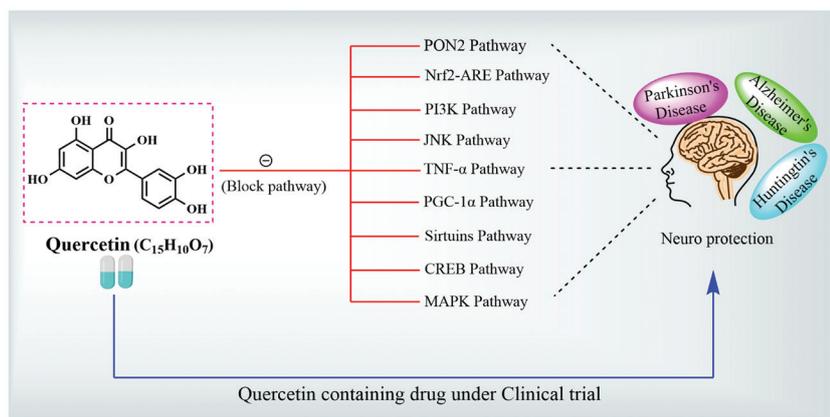


Mechanistic Insights and Therapeutic Potential of Quercetin in Neuroprotection: A Comprehensive Review of Pathways and Clinical Perspectives

Graphical abstract



Highlights

- This review explores quercetin's multi-targeted neuroprotective mechanisms in AD, PD, and HD.
- It describes the modulation of Nrf2-ARE, PI3K/Akt, MAPK, and PON2 pathways.
- It also demonstrates SAR-based insights linking quercetin's structure to its therapeutic actions.
- Novel delivery strategies to overcome bioavailability challenges are emphasized.
- It advocates for quercetin's role in precision medicine and translational neurotherapeutics.

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In brief

This review critically examines quercetin's multifaceted neuroprotective effects across Alzheimer's, Parkinson's, and Huntington's diseases. Emphasis is placed on mechanistic pathways, including oxidative stress, inflammation, mitochondrial dysfunction, and protein aggregation, and translational relevance. Integration of SAR, pharmacokinetics, and delivery systems highlights quercetin's promise as a multi-targeted therapeutic in neurodegenerative disease management and precision neurotherapeutics.

Mechanistic Insights and Therapeutic Potential of Quercetin in Neuroprotection: A Comprehensive Review of Pathways and Clinical Perspectives

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Abstract

Quercetin, a bioactive flavonoid abundant in diverse plant species, has been extensively investigated for its neuroprotective properties against neurodegenerative diseases (NDDs), such as Alzheimer's, Parkinson's, and Huntington's diseases. This review systematically explored the multifaceted therapeutic potential of quercetin, emphasizing the mechanisms of action, pharmacologic efficacy, and translational significance in modern neurotherapeutics. Quercetin demonstrated potent antioxidant effects by scavenging reactive oxygen species and modulating the Nrf2-ARE pathway, thereby mitigating oxidative stress, a hallmark of NDDs associated with mitochondrial dysfunction, protein aggregation, and neuronal apoptosis. Furthermore, the ability of quercetin to regulate the PI3K/Akt pathway promoted mitochondrial biogenesis and preserved neuronal integrity by stabilizing membrane potential. Anti-inflammatory effects were evident vis-a-vis inhibition of the NF- κ B and MAPK pathways, suppression of microglial activation, and cytokine release. In addition, quercetin disrupted tau hyperphosphorylation via GSK3 β inhibition and attenuated amyloid-beta toxicity, offering cognitive protection. Preclinical studies highlighted the ability of quercetin to modulate excitotoxicity and enhance neuroplasticity, while emerging evidence support synergy of quercetin with existing pharmacologic agents. Genetic variations influencing key pathways, including Nrf2 and PI3K, underscore the necessity for personalized therapeutic approaches. Advances in drug delivery systems, scaffold modelling, and CRISPR-mediated interventions revealed the potential for optimizing the bioavailability and specificity of quercetin. This review bridges critical knowledge gaps by integrating mechanistic insights with clinical perspectives, advocating for translating quercetin-based therapies into precision medicine. By addressing challenges in bioavailability and exploring innovative strategies, this article underscores the promise of quercetin as a cornerstone for neuroprotective interventions in NDDs.

Keywords

Inflammatory pathways, neurodegenerative diseases, neuroprotection, oxidative stress, quercetin, therapeutic potential.

Introduction

Quercetin, a bioactive flavonoid, has emerged as a significant neuroprotective agent with multifaceted therapeutic potential in combating neurodegenerative diseases (NDDs), such as Alzheimer's (AD), Parkinson's (PD), and Huntington's diseases (HD) [1]. These progressive disorders, driven by mechanisms like oxidative stress, mitochondrial dysfunction, neuro-inflammation, and apoptotic pathways, represent a growing global health burden with limited curative options [2, 3]. This review aims to comprehensively elucidate the role of quercetin in mitigating these pathologic processes, emphasizing the underlying molecular mechanisms,

pharmacologic applications, and future clinical perspectives. Drawing upon extensive findings, including the findings in the provided documents, the review sought to bridge knowledge gaps and underscore the relevance of quercetin in modern neurotherapeutics. The therapeutic potential of quercetin lies in robust antioxidant activity of quercetin, mediated by an ability to scavenge reactive oxygen species (ROS) and enhance the nuclear factor erythroid 2-related factor 2 (Nrf2)-ARE pathway [4]. This mechanism is pivotal in reducing oxidative stress, a hallmark of NDDs that exacerbates protein aggregation, mitochondrial damage, and neuronal apoptosis [5]. The structural components of quercetin, including hydroxyl groups

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and conjugated systems, further augment the efficacy of quercetin in targeting ROS and inhibiting lipid peroxidation. These properties have been validated *in vitro* and *in vivo*, demonstrating protection against amyloid-beta (A β) accumulation in AD models and α -synuclein fibrillization in PD [6, 7]. Mitochondrial dysfunction, another critical factor in NDDs, is effectively countered by quercetin [3]. Quercetin enhances mitochondrial biogenesis and maintains membrane potential by modulating the PI3K/Akt pathway, thereby reducing apoptosis and energy deficits [8]. Studies highlight the ability of quercetin to restore mitochondrial function in HD models, mitigating oxidative damage and preserving neuronal integrity. Furthermore, the ability of quercetin to inhibit glycogen synthase kinase-3 β (GSK3 β) disrupts tau (τ) hyperphosphorylation and A β toxicity, offering neuroprotection against cognitive decline in AD [9]. The anti-inflammatory properties of quercetin suppress microglial activation and cytokine release, primarily through the NF- κ B and mitogen-activated protein kinase (MAPK) pathways, thereby minimizing neuroinflammation, a driving force behind neuronal damage in AD and PD [10]. Additionally, the interaction of quercetin with the paraoxonase-2 (PON2) pathway enhances antioxidant capacity, further protecting neurons from inflammatory and oxidative insults [11]. Quercetin mitigates excitotoxicity in HD by modulating glutamate receptor activity, which provides neuroprotection against excitatory amino acid-induced damage [12]. Emerging studies underscore the potential of quercetin in precision medicine. Genetic polymorphisms influencing the efficacy of the Nrf2 and PI3K pathways necessitate personalized approaches to optimize quercetin therapy [13]. The integration of quercetin with existing pharmacologic agents, such as cholinesterase inhibitors in AD, exemplifies the synergistic potential of quercetin [14]. Moreover, the ability of quercetin to target gene expression, as occurs with CRISPR-modulated SIRT1 activation, opens avenues for combination therapies addressing the multifactorial nature of NDDs [15]. The structural analogs of quercetin (scaffold modelling), derived through rational design and computational modelling, promise enhanced specificity and potency against neurodegenerative targets [16]. The inclusion of marine-derived flavonoids and other polyphenols in quercetin-based research broadens the scope for novel therapeutics [17]. This review evaluated current knowledge and highlighted future directions, emphasizing the need for innovative strategies to enhance the clinical translation of quercetin. The integration of advanced drug delivery systems, personalized medicine, scaffold-based drug development, and computational modelling enhances specificity and potency against neurodegenerative targets.

