significant neurogenic effects by promoting neural stem cell proliferation and differentiation (73). This property is particularly relevant for neurodegenerative conditions where neuronal loss is a key feature. Furthermore, sesquiterpenes like farnesene have been shown to modulate mitochondrial function, thereby preventing neuronal apoptosis in PD models (74).

- **Promising Results with Triterpenes**

Triterpenes, including betulinic acid, ursolic acid, and ginsenosides, have emerged as promising candidates for neuroprotection due to their ability to target multiple pathological pathways involved in neurodegenerative diseases.

Betulinic acid, found in birch bark, has been shown to exert neuroprotective effects by enhancing brain-derived neurotrophic factor (BDNF) expression and reducing oxidative stress (75). Ursolic acid, present in rosemary and apple peels, has demonstrated neuroprotective properties by inhibiting apoptosis and mitigating neuroinflammation in AD and PD models (76). Ginsenosides, bioactive compounds in Panax ginseng, have been extensively studied for their cognitive-enhancing and neuroprotective effects. Ginsenoside Rg1 has been shown to attenuate Aβ-induced neurotoxicity by modulating synaptic plasticity and reducing neuroinflammation (77). Additionally, Rb1 and Rd ginsenosides exhibit protective effects against dopaminergic neuronal loss in PD models by modulating mitochondrial dynamics and reducing oxidative stress (78).Furthermore, emerging research indicates that triterpenes may regulate autophagic pathways, thereby enhancing the clearance of misfolded proteins implicated in neurodegenerative disorders (79). Their multi-target approach makes them attractive candidates for further drug development.

**Mechanisms of Neuroprotection**

**A. Antioxidant Activity**

Neurodegenerative diseases (NDs), such as Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS), are characterized by oxidative stress-induced neuronal damage. Oxidative stress arises from an imbalance between reactive oxygen species (ROS) and the antioxidant defense system, leading to lipid peroxidation, protein oxidation, and DNA damage (80). Emerging evidence suggests that phytochemicals—bioactive compounds derived from plants—exert significant neuroprotection through antioxidant mechanisms. Two primary pathways of antioxidant activity in neuroprotection include novel pathways of free radical scavenging and the upregulation of endogenous antioxidant systems.

- **Novel Pathways of Free Radical Scavenging**

Phytochemicals mitigate oxidative stress by directly scavenging free radicals and inhibiting the generation of ROS. Unlike traditional antioxidant molecules such as vitamin C and E, several plant-derived compounds engage in novel radical-neutralizing pathways.

1. Polyphenols and Flavonoids: These compounds, including quercetin, resveratrol, and curcumin, exhibit hydrogen-donating capabilities that stabilize free radicals, thereby reducing neuronal damage (81). Studies indicate that polyphenols enhance mitochondrial function, preventing ROS leakage from dysfunctional mitochondria (82).

2. Carotenoids and Terpenoids: These lipid-soluble antioxidants, such as astaxanthin and lycopene, integrate into cellular membranes, reducing lipid peroxidation and reinforcing neuronal membrane integrity (83).

3. Sulfur-Containing Compounds: Sulforaphane, a potent neuroprotective compound from cruciferous vegetables, activates nuclear factor erythroid 2-related factor 2 (Nrf2), enhancing cellular resilience against oxidative stress (84).

4. Chelation Therapy: Several phytochemicals, such as epigallocatechin gallate (EGCG), reduce iron-induced oxidative stress by chelating transition metals, thereby preventing Fenton reactions that amplify ROS generation (85).

- **Upregulation of Endogenous Antioxidant Systems**

Apart from directly scavenging ROS, phytochemicals activate endogenous antioxidant defense mechanisms, enhancing cellular resistance against oxidative stress.

1. **Nrf2-ARE Pathway Activation**: The Nrf2-antioxidant response element (ARE) pathway is the master regulator of oxidative stress resistance. Phytochemicals like curcumin, resveratrol, and sulforaphane upregulate Nrf2, leading to increased expression of antioxidant enzymes such as superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT) (86).

2. **Glutathione Enhancement**: Glutathione (GSH) is a crucial intracellular antioxidant that neutralizes ROS. Certain flavonoids boost GSH synthesis by increasing the expression of γ-glutamylcysteine synthetase (γ-GCS), the rate-limiting enzyme in GSH biosynthesis (87).