Sources of quercetin from nature

The term, quercetin, originated from the Latin word, quercetum, in 1857 and refers to oak, reflecting the natural prevalence of quercetin in plant ecosystems [18]. Quercetin is

commonly found as glycosides, such as rutin, isoquercetin, and hyperin. Quercetin is a potent plant antioxidant that protects the human body from oxidative damage and offers numerous health benefits [19]. Quercetin is abundant in fruits (apples, grapes, and berries) and vegetables (onions, garlic, and tomatoes). In addition, quercetin is present in medicinal plants and extracted from the leaves, fruits, or flowering tops with these sources being particularly rich in quercetin [20, 21]. **Table 1** describes the biological sources of quercetin (quercetin is extracted from parts of plants under different families).

Dose-dependent effects, administration regimens, and toxicologic considerations

Dose-dependent biphasic effects of quercetin

Quercetin exhibits a biphasic dose-response curve (hormesis), i.e., low-to-moderate doses confer neuroprotection and high doses induce cytotoxicity. *In vitro* studies indicated that concentrations < 10–20 μ M are generally neuroprotective via antioxidant and anti-inflammatory effects [6]. However, a quercetin concentration >50 μ M may result in mitochondrial membrane disruption, DNA damage, and pro-oxidant activity [22]. Animal models have revealed that chronic administration > 50 mg/kg/day may impair hepatic antioxidant defenses and trigger apoptotic pathways in non-target cells [23].

Pharmacokinetics and bioavailability challenges

Oral bioavailability of quercetin is low (< 10%) due to poor water solubility, gastrointestinal degradation, and rapid phase II metabolism [24]. Quercetin undergoes extensive glucuronidation, sulfation, and methylation in the liver and intestines, limiting the concentration in the systemic circulation. Peak plasma concentrations of quercetin following a typical dietary intake (~100 mg/day) rarely exceed 1–2 μ M, which is significantly lower than doses used in *in vitro* models [25, 26].

Routes of administration and novel delivery systems

Novel delivery strategies, nanoparticles, liposomes, solid lipid carriers, and PEGylated formulations have been developed to overcome poor oral absorption, enhance CNS penetration, and protect the compound from rapid metabolism. Intranasal administration has emerged as a promising non-invasive route for direct delivery to the brain, bypassing the blood-brain barrier (BBB) [27, 28].

Table 1 Sources of Quercetin From Nature

Serial No.	Family	Scientific Names	Common Names	Quercetin Presence in Plant Parts	References
1.	Amaryllidaceae	<i>Allium cepa</i>	Onion (red)	Bulb	[195]
		<i>Allium sativum L.</i>	Garlic	Leaves, cloves	
2.	Moraceae	<i>Morus alba</i>	White mulberry	Leaves	[196]
3.	Rosaceae	<i>Cydonia oblonga</i>	Quince	Fruits, leaves	[197]
		<i>Malus domestica</i>	Apple	Fruits	[198]
		<i>Prunus avium</i>	Sweet cherry	Leaves, fruits, flowers, stems	[199]
		<i>Prunus domestica</i>	European plum, Prune plum, Bullace, Damson, Dawson, Gage, Gardalu, and Greengage	Fruit	[200]
4.	Moringaceae	<i>Moringa oleifera</i>	Drumstick tree	Leaves, flowers	[201]
5.	Lythraceae	<i>Punica granatum</i>	Pomegranate	Fruits	[202]
6.	Sapotaceae	<i>Achras sapota</i>	Sapodilla	Fruits	[3]
7.	Lamiaceae	<i>Mentha piperita L.</i>	Peppermint	Leaves, herbs	[203]
		<i>Mentha spicata</i>	Spearmint	Leaves, herbs	[204]
8.	Rhamnaceae	<i>Rhamnus alaternus</i>	Buckthorn	Bark	[205]
9.	Asteraceae	<i>Achillea millefolium L.</i>	Yarrow	Flowering top	[206]
		<i>Lactuca sativa</i>	Lettuce	Leaves	[207]
10.	Ginkgoaceae	<i>Ginkgo biloba</i>	Maidenhair tree	Leaves	[208]
11.	Anacardiaceae	<i>Mangifera indica</i>	Mango	Fruits	[209]
12.	Compositae	<i>Cichorium intybus</i>	Chicory	Leaves	[210]
13.	Ericaceae	<i>Vaccinium myrtillus</i>	Blueberry, bilberry	Fruits	[211]
		<i>Vaccinium oxycoccus</i>	Cranberry	Fruits, leaves	[212]
14.	Theaceae	<i>Camellia sinensis</i>	Green tea	Leaves	[213]
15.	Brassicaceae	<i>Brassica oleracea var. Italica</i>	Broccoli	Leaves, flower	[214]
		<i>Brassica oleracea var. Sabellica</i>	Kale	Leaves	[215]
		<i>Nasturtium officinale</i>	Watercress	Flowers, leaves, stem	[216]
16.	Hypericaceae	<i>Hypericum perforatum L.</i>	St. John's wort	Aerial parts (leaves, flowers)	[217, 218]
17.	Apiaceae	<i>Centella asiatica</i>	Indian pennywort, spade leaf, coin worth, or gotu kola	Leaves	[219]
		<i>Apium graveolens L.</i>	Celery	Seeds	[220]
		<i>Coriandrum sativum</i>	Cilantro, Chinese parsley	Leaves, seeds	[221]
18.	Chenopodiaceae	<i>Spinacia oleracea</i>	Spinach	Leaves	[222]
19.	Maleaceae	<i>Azadirachta indica</i>	Neem	Leaves, bark	[223]
20.	Fabaceae	<i>Mimosa pudica</i>	“Touch me not” or “Sensitive plant”	Whole plant	[224]
		<i>Sesbania grandiflora</i>	Agati, Corkwood tree, and West Indian pea	Leaves	[225]
		<i>Delonix regia</i>	Gulmohar	Leaves	[226]
21.	Cannabaceae	<i>Cannabis sativa</i>	Hemp, marijuana	Leaves	[227]
22.	Acanthaceae	<i>Andrographis paniculata</i>	Kalmegh	Leaves	[228]
		<i>Justicia adhatoda</i>	Basak	Leaves	[229]
23.	Libiatae	<i>Ocimum sanctum</i>	Tulshi	Leaves	[230]
24.	Musaceae	<i>Musa acuminata</i>	Colla, banana	Fruit pulp	[231]
25.	Solanaceae	<i>Solanum lycopersicum</i>	Tomato	Fruit, seeds	[232, 233]

Clinical considerations and therapeutic index

The therapeutic window for quercetin is narrow and may vary based on individual metabolic capacity, genetic polymorphisms (e.g., UGT and COMT), and co-morbid diseases. There is an urgent need for standardized clinical trials evaluating dose escalation, long-term safety, and pharmacokinetic-pharmacodynamic (PK-PD) correlations. Personalized medicine approaches may be required to tailor quercetin dosages, especially in patients with

neurodegenerative disorders who may have altered hepatic or renal function [29].

Molecular mechanisms of quercetin-induced cellular damage at high concentrations

Mitochondrial membrane disruption

Quercetin accumulates within mitochondria at high concentrations, destabilizing the mitochondrial membrane

potential. This effect occurs due to the interaction of quercetin with inner mitochondrial membrane phospholipids, especially cardiolipin, leading to permeabilization. Mitochondrial permeability transition pores (mPTPs) open, causing cytochrome c release, calcium dysregulation, ATP depletion, and ultimately initiating intrinsic apoptosis [30].

Pro-oxidant activity

Quercetin exhibits dual redox properties. Quercetin scavenges ROS at physiologic concentrations. However, quercetin undergoes autoxidation at supra-physiologic levels, forming semiquinone radicals and quercetin-quinone (QQ) species. These intermediates deplete intracellular glutathione (GSH), elevate hydrogen peroxide (H₂O₂), and catalyze Fenton reactions with transition metals (Fe²⁺ and Cu²⁺), producing hydroxyl radicals and exerting oxidative stress [31].

DNA damage and genotoxicity

Quercetin-quinone metabolites can covalently bind to DNA and nucleophilic cellular proteins, leading to strand breaks and chromatin damage. Studies using the Comet assay and micronucleus formation *in vitro* have revealed that high-dose quercetin (≥ 100 μM) causes double-stranded DNA breaks, chromosomal aberrations, and p53 pathway activation, potentially inducing cell cycle arrest or apoptosis [32].

Interference with cellular enzymes

At cytotoxic levels, quercetin inhibits topoisomerase II, impairs telomerase function, and alters redox-sensitive transcription factors (NF-κB and AP-1) in a deleterious manner. This suppression disrupts normal cellular repair and survival processes, contributing to carcinogenic risk under chronic high-dose exposure [33].

These findings emphasize the importance of careful dose calibration and duration of administration. While quercetin is generally regarded as safe at dietary levels, high-dose, long-term use, especially in the supplement form, requires caution and additional pharmacovigilance.

Description of chemical structure and pharmacokinetics of quercetin for the multifaceted neuroprotective potential in NDDs

Chemical structure

Quercetin, a prominent flavonoid belonging to the flavonol subclass, has the following molecular formula: C₁₅H₁₀O₇

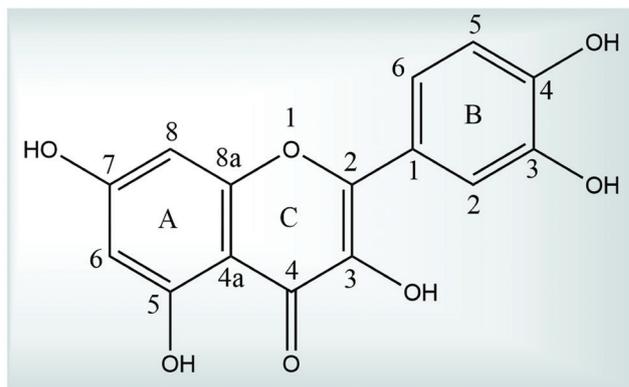


Figure 1 Chemical structure of quercetin.

[34]. Structurally, quercetin consists of two aromatic rings (A and B) connected by a heterocyclic pyrone (C ring) with five hydroxyl groups at positions 3, 3', 4', 5, and 7 [35]. This polyphenolic configuration allows quercetin to scavenge free radicals, making quercetin one of the most potent antioxidants among dietary polyphenols. Quercetin also exists as glycosides, in which a glycosyl group attaches to the hydroxyl group (typically at position 3), which enhances solubility in aqueous media and reduces the free radical scavenging potential (Figure 1) [35, 36].

Pharmacokinetics

Quercetin undergoes passive diffusion and is absorbed in the glycosidic and aglycone forms via organic anion-transporting polypeptides (OATPs) in the small intestine. Quercetin is rapidly metabolized inside the liver, intestines, and kidneys upon absorption and forms conjugated forms, such as glucuronides, sulfates, and methylated derivatives. The bioavailability of quercetin, which ranges from 0–50%, is considered poor due to extensive first-pass metabolism and rapid clearance with a half-life of 1–2 h. Strategies to overcome these limitations include the development of nano-formulations, such as nanoparticles, micelles, and mucoadhesive emulsions, which enhance bioavailability and brain penetration [3, 37].

Quercetin undergoes extensive and rapid metabolism after dietary absorption, which explains why the pharmacologic effects are more prominent in *in vitro* studies compared to *in vivo* conditions [38, 39]. The limitations of quercetin, including poor bioavailability, aqueous solubility, permeability, and instability, have restricted the application of quercetin for neurodegenerative diseases. Several studies have focused on structural modifications to address these challenges, improve these properties, and enhance the neuroprotective potential [3, 40]. Innovative formulations, such as quercetin-loaded gels, nanoparticles, polymeric micelles, and mucoadhesive nanoemulsions, have been developed to boost brain bioavailability [41]. Structural alterations, such as conjugation, have also improved the scavenging and antioxidant activities of quercetin [42].

Structure-activity relationship (SAR) of quercetin with the neuroprotective mechanism

The neuroprotective mechanisms underlying quercetin are intricately linked to the SAR because the polyphenolic structure governs interactions with cellular targets and molecular pathways critical in combating neurodegeneration (Figure 2). Below is a detailed correlation between the SAR of quercetin and the neuroprotective mechanisms.

Antioxidant activity and free radical scavenging

SAR insight

The -OH groups at positions 3, 5, and 7 (A and C rings) and the ortho-dihydroxy structure in ring B significantly enhance the radical scavenging ability of quercetin. These groups stabilize ROS by donating hydrogen atoms, which neutralizes free radicals [43, 44].

Mechanistic correlation

Quercetin mitigates oxidative stress by scavenging ROS and reactive nitrogen species (RNS), which are the most significant contributors to neuronal damage in neurodegenerative diseases [45]. Quercetin stimulates the Nrf2/ARE pathway due to the radical-scavenging functional groups, which increases the expression of endogenous antioxidants, such

as GSH, superoxide dismutase (SOD), and catalase (CAT) [18, 46].

Metal chelation

SAR insight

The 'oxo' group at the 4 position of ring C and the catechol group in the B ring form chelates with neurotoxic metal ions, such as Fe²⁺ and Cu²⁺. This chelation prevents Fenton reactions, which produce harmful ROS [47]. In addition, quercetin inhibits HIF-prolyl hydroxylase (HPH) by chelating iron, especially through hydroxyl (-OH) groups at the 3 position on the C ring and the 3',4' positions on the B ring, which further helps regulate the cellular response [48].

Mechanistic correlation

Excessive metal ions (Fe²⁺ and Cu²⁺) catalyze the production of ROS in AD, exacerbating oxidative stress and promoting Aβ aggregation. The chelation properties of quercetin neutralize these metal ions, reducing the formation of neurotoxic aggregates and protecting neuronal integrity [49].

Inhibition of protein aggregation

SAR insight

The catechol group in ring B and the conjugated π-electron system in the C ring interact with amyloidogenic proteins through hydrogen bonding and hydrophobic interactions [50].

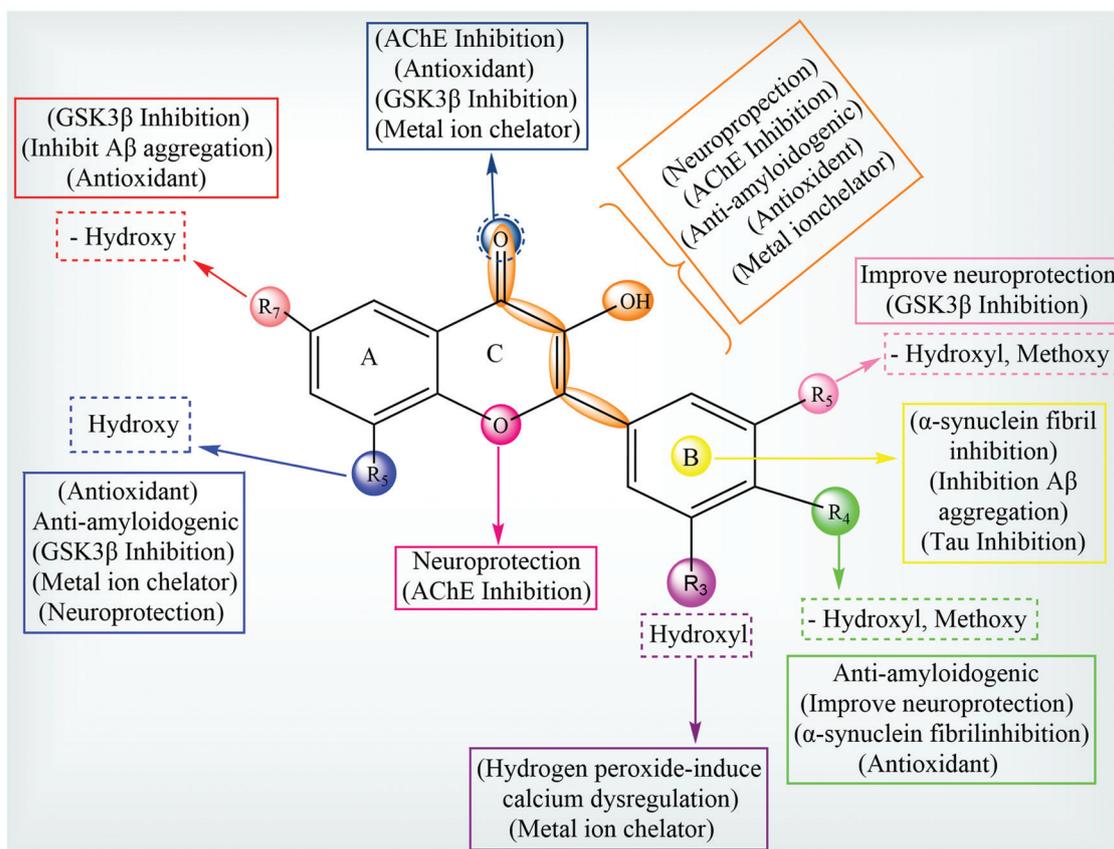


Figure 2 Quercetin SAR in relation to neuroprotective targets.