3. **Mitochondrial Protection**: Mitochondrial dysfunction exacerbates oxidative stress in neurodegenerative diseases. Phytochemicals like ginsenosides and anthocyanins enhance mitochondrial biogenesis, improve electron transport chain efficiency, and decrease oxidative burden within neurons (88).

4. **Reduction of Pro-Oxidative Enzymes**: Phytochemicals inhibit enzymes such as NADPH oxidase (NOX), cyclooxygenase-2 (COX-2), and inducible nitric oxide synthase (iNOS), all of which contribute to oxidative stress and neuroinflammation (89).

**B.Anti-inflammatory Effects**

Neuroinflammation plays a critical role in the progression of neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS). Chronic inflammation in the central nervous system (CNS) is primarily mediated by activated microglia and astrocytes, which release pro-inflammatory cytokines, chemokines, and reactive oxygen species (ROS). Excessive neuroinflammation leads to neuronal dysfunction and cell death. Phytochemicals—bioactive compounds derived from plants—have shown promise in modulating neuroinflammatory responses, thereby exerting neuroprotective effects. This section explores the role of phytochemicals in modulating neuroinflammatory signaling cascades and regulating microglial activation.

**Modulation of Neuroinflammatory Signaling Cascades**

Neuroinflammatory signaling cascades are primarily regulated by nuclear factor kappa B (NF-κB), mitogen-activated protein kinases (MAPKs), and Janus kinase/signal transducers and activators of transcription (JAK/STAT) pathways. These pathways mediate inflammatory responses by upregulating the expression of cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1β (IL-1β).

1. **NF-κB Pathway Inhibition**: NF-κB is a crucial transcription factor involved in neuroinflammation. Phytochemicals such as curcumin (from turmeric) and resveratrol (from grapes) suppress NF-κB activation by inhibiting IκB kinase (IKK) activity, preventing NF-κB translocation to the nucleus, and reducing pro-inflammatory cytokine production (90).

2. **MAPK Pathway Regulation**: The MAPK pathway, including p38 MAPK, extracellular signal-regulated kinases (ERKs), and c-Jun N-

terminal kinases (JNKs), plays a role in the regulation of inflammation-induced neuronal death. Polyphenols like epigallocatechin gallate (EGCG) from green tea attenuate p38 MAPK activation, thereby reducing neuroinflammation and promoting neuronal survival (91).

3. **JAK/STAT Pathway Suppression**: The JAK/STAT signaling pathway contributes to the production of inflammatory cytokines in neurodegenerative diseases. Flavonoids such as quercetin and luteolin inhibit STAT3 phosphorylation, thereby reducing the production of pro-inflammatory mediators (92).

**Regulation of Microglial Activation**

Microglia, the resident immune cells of the CNS, play a dual role in neuroprotection and neurotoxicity. Under pathological conditions, activated microglia release ROS, nitric oxide (NO), and cytokines that exacerbate neuronal damage. Regulating microglial activation is a promising strategy for neuroprotection.

1. **Shifting Microglial Phenotype**: Microglia exist in pro-inflammatory (M1) and anti-inflammatory (M2) states. Phytochemicals like ginsenosides from ginseng promote the transition of microglia from the M1 (pro-inflammatory) to the M2 (anti-inflammatory) phenotype by upregulating anti-inflammatory cytokines such as IL-10 and transforming growth factor-beta (TGF-β) (93).

2. **Inhibition of ROS and NO Production**: Overproduction of ROS and NO contributes to oxidative stress and neurodegeneration. Anthocyanins from berries reduce NO production by inhibiting inducible nitric oxide synthase (iNOS) expression in microglia (94).

3. **Suppression of Inflammasome Activation**: The NLRP3 inflammasome is a key regulator of neuroinflammatory responses in microglia. Natural compounds like berberine from Berberis species suppress NLRP3 inflammasome activation, thereby reducing IL-1β release and protecting neurons from inflammatory damage (95)

**C. Mitochondrial Function Enhancement**

Mitochondrial dysfunction is a hallmark of neurodegenerative diseases (NDs), such as Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD). The impairment of mitochondrial bioenergetics, excessive oxidative stress, and alterations in mitochondrial dynamics significantly contribute to neuronal death. Enhancing mitochondrial function through various approaches, particularly using phytochemicals, offers promising neuroprotective strategies. This section explores new insights into bioenergetics, mitochondrial dynamics, and phytochemical interventions for neuroprotection.