Mechanistic correlation

Quercetin inhibits the aggregation of misfolded proteins, including A β and α -synuclein in AD and PD, respectively. Quercetin disrupts fibril formation and oligomerization by stabilizing proteins in non-toxic forms, thereby reducing synaptic dysfunction and neuronal death. This mechanism performs a crucial role in NDDs, which are characterized by toxic protein aggregates [51].

Anti-inflammatory activity

SAR insight

The A and B ring hydroxyl groups allow quercetin to inhibit enzymes and signalling pathways associated with inflammation, like the cyclooxygenase (COX) and lipoxygenase (LOX) pathways. Additionally, the C ring conjugated system enhances the interaction with inflammatory mediators [52].

Mechanistic correlation

Quercetin lowers the expression of pro-inflammatory cytokines, such as tumor necrosis factor- α (TNF- α), interleukin (IL)-6, and IL-1 β , by blocking NF- κ B pathway activation. Additionally, quercetin inhibits the activity of inflammatory enzymes (LOX and COX) [53]. This anti-inflammatory action prevents microglial activation and reduces neuroinflammation, which are hallmark features of multiple sclerosis (MS) and amyotrophic lateral sclerosis (ALS) [54].

Regulation of mitochondrial function

SAR insight

The hydroxyl group at position 3 and the catechol group of the B ring interact with mitochondrial enzymes and ion channels, preserving mitochondrial integrity [52, 55].

Mechanistic correlation

Quercetin enhances mitochondrial bioenergetics by stabilizing the mitochondrial membrane potential and preventing calcium overload. Quercetin reduces mitochondrial ROS production, thereby preventing mitochondrial DNA and protein damage due to oxidative stress [56]. Additionally, quercetin stimulates the PI3K/Akt signalling pathway, promoting mitochondrial biogenesis and improving energy metabolism, which is critical for neuronal survival in conditions, like HD and PD [15, 57].

Inhibition of apoptotic pathways

SAR insight

The conjugated system increases the binding affinity of quercetin to enzymes like caspases and kinases, while the -OH groups create hydrogen bonds with important residues in apoptotic proteins [58].

Mechanistic correlation

Quercetin suppresses apoptotic cascades by inhibiting the stimulation of pro-apoptotic proteins like caspase-3 and -9.

Quercetin also downregulates the MAPK pathway, particularly the JNK and p38 branches, which are activated in response to cellular stress [59, 60]. By preventing neuronal apoptosis, quercetin preserves neural networks and cognitive function in diseases, like AD and HD [61].

Cholinesterase inhibition

SAR insight

The hydroxyl groups, particularly at position 3, interact with the catalytic active site of acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) through hydrogen bonding and hydrophobic interactions [62].

Mechanistic correlation

Quercetin inhibits AChE activity, increasing acetylcholine (ACh) levels in the synaptic cleft. This action enhances synaptic transmission and alleviates cognitive deficits associated with AD. BChE inhibition further supports the role of quercetin in preserving cholinergic function [63, 64].

Gene modulation

SAR insight

The conjugated polyphenolic system, including hydroxyl groups and the B ring catechol structure, allows interaction with transcription factors like Nrf2 and cyclic AMP response element binding protein (CREB) [65].

Mechanistic correlation

Quercetin increases the synthesis of antioxidant enzymes by stimulating the Nrf2/ARE pathway, which controls gene expression. Additionally, quercetin promotes neurogenesis and synaptic repair by increasing the expression of brain-derived neurotrophic factor (BDNF). These effects contribute to the neuroprotective potential of quercetin in NDDs, like ALS and HD [66, 67].

Quercetin demonstrates strong inhibition of GSK3 β , binding with high affinity and forming four hydrogen bonds with essential amino acids (Asp200, Arg141, and Val135) [3, 68]. Neuroprotective activity is further improved by specific substitutions in the structure of quercetin, such as hydroxyl groups at carbon positions 5, 7, 3, and OCH₃ or H substitutions at the carbon 3 and 4 positions. The modifications have been confirmed through *in vitro* studies with neuron cell cultures. Important structural elements that have been demonstrated to lessen H₂O₂-induced Ca²⁺ imbalance and oxidative stress include polyphenolic structures, like a 2,3-double bond conjugated with the 4-oxo group on ring C and the -OH group at the 3',4'-hydroxyl group of the B ring [3, 6, 69]. Moreover, hydroxyl substitutions on the A ring, a 4-carbonyl group in the C ring, and ortho-dihydroxy substitution in the B ring are responsible for the metal ion-chelating action of quercetin. The ortho-dihydroxyl group also inhibits α -synuclein fibril formation, underscoring the therapeutic potential of quercetin in managing PD [70].

The structural basis for the neuroprotective activity of quercetin is highly dependent on specific functional groups and substitutions. Various functional elements, such as hydroxyl ($-OH$), carbonyl ($=O$), and methoxy ($-OCH_3$) groups, are linked to specific biological effects (e.g., antioxidant, metal chelation, anti-aggregation, and anti-inflammatory activities) to facilitate a clearer understanding of these structural-functional relationships of the quercetin SAR. **Figure 2** illustrates the quercetin SAR, highlighting the various biological effects associated with different functional groups (mainly hydroxyl and methoxy) at specific positions on the flavonoid skeleton. The substitutions at R_3 , R_4 , R_5 , R_5' , and R_7 significantly contribute to neuroprotection through diverse mechanisms. Hydroxyl or methoxy groups at R_3 , R_4 , and R_5' enhance antioxidant activity, anti-amyloidogenic effects, α -synuclein fibril inhibition, and improve neuroprotection. Hydroxyl groups at R_5 and R_7 are particularly important for inhibition of GSK3 β , inhibition of A β aggregation, and metal ion chelation mechanisms linked to AD pathology. The central C ring, especially the C2=C3 double bond and 4-oxo group, has a vital role in AChE inhibition and antioxidant action and further supports metal ion chelation. The overall structure suggests that multiple substitutions contribute synergistically to neuroprotection by targeting oxidative stress, protein aggregation (A β and τ), and dysregulated kinase activity (GSK3 β), while also modulating calcium signalling and metal ion toxicity. This comprehensive mapping shows how specific functional groups on flavonoids can be tailored to enhance therapeutic efficacy against NDDs.

Pathophysiologic mechanism of NDDs

NDDs (AD, PD, and HD) are described by gradual neuronal loss, often with age-dependent onset. These conditions are marked by cognitive decline, motor dysfunction, and behavioral changes, underpinned by complex pathophysiologic processes, like protein misfolding and aggregation, oxidative stress, mitochondrial dysfunction, and inflammation [71]. Each disease has distinct pathologic hallmarks, as follows: A β plaques and neurofibrillary tangles in AD; α -synuclein aggregation in PD; and mutant huntingtin proteins in HD. These misfolded proteins destroy cellular function and cause the death of neurons in specific brain regions in major NDDs [72].

Mechanisms in AD

Amyloid plaque formation

The formation of A β plaques is the hallmark of AD. A β plaques are caused by beta (β) and gamma (γ)-secretases cleaving the amyloid precursor protein (APP). The toxic A β oligomers accumulate extracellularly, disrupting synaptic function and triggering neuronal death [73]. Drugs, like aducanumab, a monoclonal antibody targeting A β , aim to reduce amyloid plaques, although the efficacy remains controversial [74]. BACE1 inhibitors (e.g., verubecestat)

also target amyloid plaque formation by inhibiting the beta-secretase enzyme [75].