**New Insights into Bioenergetics and Neuroprotection**

Neurons are highly dependent on mitochondrial ATP production to sustain synaptic transmission, ion homeostasis, and neurotransmitter release. Bioenergetic failure leads to synaptic dysfunction, oxidative damage, and neuronal apoptosis, which are key contributors to neurodegeneration (96). Recent research highlights the importance of preserving mitochondrial function through improved oxidative phosphorylation (OXPHOS), enhanced ATP synthesis, and balanced reactive oxygen species (ROS) production (97,98).Several phytochemicals exhibit bioenergetic-enhancing properties. Polyphenols, such as resveratrol and curcumin, activate AMP-activated protein kinase (AMPK) and sirtuin-1 (SIRT1), both of which

regulate mitochondrial biogenesis and energy metabolism (99,100). Flavonoids, including quercetin and epigallocatechin gallate (EGCG), improve mitochondrial efficiency by increasing electron transport chain (ETC) activity and reducing ROS levels (101). Moreover, ginsenosides and alkaloids have been found to modulate mitochondrial permeability transition pore (mPTP) opening, preventing cytochrome c release and apoptosis (102,103).Additionally, coenzyme Q10 (CoQ10), a mitochondrial electron carrier, enhances ATP production and reduces oxidative stress, mitigating neurodegeneration in PD and AD models (104). Another critical pathway involves peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC-1α), a key regulator of mitochondrial biogenesis. Phytochemicals like berberine and kaempferol upregulate PGC-1α, promoting mitochondrial proliferation and function (105).

**Mitochondrial Dynamics and Phytochemical Interventions**

Mitochondrial dynamics, including fission, fusion, and mitophagy, play an essential role in maintaining neuronal health. An imbalance in these processes results in mitochondrial fragmentation, impaired bioenergetics, and increased oxidative stress, all of which are implicated in NDs (106).Mitochondrial fission, regulated by dynamin-related protein 1 (Drp1), is necessary for quality control but excessive fission leads to mitochondrial fragmentation and apoptosis (107). Phytochemicals such as curcumin and baicalein inhibit Drp1 activation, thereby reducing mitochondrial fragmentation and neurotoxicity (108). Conversely, mitochondrial fusion proteins, mitofusin-1 (Mfn1) and mitofusin-2 (Mfn2), facilitate mitochondrial networking and enhance ATP production. Resveratrol and sulforaphane have been shown to promote fusion and improve mitochondrial connectivity in neuronal cells (109).Mitophagy, the selective degradation of damaged mitochondria, is crucial for cellular homeostasis. Phytochemicals such as fisetin and luteolin activate PTEN-induced putative kinase 1 (PINK1) and Parkin-mediated mitophagy, clearing dysfunctional mitochondria and preventing neurodegeneration (110). Autophagy enhancers like spermidine also promote mitophagy, enhancing neuronal survival (111).Furthermore, phytochemicals like ginkgo biloba extract and rosmarinic acid modulate mitochondrial membrane potential and calcium homeostasis, thereby reducing excitotoxicity and apoptotic cascades in ND models (112).

**D. Protein Aggregation Inhibition**

Neurodegenerative diseases, such as Alzheimer's disease (AD), Parkinson's disease (PD), and other tauopathies, are characterized by the accumulation of misfolded and aggregated proteins. The formation of amyloid-beta (Aβ) plaques, tau tangles, and alpha-synuclein (α-syn) aggregates leads to neuronal dysfunction and cell death. Phytochemicals, derived from natural sources, have emerged as promising neuroprotective agents due to their potential in modulating protein aggregation pathways and preventing neurodegeneration.

**Targeting Amyloid-Beta and Tau Protein Aggregation**

Aβ plaques and tau tangles are the primary pathological hallmarks of AD. Aβ peptides, derived from the amyloid precursor protein (APP), aggregate into oligomers and fibrils, leading to synaptic dysfunction and neuroinflammation. Tau, a microtubule-associated protein, undergoes hyperphosphorylation and forms toxic fibrillar aggregates that disrupt neuronal function [113,114].