Tau hyperphosphorylation and tangle formation

The τ protein, essential for microtubule stabilization in neurons, becomes hyperphosphorylated in AD, forming neurofibrillary tangles that interfere with axonal transport. This accumulation impairs intracellular transport and cell viability [76]. Investigational sigma-1 receptor agonists, like ANAVEX2-73 (blarcamesine), are being studied for the ability to modify τ phosphorylation [77]. Tau aggregation inhibitors, like TRx0237 (LMTX), target τ pathology although clinical success has been limited [78].

Neuroinflammation

Neuroinflammatory responses, primarily mediators, like activated microglia and astrocytes, are prominent in AD pathology. These cells release cytokines, such as IL-1 β and TNF- α , exacerbating A β -induced neurotoxicity [79]. Anti-inflammatory agents (e.g., ibuprofen) and immunomodulatory drugs, like sargramostim (leukine, a colony-stimulating factor), are explored for the potential to reduce neuroinflammation, although results vary across clinical trials [80].

Cholinergic deficiency

The resulting cholinergic neuron death from depletion of ACh is a characteristic of AD and causes cognitive impairments [81]. Donepezil, rivastigmine, and galantamine are examples of cholinesterase inhibitors that temporarily improve cognitive and memory abilities in mild-to-moderate stages of AD by inhibiting acetylcholinesterase while preserving ACh levels [82].

Mechanisms in PD

α -Synuclein aggregation and Lewy body formation

The misfolding and accumulation of α -synuclein protein in PD lead to the formation of Lewy bodies in dopaminergic neurons. These inclusions disrupt cellular homeostasis and promote neurotoxicity [83]. Clinical trial therapies that reduce alpha-synuclein accumulation include NPT200-11 and PRX002/RG7935, which are alpha-synuclein aggregation inhibitors and anti-alpha-synuclein monoclonal antibodies, respectively [84, 85].

Dopaminergic neuronal loss in the substantia nigra

The primary cause leading to the pathogenesis of PD involves substantia nigra dopaminergic nerve cell degradation, which

leads to dopamine insufficiency [86]. Levodopa, often combined with carbidopa, remains the gold standard for symptomatic treatment by replenishing dopamine levels [87]. The dopamine agonists, ramipexole and ropinirole, are also used to stimulate dopamine receptors directly [88].

Mitochondrial dysfunction and oxidative stress

Mitochondrial complex I dysfunction in PD increases ROS production, which contributes to oxidative stress and neuronal death. Antioxidants, like coenzyme Q10 and N-acetylcysteine, protect against mitochondrial damage, while drugs, like rasagiline (a monoamine oxidase-B inhibitor), provide neuroprotection by reducing dopamine metabolism-induced ROS [89, 90].

Neuroinflammation

Chronic inflammation in PD, which is driven by activated microglia, releases cytokines that exacerbate dopaminergic neuron loss. Inhibitors of microglial activation, such as minocycline (an antibiotic with anti-inflammatory effects), are under investigation [91]. Ibuprofen has been shown to have the potential to reduce neuroinflammation in preclinical PD models, although the clinical efficacy in PD remains uncertain [92].

Mechanisms in HD

Mutant huntingtin (mHTT) aggregation

HD occurs due to the amplification of the huntingtin (*HTT*) gene of cytosine, adenine, and guanine (CAG) repeats, which results in mutant HTT aggregation. This aggregation disrupts cellular processes, which causes neuronal loss [93, 94]. Branaplam, a small molecule splicing modulator, and tominersen, an antisense oligonucleotide (ASO), are in development to reduce HTT production, targeting the root cause of HD. Branaplam is presently being tested in phase II HD research (NCT05111249) [94, 95].

The clinical trial (NCT02519036) with tominersen involving 46 HD patients was carried out for 28 weeks (including a phase I/II trial) and showed a dramatic reduction in the levels of mutant huntingtin in cerebrospinal fluid, which raised hopes for the medication [96]. However, Roche halted a clinical trial (NCT03761849) in March 2021 with 899 HD disease patients. Data review indicated that the potential benefits of tominersen did not justify the associated risks after 2 years in a phase III trial. The trial evaluated two dosing regimens of tominersen (120 mg administered every 8 weeks and 120 mg every 16 weeks). Patients receiving a higher dosage (120 mg every 8 weeks) had more motor and cognitive deterioration after 69 weeks than patients receiving a placebo. However, patients receiving the lesser dosage (120 mg per 16 weeks) did not exhibit any significant benefits above the placebo group. Additionally, both tominersen treatment groups exhibited

significantly increased brain ventricle volumes relative to the placebo group. Although tominersen decreased the synthesis of the mutant huntingtin protein, tominersen also inhibited the creation of healthy wild-type protein, which may have had neurotoxic effects. Shortly after terminating the trial, Wave Life Sciences announced ceasing the formation of two ASOs that were in phase I/II trials for HD [97, 98].

Mitochondrial dysfunction and energy deficiency

mHTT impairs mitochondrial function, resulting in ATP depletion and enhanced ROS production [99]. Therapies, like creatine, enhance mitochondrial function, although clinical trials have yielded mixed results [100]. Coenzyme Q10 has also been investigated for improving mitochondrial bioenergetics in HD, although larger studies are needed [101].

Excitotoxicity and glutamate toxicity

HD is marked by excessive glutamate release, causing excitotoxicity and neuronal death. Memantine, which is an antagonist of NMDA receptors, is used experimentally to block glutamate receptors and protect against excitotoxic damage [102]. Riluzole, another glutamate antagonist, has shown neuroprotective effects in HD models [103].

Dysregulated apoptosis and cell death

Increased pro-apoptotic signalling, partly due to mHTT toxicity, results in neuronal apoptosis. Drugs, like minocycline, show potential in inhibiting caspase activity and reducing apoptosis in HD models. Minocycline exhibits neuroprotective effects by suppressing hypoxia-induced activation of rodent microglia, inhibiting caspase-1 and -3 expression in an HD transgenic mouse model, and facilitating mitochondrial permeability-transition-mediated cytochrome c release from mitochondria in an ALS animal model [104]. Additionally, pifithrin- α , an experimental drug targeting p53-mediated apoptosis, has been explored for neuroprotective effects in HD [105].

Effectiveness of quercetin in NDDs

Quercetin in AD

Quercetin exhibits profound neuroprotective effects in AD primarily through the capacity to counteract A β aggregation, τ hyperphosphorylation, and neuroinflammation [6, 57]. Research has shown that quercetin reduces amyloidogenic processing of the APP by inhibiting the activities of β - and γ -secretase, two important enzymes that cause A β plaque formation. Additionally, quercetin modulates τ

protein, decreasing hyperphosphorylation and preventing neurofibrillary tangle formation, which are crucial pathologic hallmarks of AD. The strong antioxidant qualities of quercetin are achieved by activation of the Nrf2-ARE pathway, which increases the expression of endogenous antioxidant enzymes, like GSH peroxidase and SOD. Additionally, quercetin inhibits the NF- κ B signaling pathway, which lowers the production of pro-inflammatory cytokines, like IL-6, TNF- α , and IL-1 β , which attenuate neuroinflammatory cascades [106, 107]. Quercetin has been shown to improve cognitive deficits and memory function in aged triple-transgenic AD experimental rats by reversing extracellular amyloidosis, astrogliosis, and microgliosis. The ability of quercetin to inhibit AChE also elevates ACh levels, restoring synaptic function and cognitive abilities [108]. Structural modifications and delivery enhancements, such as nanoparticle-based formulations, further enhance the bioavailability and effectiveness against AD, paving the way for advanced clinical applications. **Figure 3** depicts an integrated visual representation of the neuroprotective mechanisms of quercetin in AD. Quercetin reduces A β accumulation by inhibiting β - and γ -secretase activity and interferes with the hyperphosphorylation of τ proteins through GSK-3 β inhibition. Quercetin enhances antioxidant defenses by activating the Nrf2-ARE pathway and increasing endogenous antioxidant enzyme levels, such as SOD, CAT, and GSH. The diagram also shows the role of quercetin in suppressing inflammatory cascades via NF- κ B inhibition and downregulation of cytokines, like TNF- α , IL-6, and IL-1 β . Moreover, quercetin boosts cholinergic neurotransmission by inhibiting AChE, thereby increasing ACh levels in the synaptic cleft [109] (**Figure 3; Table 2**).

Quercetin in PD

A neurodegenerative disease linked to aging (PD) is typified by the death of dopaminergic neurons in the substantia nigra pars compacta (SNpc). Clinical signs and symptoms include stiffness, tremors, and bradykinesia [110]. According to Grewal AK et al., isoquercetin prevents α -synuclein fibrillization in PD and enhanced motor function [3]. Quercetin in PD targets multiple pathogenic mechanisms, including oxidative stress, mitochondrial dysfunction, α -synuclein aggregation, and neuroinflammation. Through the activation of the Nrf2 pathway, quercetin improves cellular antioxidant defenses, reducing oxidative damage in substantia nigra dopaminergic neurons. Quercetin even stabilizes mitochondrial membranes and improves mitochondrial bioenergetics, which is crucial for neuronal survival. Quercetin inhibits alpha-synuclein aggregation and the synthesis of Lewy bodies, which are toxic to neuronal cells. Furthermore, quercetin reduces neuroinflammatory responses by suppressing microglial activation and decreasing levels of pro-inflammatory mediators. Quercetin preserved dopamine levels, decreased lipid peroxidation, and restored the amount of GSH in the striatum, exhibiting neuroprotective effects in animal studies. Quercetin also ameliorates motor deficits and behavioral impairments in 6-OHDA-induced PD models [2, 111]. Isoquercetin, a glycoside of quercetin,

has shown improved bioavailability and efficacy in PD by reducing α -synuclein fibrillization and enhancing motor performance. These results highlight the promise of quercetin as a PD treatment candidate. The practical applicability of quercetin is further enhanced by sophisticated delivery methods, such as liposomal encapsulation. The neuroprotective benefits of quercetin were investigated by Zhang et al. in PC12 cells and zebrafish. Sehar et al. and Zhang et al. reported that quercetin suppresses pro-inflammatory gene upregulation (IL-1s, COX-2, and TNF- α) in zebrafish while inhibiting excessive NO generation and iNOS overexpression in PC12 cells (**Figure 4; Table 3**) [112, 113].

Figure 4 illustrates the multifaceted roles of quercetin in mitigating the pathogenesis of PD, brain ischemia, and HD. Quercetin not only inhibits α -synuclein aggregation and preserves dopaminergic neurons in PD but also exerts significant anti-ischemic and mitochondrial-protective actions. **Figure 4** highlights how quercetin improves mitochondrial dynamics by enhancing mitophagy and reducing mitochondrial-derived ROS. Quercetin also modulates neuroinflammation by suppressing microglial activation and the expression of pro-inflammatory mediators, such as TNF- α and iNOS. Furthermore, the ability of quercetin to stabilize the BBB and protect neuronal integrity under ischemic conditions underscores the vasculoneuroprotective potential, which is particularly relevant in PD, in which vascular dysfunction exacerbates neurodegeneration [114].

Quercetin and HD

Quercetin targets the primary pathogenic mechanisms of neuroinflammation, oxidative stress, excitotoxicity, and mitochondrial dysfunction in HD. Quercetin restores ATP synthesis and lessens oxidative damage by preventing mitochondrial swelling and lipid peroxidation [115]. Quercetin reduces oxidative stress in neuronal cells by boosting the activity of antioxidant enzymes, including CAT and SOD. The neuroprotective effects of quercetin extend to reducing excitotoxicity by modulating NMDA receptor activity and restoring calcium homeostasis [116]. Quercetin supplementation improves motor coordination, reduced neurobehavioral deficits, and diminished astrogliosis in the striatum using animal models. Histopathologic studies have revealed reduced neuronal apoptosis and pyknotic nuclei in HD models treated with quercetin. Quercetin also attenuates quinolinic acid-induced neurotoxicity by decreasing TNF- α levels and preserving neurotransmitter levels, including dopamine and serotonin. Advanced formulations, such as quercetin-loaded nanoparticles, have been developed to enhance brain bioavailability, further validating the therapeutic potential in HD. The ability of quercetin to modulate gene expression and signalling pathways implicated in HD highlights the promise of quercetin for disease modification and symptom management [117–119]. Kuhad and colleagues conducted another study to assess the protective properties of quercetin against quinolinic acid (QA)-induced neurotoxicity. QA exposure decreased dopamine, serotonin, and norepinephrine levels in the rat forebrain and markedly increased TNF- α levels, which are indicative of neuroinflammatory injury.

Table 2 Biological Activities of Quercetin and the Neuroprotective Outcomes, as Reported in AD

Serial No.	Biological Activities of Quercetin	Outcomes (Effect Produced)	References
1.	Antioxidant, anti-inflammatory	Decrease taupathy, microgliosis, and astrogliosis	[234]
2.	Antioxidant	Preventing tau protein hyperphosphorylation through PI3K/Akt/GSK3β signalling pathways and MAPKs	[153]
3.	Anti-inflammatory	Decrease amyloid precursor protein (APP) maturation, altering Aβ production and accumulation	[3]
		Decrease the AChE level	[3]
		Reduce the cytotoxicity and apoptosis caused by Aβ(1-42)	[6]
4.	Inhibiting neuronal apoptosis	Suppress the expression of the <i>iNOS</i> gene in microglia	[3]
		Lowering inflammatory cytokines in activated macrophages, such as TNF-α, IFN-γ, interleukin (IL)-1β, IL-6, IL-12, and COX-2	[235]
5.	Antioxidant, Attenuating oxidative stress	Improving calcium homeostasis, growth factor signalling, and neuroplasticity	[236]
5.	Antioxidant, Attenuating oxidative stress	Ameliorate cellular oxidative stress and inhibit the production of nitric oxide (NO)	[237]
		Modulating cell antioxidant pathways, like Nrf-2-ARE and paraoxonase 2 (PON2) pathways	[11]

Table 3 Biological Activities of Quercetin and Neuroprotective Outcomes, as Reported in Parkinson's Disease

Serial No.	Outcomes (Produced Effects)	Biological Actions of Quercetin	References
1.	Inhibit mitochondrial activity	Reduce the rate of dopaminergic degeneration	[238]
2.	Mitochondrial function	Increase mitophagy	[239]
3.	Antioxidant	Improve cognitive impairment	[240]
		Increase in striatal dopamine concentrations	[241]
4.	Anti-inflammatory	Reduce oxidative stress and induce autophagy.	[242]
		Increase in production of NO and overexpression of iONS	[243]
5.	Reduces cellular apoptosis	Reduced elevated expression of the <i>p53</i> , <i>TNF-α</i> , <i>IκKB</i> , <i>NF-κB</i> , and <i>IL-1β</i> genes	[244]
		Attenuates nuclear condensation	[245]

acting on these convergent targets, reinforcing the relevance as a multi-targeted therapeutic candidate [120, 121].

Role of quercetin in vascular endothelial function and neurovascular protection

Clinical application of quercetin in Russia: Capilar formulation

Quercetin is available in Russia under the commercial name, Capilar, which contains 10 mg of quercetin per tablet and is primarily used among the aging population for improving capillary function and preventing venous insufficiency. Capilar is marketed as a vasoprotective supplement intended to improve microcirculation and support cardiovascular and peripheral vascular health. The long-standing clinical use of quercetin in this formulation underscores the systemic protective effects, including potential benefits on cerebral microvasculature integrity, which is closely linked to neuroprotection in elderly individuals [122].

Neurovascular unit and BBB integrity

The neurovascular unit (NVU), which is comprised of endothelial cells, astrocytes, neurons, and pericytes, is

essential for maintaining brain homeostasis [123]. Quercetin has been shown to enhance the integrity of the NVU by reducing oxidative stress and inflammation in endothelial cells, preserving tight junction proteins, such as claudin-5 and occludin. These effects mitigate BBB disruption, a common pathologic feature in NDDs, such as AD and vascular dementia [124, 125].