Phytochemicals such as polyphenols, flavonoids, and alkaloids have been extensively studied for their ability to inhibit Aβ aggregation and tau fibril formation. Curcumin, a polyphenol from *Curcuma longa*, has demonstrated strong anti-amyloidogenic properties by binding to Aβ oligomers, reducing fibril formation, and promoting disaggregation [115,116]. Similarly, resveratrol, a polyphenol found in grapes, inhibits Aβ oligomerization and promotes autophagic clearance of tau aggregates [117,118]. Epigallocatechin gallate (EGCG), a green tea catechin, interacts with Aβ fibrils, preventing their toxic effects and reducing tau hyperphosphorylation [119]. Other natural compounds, such as quercetin, genistein, and baicalein, have shown neuroprotective effects by modulating tau aggregation pathways. Quercetin reduces tau phosphorylation by inhibiting glycogen synthase kinase-3β (GSK-3β), a key enzyme involved in tau pathology [120]. Genistein, an isoflavone found in soy, decreases tau aggregation by modulating protein kinases and heat shock proteins (HSPs) [121]. Baicalein prevents tau fibrillization by binding to its monomeric form and stabilizing its native structure [122].

## Novel Approaches to Alpha-Synuclein Aggregation

Alpha-synuclein (α-syn) aggregation is a key pathological feature of PD and Lewy body dementias. The misfolding and accumulation of α-syn lead to mitochondrial dysfunction, oxidative stress, and neuroinflammation, ultimately resulting in dopaminergic neuron loss [123,124].Natural compounds have demonstrated potential in targeting α-syn aggregation through multiple mechanisms. Berberine, an isoquinoline alkaloid, reduces α-syn fibril formation and enhances autophagic clearance [125]. Silymarin, a flavonolignan from *Silybum marianum*, prevents α-syn oligomerization by modulating its fibrillization kinetics [126]. Polyphenols such as myricetin and nordihydroguaiaretic acid (NDGA) exhibit anti-aggregation properties by directly binding to α-syn fibrils and inhibiting their elongation [127,128]. Additionally, rosmarinic acid, found in rosemary, disrupts α-syn oligomerization and reduces its cytotoxic effects [129].Novel therapeutic strategies involving phytochemicals include nano-formulations and combination therapies. Nanoparticle-based delivery systems have been explored to enhance the bioavailability of neuroprotective phytochemicals [130]. For example, curcumin-loaded nanoparticles improve brain penetration and exert stronger anti-aggregation effects on α-syn fibrils [131]. Combination therapies, involving multiple phytochemicals targeting different aspects of protein aggregation, offer a promising approach for neuroprotection [132].

## Emerging Phytochemicals in Neurodegenerative Disease Research

Neurodegenerative diseases (NDs), such as Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD), pose significant challenges to global health. Increasing evidence suggests that phytochemicals—bioactive compounds derived from plants—offer promising neuroprotective benefits due to their anti-inflammatory, antioxidant, and anti-apoptotic properties. This review explores four emerging phytochemicals in neurodegenerative disease research: Curcumin analogs and derivatives, Resveratrol and its synergistic combinations, Cannabidiol and other non-psychoactive cannabinoids, and Sulforaphane and other isothiocyanates.

### A. Curcumin Analogs and Derivatives

Curcumin, the active compound in turmeric (Curcuma longa), has been widely studied for its neuroprotective effects, but its poor bioavailability limits its therapeutic potential. Researchers have developed curcumin analogs and derivatives to overcome this challenge. For instance, dimethoxycurcumin and bisdemethoxycurcumin exhibit enhanced stability and bioactivity. Additionally, synthetic analogs such as CBN-028 and curcumin-based nanoparticles have demonstrated improved blood-brain barrier (BBB) permeability and neuroprotective effects in preclinical models. These derivatives exhibit potent anti-inflammatory effects by modulating nuclear factor-kappa B (NF-κB) signaling and reducing oxidative stress through Nrf2 pathway activation [133-136].

### B. Resveratrol and Its Synergistic Combinations

Resveratrol, a polyphenolic compound found in grapes and red wine, has shown promise in ameliorating neurodegeneration. It exerts neuroprotection via sirtuin 1 (SIRT1) activation, leading to enhanced mitochondrial function and reduced amyloid-beta (Aβ) toxicity in AD models. However, its poor solubility and rapid metabolism hinder its clinical efficacy. Recent studies highlight the synergistic potential of resveratrol with compounds such as pterostilbene, quercetin, and epigallocatechin gallate (EGCG). These combinations enhance bioavailability and promote neuroprotection by reducing tau hyperphosphorylation and improving synaptic plasticity [137-141].