Antioxidant effects on cerebral microcirculation

The antioxidant actions of quercetin reduce oxidative damage to endothelial cells and improve NO bioavailability. This effect promotes vasodilation, reduces leukocyte adhesion, and enhances cerebral perfusion [126]. Quercetin administration restores cerebrovascular tone and reduces infarct volume in rodent models of ischemia-reperfusion injury, indicating that the vascular protective role of quercetin extends to cerebral blood flow regulation and ischemic neuroprotection [127].

Anti-inflammatory modulation of endothelial dysfunction

Endothelial dysfunction is a key contributor to chronic neuroinflammation. Quercetin exerts anti-inflammatory effects

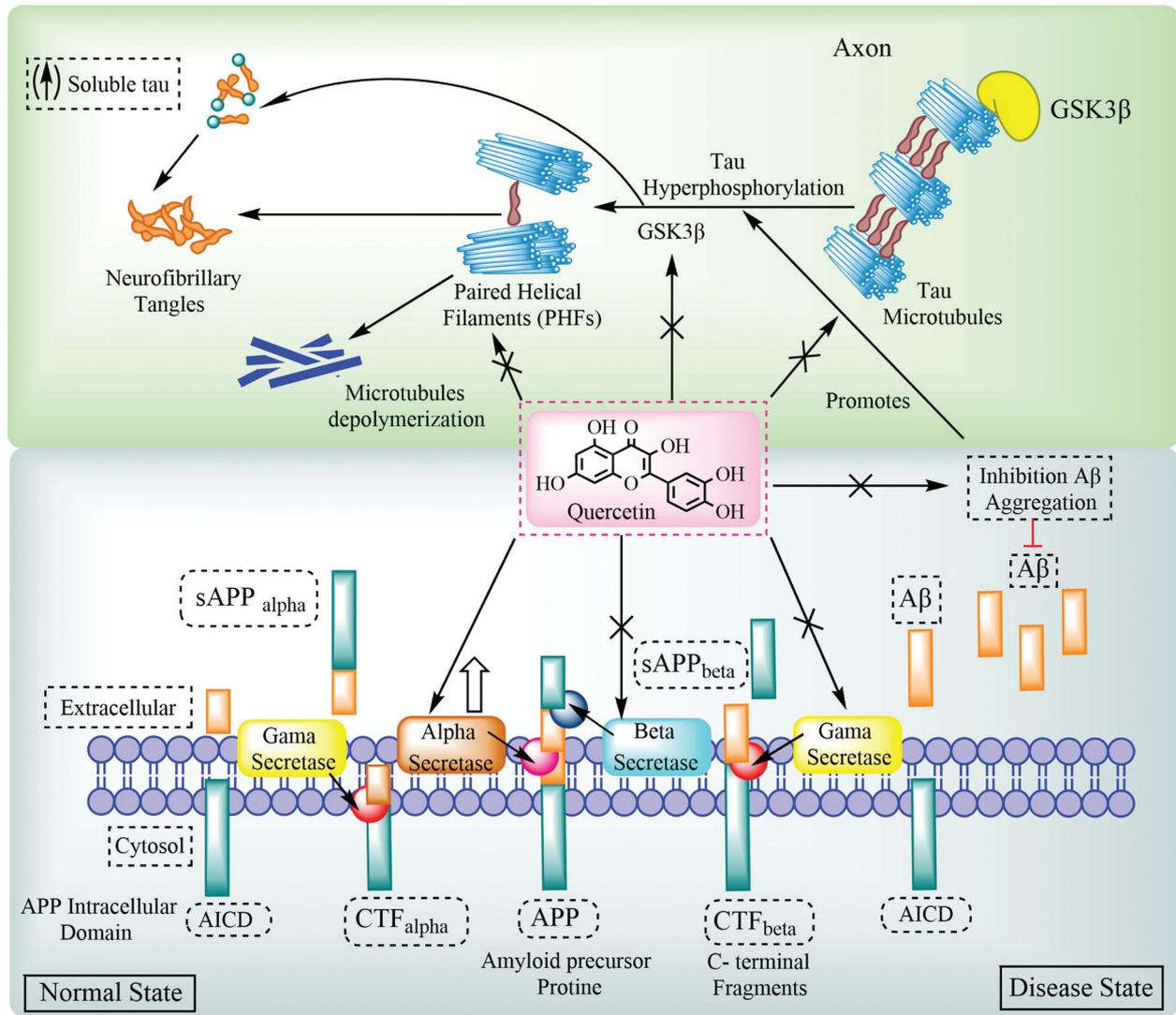


Figure 4 The mechanism and function of quercetin in the pathophysiology of brain ischemia, Parkinson's disease, and Huntington's disease.

by inhibiting endothelial NF-κB activation, which reduces the expression of vascular adhesion molecules (e.g., ICAM-1 and VCAM-1) and limits immune cell infiltration into neural tissues. Such modulation reduces the initiation and propagation of neuroinflammatory cascades, further supporting cognitive health and neuronal survival [128, 129].

Evidence from clinical and nutraceutical use

The success of Capilar in clinical practice in Russia offers indirect yet valuable insight into the tolerability and utility of quercetin for vascular-related disorders in aging populations [122]. Although primarily used for peripheral circulation, the systemic effects of quercetin suggest a plausible benefit in supporting cerebral perfusion and preventing age-associated cognitive decline. These observations advocate for further clinical studies targeting the role of quercetin in maintaining neurovascular health and delaying neurodegeneration [130].

Synergistic neurovascular and neuronal mechanisms

Dual modulation of vascular and neuronal pathways by quercetin is through the PI3K/Akt, Nrf2-ARE, and MAPK cascades and facilitates cross-talk between endothelial and neural cells [125]. This integrated mechanism protects against ischemia-induced neuronal apoptosis and may explain the cognitive benefits observed in aging populations consuming quercetin-rich supplements [130].

Comparative neuroprotective efficacy of quercetin and other flavonoids

Quercetin exhibits multi-targeted neuroprotective actions and is superior to many flavonoids due to the SAR involving catechol and hydroxyl groups in the B and C rings. These functional groups enable quercetin to scavenge ROS, chelate metal ions, and inhibit protein aggregation. Quercetin

Table 4 Biological Activities of Quercetin and Neuroprotective Outcomes, as Reported in Huntington's Disease

Serial No.	Outcomes (Effect Formed)	Biological Actions of Quercetin	References
1.	Antioxidant	Within the mitochondria, quercetin increases the total thiol level in 3-3-nitropropionic acid (NP)-treated animals Lower lipid peroxidation in mitochondria also inhibits the formation of malondialdehyde (MDA) inside the brain Diminish astrogliosis and pyknotic nuclei Enhancing MnSOD levels to decrease mitochondrial oxidative stress Reduces the anxiety, poor motor coordination, and gait despair brought on by 3-NP	[246] [246] [246] [247] [248]
2.	Anti-inflammatory	Decreased microglial proliferation Reduces changes in behavior, biochemistry, and neurochemistry	[249] [250]