### C. Cannabidiol and Other Non-Psychoactive Cannabinoids

Cannabidiol (CBD), a non-psychoactive cannabinoid derived from Cannabis sativa, has garnered attention for its neuroprotective potential in NDs. Unlike tetrahydrocannabinol (THC), CBD does not induce psychoactive effects but interacts with cannabinoid receptors (CB1 and CB2) to modulate neuroinflammation, oxidative stress, and excitotoxicity. Preclinical studies suggest that CBD reduces neuroinflammation in models of AD and PD by inhibiting microglial activation and reducing pro-inflammatory cytokines. Other cannabinoids, such as cannabigerol (CBG) and cannabidivarin (CBDV), also show neuroprotective effects by modulating endocannabinoid signaling and mitochondrial function [142-143]

| Phytochemical | Natural Source | Neuroprotective Mechanisms | Targeted Neurodegenerative Diseases | Challenges | Reference |
|---|---|---|---|---|---|
| **Curcumin** | *Curcuma longa* (Turmeric) | Antioxidant, Anti-inflammatory, Inhibits amyloid-beta aggregation, Mitochondrial protection | Alzheimer's (AD), Parkinson's (PD), Huntington's (HD) | Poor bioavailability, Rapid metabolism | [146] |
| **Resveratrol** | Grapes, Red Wine, Peanuts | Antioxidant, SIRT1 activator, Mitochondrial enhancer, Anti-inflammatory | AD, PD, Amyotrophic lateral sclerosis (ALS) | Low stability, Limited brain penetration | [147] |
| **Quercetin** | Onions, Apples, Berries | Antioxidant, Anti-inflammatory, Modulates | AD, PD, HD | Low water solubility, | [148] |

| | | | | | |
|---|---|---|---|---|---|
| | | autophagy, Reduces oxidative stre | | Rapid excretion | |
| **Epigallocatechin gallate (EGCG)** | Green Tea | Antioxidant, Anti-inflammatory, Prevents amyloid-beta toxicity, Enhances synaptic plasticity | AD, PD | Gastrointestinal degradation, Low bioavailability | [149] |
| **Ginsenosides** | *Panax ginseng* | Neurogenesis stimulator, Antioxidant, Reduces neuroinflammation, Enhances cognition | AD, PD, Stroke recovery | Variable extract standardization, High metabolism | [150] |

### D. Sulforaphane and Other Isothiocyanates

Sulforaphane, an isothiocyanate derived from cruciferous vegetables like broccoli, has been identified as a potent activator of the Nrf2 pathway, which regulates antioxidant defenses. Sulforaphane enhances glutathione synthesis, reduces neuroinflammation, and protects against protein aggregation in ND models. Studies indicate its potential in AD by attenuating Aβ-induced oxidative stress and synaptic dysfunction. Other isothiocyanates, such as allyl isothiocyanate and phenethyl isothiocyanate, exhibit similar neuroprotective properties through epigenetic modulation and anti-inflammatory pathways [144].

### E. Quercetin

Quercetin, a flavonoid found in various fruits and vegetables, exhibits significant neuroprotective potential through its antioxidant, anti-inflammatory, and anti-apoptotic properties. It effectively scavenges reactive oxygen species (ROS), reducing oxidative stress—a major factor in neurodegenerative diseases like Alzheimer's and Parkinson's. Additionally, quercetin suppresses pro-inflammatory cytokine release, mitigating neuroinflammation. It modulates critical pathways such as NF-κB (reducing inflammation), sirtuins (promoting neuronal survival), and PI3K/Akt (enhancing cell growth and protection). Preclinical studies suggest its efficacy in alleviating neurodegenerative symptoms, highlighting its therapeutic potential despite challenges like low bioavailability. [145]

## Innovative Delivery Systems for Enhanced Bioavailability

Neurodegenerative diseases (NDs) such as Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD) pose significant therapeutic challenges due to the limited bioavailability of neuroprotective phytochemicals. Various innovative delivery systems have emerged to enhance the bioavailability and therapeutic efficacy of these compounds. This review discusses four key approaches: nanoencapsulation techniques, lipid-based delivery systems, exosome-mediated delivery, and blood-brain barrier (BBB) penetration strategies.

### A. Nanoencapsulation Techniques

Nanoencapsulation improves the stability, solubility, and targeted delivery of phytochemicals, enhancing their bioavailability and efficacy. Nanocarriers such as polymeric nanoparticles, liposomes, and micelles have

shown promise in delivering neuroprotective compounds across biological barriers.

1. **Polymeric nanoparticles:** Biodegradable polymers like poly(lactic-co-glycolic acid) (PLGA) and chitosan have been used to encapsulate curcumin and resveratrol, improving their pharmacokinetics and brain uptake [151]
2. **Liposomes:** Phospholipid-based vesicles provide sustained drug release and protect against enzymatic degradation, increasing the stability of flavonoids and alkaloids used in NDs [152]
3. **Dendrimers:** Highly branched nanoscale polymers that enhance solubility and enable controlled drug release, benefiting phytochemicals such as quercetin and catechins [153]

**B. Lipid-Based Delivery Systems**

Lipid-based carriers enhance the lipophilicity and absorption of poorly soluble phytochemicals, facilitating their uptake into the central nervous system (CNS).

1. **Solid lipid nanoparticles (SLNs):** These nanoparticles enhance the stability and bioavailability of curcumin and epigallocatechin gallate (EGCG) [154]
2. **Nanostructured lipid carriers (NLCs):** These carriers have a flexible lipid matrix that improves drug loading capacity and reduces burst release, aiding in neuroprotection [155]
3. **Self-emulsifying drug delivery systems (SEDDS):** Lipid-based formulations that spontaneously form nano-emulsions in the gastrointestinal tract, increasing the permeability and absorption of phytochemicals [156]

**C. Exosome-Mediated Delivery**

Exosomes are naturally occurring extracellular vesicles that facilitate targeted delivery of bioactive compounds to the brain.

1. **Neural exosome-based transport:** Exosomes derived from neural stem cells can carry curcumin and resveratrol, improving their stability and bioavailability [157]
2. **Functionalized exosomes:** Engineered exosomes with surface modifications enhance their ability to cross the BBB and deliver therapeutic molecules [158]
3. **Exosome-mimetic nanocarriers:** Synthetic vesicles that mimic exosome properties to improve drug loading and targeting [159]

**D. Blood-Brain Barrier Penetration Strategies**

The BBB presents a major challenge in delivering neuroprotective phytochemicals. Several novel strategies have been developed to enhance BBB penetration.

1. **Receptor-mediated transcytosis (RMT):** Targeting transporters such as transferrin and low-density lipoprotein (LDL) receptors facilitates the uptake of curcumin and resveratrol [160]
2. **Nanocarrier surface modification:** Coating nanoparticles with ligands like lactoferrin and TAT peptides improves BBB penetration and drug accumulation in the brain [161]
3. **Ultrasound and magnetic targeting:** Low-intensity ultrasound and magnetic nanoparticles enhance drug delivery across the BBB by transiently opening tight junctions [162]

**Personalized Phytochemical Therapies in Neurodegenerative Diseases**

Neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS) exhibit significant genetic and molecular heterogeneity, making conventional treatment strategies less effective in many cases. Personalized phytochemical therapies, leveraging nutrigenomics and pharmacogenomics, offer a promising approach to tailoring interventions to individual patients. These therapies aim to optimize the effects of bioactive compounds based on genetic, metabolic, and disease-specific profiles.

### A. Nutrigenomics and Pharmacogenomics Approaches

Nutrigenomics and pharmacogenomics focus on understanding how genetic variations influence an individual's response to dietary components and drugs, respectively. Phytochemicals such as polyphenols, flavonoids, and alkaloids can modulate gene expression and metabolic pathways involved in neurodegeneration [163]. For example, curcumin from *Curcuma longa* has been shown to regulate the expression of genes associated with neuroinflammation and oxidative stress, including nuclear factor erythroid 2-related factor 2 (Nrf2) and nuclear factor-kappa B (NF-κB) pathways. In AD patients with APOE4 polymorphism, curcumin has demonstrated differential efficacy in reducing amyloid-beta (Aβ) deposition compared to APOE3 carriers. Similarly, resveratrol, a polyphenol from grapes, influences sirtuin-1 (SIRT1) expression, which is crucial in neuroprotection, but its effectiveness varies based on genetic variations in SIRT1-related pathways [164]. Another example includes catechins from green tea (*Camellia sinensis*), which have been found to interact with brain-derived neurotrophic factor (BDNF) signaling pathways. Individuals with polymorphisms in the BDNF gene exhibit varying responses to catechin supplementation, affecting cognitive outcomes in neurodegenerative conditions [165]. Such findings underscore the importance of pharmacogenomics in designing personalized phytochemical interventions.

### B. Tailoring Phytochemical Interventions to Specific Neurodegenerative Conditions

Different neurodegenerative diseases involve distinct molecular mechanisms, necessitating tailored phytochemical approaches. For AD, phytochemicals like quercetin and genistein have been identified as potential therapeutic agents due to their ability to inhibit tau hyperphosphorylation and Aβ aggregation. In contrast, PD treatment strategies focus on modulating dopaminergic signaling, where compounds like berberine and ginsenosides have shown promise in protecting dopaminergic neurons and reducing α-synuclein aggregation [166]. In ALS, oxidative stress and mitochondrial dysfunction play a critical role in disease progression. Phytochemicals such as sulforaphane, found in cruciferous vegetables, activate Nrf2 pathways, offering neuroprotection in ALS models. Similarly, astaxanthin, a marine carotenoid, has demonstrated the potential to mitigate neuroinflammation and enhance mitochondrial function in ALS and multiple sclerosis (MS) [167]. A personalized approach also considers metabolic differences in individuals. For instance, variations in gut microbiota composition influence the bioavailability and metabolism of polyphenols. Studies have shown that individuals with higher levels of gut bacteria capable of metabolizing ellagitannins from pomegranates exhibit greater neuroprotective effects due to the conversion of these compounds into bioactive urolithins [168,169].

### C. Combination Therapies with Synthetic Drugs

Combining phytochemicals with conventional neuroprotective drugs offers a synergistic approach to treatment. Several studies have explored the potential of phytochemicals in enhancing the efficacy of existing pharmacological treatments while reducing side effects. In AD, combining curcumin with acetylcholinesterase inhibitors (AChEIs) such as donepezil has been shown to improve cognitive function more effectively than monotherapy. Similarly, resveratrol has been studied in combination with memantine, an N-methyl-D-aspartate (NMDA) receptor antagonist, to enhance neuroprotection through antioxidant and anti-inflammatory mechanisms [170,171]. For PD, co-administration of EGCG with levodopa has been investigated for its potential to enhance dopaminergic neuron survival and reduce levodopa-induced oxidative stress . Additionally, berberine combined with monoamine oxidase B (MAO-B) inhibitors such as selegiline has demonstrated improved neuroprotection in PD models .In ALS, co-treatment with sulforaphane and riluzole, the only FDA-approved drug for ALS, has been reported to enhance motor neuron survival and delay disease progression [172,173].

## Challenges and Future Directions in Phytochemical-Based Neuroprotection

Phytochemicals hold immense promise for neurodegenerative disease therapy due to their antioxidant, anti-inflammatory, and neuroprotective properties. However, several challenges hinder their clinical translation, including poor bioavailability, potential toxicity, lack of standardization, and complexities in clinical trial design. Addressing these limitations will be essential for optimizing phytochemical-based interventions for neurodegenerative disorders.

### A. Improving Bioavailability and Brain Penetration

One of the major challenges in phytochemical therapy is their poor bioavailability and limited ability to cross the blood-brain barrier (BBB). Many bioactive compounds have low solubility, rapid metabolism, and poor systemic absorption, which reduce their therapeutic efficacy [174]. For instance, curcumin, a widely studied neuroprotective phytochemical, has limited bioavailability due to its rapid metabolism and poor intestinal absorption. Similarly, resveratrol undergoes extensive first-pass metabolism, significantly reducing its concentration in the brain [175]. To overcome these limitations, novel drug delivery approaches such as nanoformulations, liposomal encapsulation, and prodrug modifications are being explored. Nanoemulsion and polymer-based nanoparticles have shown promising results in improving phytochemical bioavailability. For example, curcumin-loaded nanoparticles have demonstrated enhanced brain penetration and neuroprotective effects in Alzheimer's disease (AD) models [176]. Likewise, liposomal resveratrol formulations have exhibited increased stability and prolonged circulation time in vivo. Future research should focus on optimizing these formulations for clinical applications.[177]

### B. Addressing Potential Toxicity and Drug Interactions

Although phytochemicals are derived from natural sources, they are not entirely free from toxicity risks or adverse interactions with conventional drugs. High doses of certain compounds may lead to hepatotoxicity, nephrotoxicity, or gastrointestinal distress [178]. For example, excessive intake of green tea catechins has been linked to liver toxicity in some individuals. Similarly, berberine, a promising neuroprotective

alkaloid, can interfere with cytochrome P450 enzymes, affecting the metabolism of various drugs. Polyphenols such as quercetin and genistein may also interact with anticoagulants, posing risks for patients on blood-thinning medications [179]. To ensure safety, preclinical toxicity studies and pharmacokinetic analyses must be conducted before advancing phytochemicals to clinical trials. Additionally, systematic evaluations of potential drug interactions should be performed to guide safe co-administration with existing neuroprotective agents.

### C. Standardization of Phytochemical Extracts

Another critical challenge in phytochemical research is the variability in the composition of plant-derived extracts. The concentration of active compounds can vary depending on the source, extraction method, and storage conditions, making it difficult to achieve consistent therapeutic effects [180]. For instance, variations in ginsenoside content in *Panax ginseng* extracts can lead to differences in neuroprotective efficacy . Similarly, the bioactive content of *Ginkgo biloba* extracts depends on the extraction process, affecting their cognitive benefits [181]. To address this issue, advanced analytical techniques such as high-performance liquid chromatography (HPLC) and mass spectrometry should be used for standardization. Developing standardized reference materials and regulatory guidelines will ensure batch-to-batch consistency, enhancing reproducibility in clinical studies.

### D. Clinical Trial Design and Implementation

Despite promising preclinical data, the translation of phytochemicals into clinical neuroprotective therapies has been slow due to limitations in trial design and implementation. Many clinical studies suffer from small sample sizes, short durations, and lack of rigorous control groups [182]. For example, some trials evaluating curcumin in AD patients have reported inconclusive results due to poor study design and inadequate outcome measures. Similarly, resveratrol trials have faced challenges in demonstrating clear cognitive benefits, partly due to variability in dosing regimens [183]. To improve the reliability of clinical trials, standardized protocols should be established, including appropriate patient selection criteria, longer follow-up periods, and objective biomarkers for neurodegeneration. Multi-center randomized controlled trials (RCTs) with sufficient statistical power are essential to validate the therapeutic potential of phytochemicals in neurodegenerative diseases.

### E. Integration with Conventional Therapies

Phytochemicals are unlikely to replace conventional neurodegenerative disease treatments but may serve as complementary therapies. However, integrating natural compounds with existing drugs requires careful evaluation of synergistic effects and potential contraindications. For instance, combining curcumin with acetylcholinesterase inhibitors (AChEIs) like donepezil has shown additive neuroprotective effects in AD models [184]. In Parkinson's disease (PD), co-administration of resveratrol with levodopa has been suggested to reduce oxidative stress and enhance dopaminergic neuron survival . A personalized approach to therapy, considering genetic, metabolic, and disease-specific factors, will be critical for optimizing phytochemical integration. Precision medicine strategies should be explored to tailor interventions based on individual patient profiles.[185]

## VIII. Conclusion

Phytochemicals have emerged as promising neuroprotective agents due to their antioxidant,

anti-inflammatory, and neuroprotective properties, with key compounds like curcumin, resveratrol, quercetin, and EGCG demonstrating potential in mitigating neurodegenerative disease pathology. Their ability to modulate oxidative stress, neuroinflammation, and protein aggregation highlights their therapeutic significance in Alzheimer's, Parkinson's, and other neurodegenerative disorders. Despite these benefits, challenges such as poor bioavailability and limited blood-brain barrier penetration necessitate advanced drug delivery strategies, including nanoformulations and synthetic derivatives, to enhance efficacy. The integration of phytochemicals into conventional neurodegenerative treatment regimens could offer a complementary, multi-targeted approach for disease management. Future research should focus on optimizing formulations, conducting rigorous clinical trials, and developing standardized therapeutic strategies to fully harness the neuroprotective potential of phytochemicals, ultimately paving the way for innovative and effective treatments for neurodegenerative diseases.

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