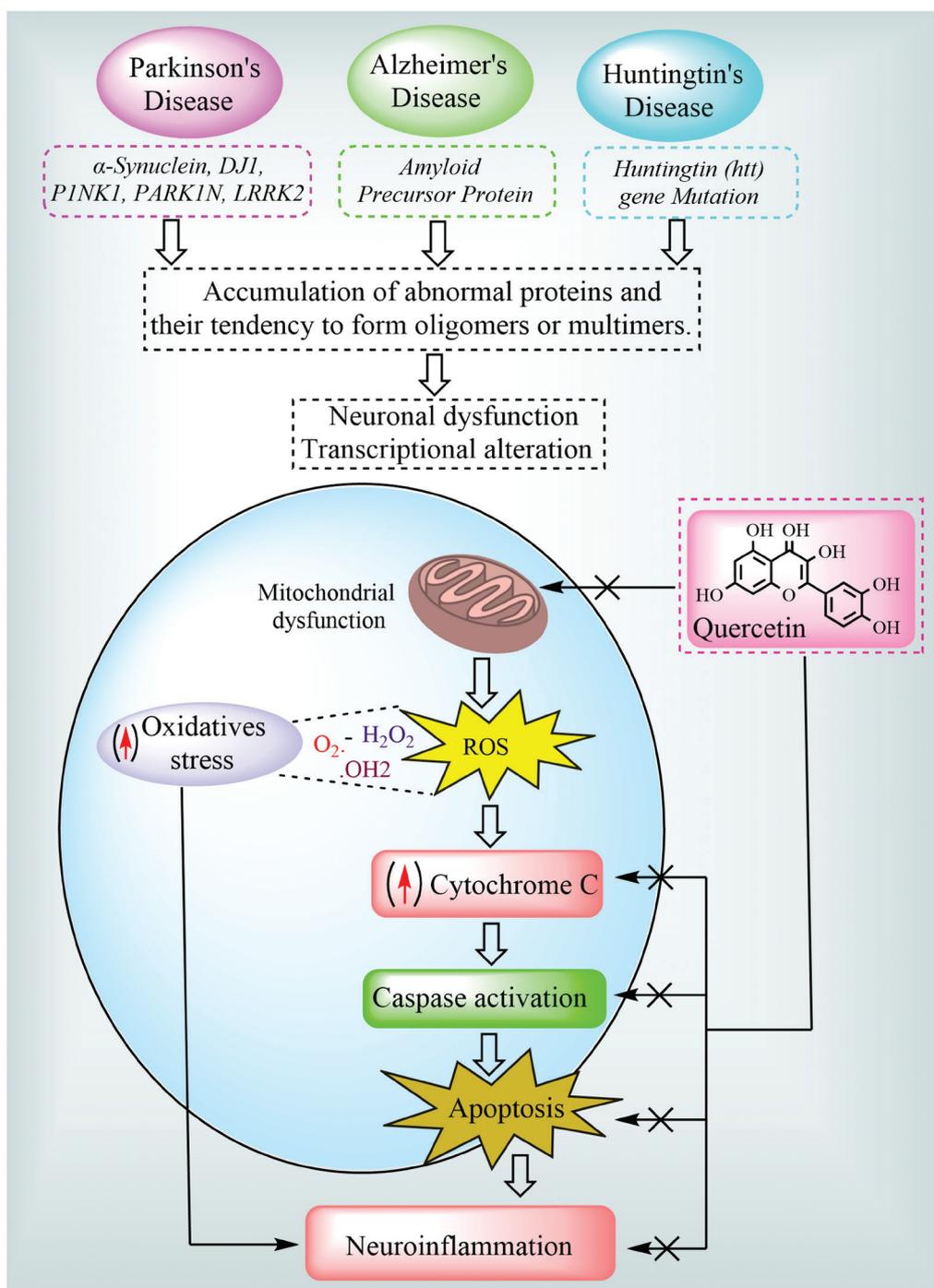


Figure 5 Neuroprotective properties of quercetin in a spectrum of neurodegenerative diseases. Quercetin directly protects neurons through a range of molecular neuroprotective mechanisms in these diseases, such as the downstream control of oxidative stress, neuroinflammation, apoptosis, and cell death.

Table 5 Comparative Evaluation of Quercetin with other Neuroprotective Flavonoids

Flavonoid	Disease Model	Mechanism	Unique Advantage	Limitation	Reference
Quercetin	AD, PD, HD, ischemia	Nrf2-ARE, PI3K/Akt, MAPK, HIF-PHD, and PON2	Strong multi-target action (oxidative stress, inflammation, apoptosis, metal chelation, and mitochondrial support)	Poor oral bioavailability, rapid metabolism	[251]
Kaempferol	AD, PD	Anti-inflammatory (NF-κB), antioxidant	Moderate AChE inhibition and improved cognitive function	Lower ROS scavenging than quercetin	[252, 253]
Luteolin	AD, ALS	Inhibition of NF-κB, MAPK, and microglial activation	High BBB permeability and neurogenesis induction	Limited clinical validation	[254]
EGCG (Epigallocatechin gallate)	AD, PD	α-synuclein and Aβ aggregation inhibition, mitochondrial protection	Potent metal chelator and proteostasis modulator	Instability at physiologic pH, GI degradation	[255, 256]
Rutin (quercetin-3-rutinoside)	AD, PD	Antioxidative, mild anti-inflammatory, AChE inhibition	Better water solubility, glycosylation improves absorption	Lower receptor binding affinity vs. quercetin aglycone	[257]
Baicalein	PD	Dopamine preservation, ROS inhibition, GSK-3β modulation	Potent mitochondrial protector, strong ROS inhibition	Less studied in human trials	[258, 259]

has higher potency in modulating Nrf2-ARE and PI3K/Akt pathways compared to kaempferol and rutin but is limited by poor bioavailability. EGCG, though potent in inhibiting aggregation, lacks metabolic stability *in vivo*. Luteolin and baicalein show strong anti-inflammatory and antioxidant actions but are not as well-characterized across multiple models as quercetin. The integration of quercetin signalling and mitochondrial and epigenetic regulation mechanisms makes quercetin a versatile candidate in precision neurotherapeutics. Table 5 describes the comparative analysis of quercetin neuroprotective efficacy with other flavonoids.

Targeting signalling pathways by quercetin for neuroprotection

Quercetin targets several critical signalling pathways that are included in the mechanism underlying NDDs, including AD and PD. Neurodegeneration is identified by complex cascades of oxidative damage, inflammatory responses, and apoptotic mechanisms, which progressively contribute to neuronal dysfunction and loss. This review systematically examined the downstream signalling pathways modulated by quercetin, including the PON2, Nrf2-ARE, and PI3K pathways, JNK mechanism, TNF-α formation and inhibition, PGC-1α, sirtuin, CREB, and MAPK pathways, by elucidating the roles in mitigating oxidative stress, reducing neuroinflammation, and enhancing cell survival. Quercetin is a promising therapeutic approach for slowing neurodegenerative processes and improving neuronal resilience by targeting these key mechanisms.

PON2 pathway

The eldest of the PON family consists of 3 genes (*PON1*, *PON2*, and *PON3*) close to the longer branch of human chromosome 7q21-22. PON2 is found in macrophages and endothelial cells and serves as an antioxidant in humans [131]. PON2 is mostly found in mitochondria based on sub-cellular research, where PON2 is vital in reducing oxidative stress brought on by free radicals. The location of PON2 in the mitochondria is crucial for protecting cells from oxidative damage and a lack of PON2 results in mitochondrial dysfunction [132]. It has been demonstrated that PON2 selectively reduces the release of superoxide from the inner mitochondrial membrane in human endothelial cells, while not affecting other reactive species, like hydrogen peroxide (H₂O₂) or peroxynitrite [133]. Unlike PON1, which primarily associates with HDL and circulates in the bloodstream, PON2 functions exclusively as an intracellular antioxidant [134].

PON2 mRNA is detected in both mouse and human brains, while PON2 protein is found in mouse, rat, human, and monkey brains, with the highest concentrations observed in dopaminergic regions of the mouse brain [135]. There is a gender-based differential in PON2 levels with female mice showing higher levels than humans and other rodent

and non-rodent species. The PON2 antioxidant qualities are essential for atherosclerosis prevention and neuroprotection. PON2-deficient murine cells are much more cytotoxic when exposed to oxidants, such as H₂O₂ and 2,3-dimethoxy-1,4-naphthoquinone (DMNQ) [136]. Similarly, compared to female cells, male mouse neurons and striatal astrocytes are far more susceptible to oxidative stress and cytotoxicity driven by these oxidants because male mouse neurons and striatal astrocytes express lower levels of PON2 [137]. PON2-deficient mice also show elevated lipid hydroperoxide levels in tissues and increased macrophage migration into arterial walls compared to wild-type controls [138].

Although quercetin has been shown to increase PON1 expression, it is still unknown what precise biochemical mechanisms flavonoids use to affect *PON2* gene expression [131]. It has been demonstrated that pomegranate flavonoids modify the DNA-binding properties of the transcription factor, AP-1, which is found in the promoter region of the *PON2* gene and may regulate expression [139]. Superoxide anion radicals are produced by the quercetin molecular target,

NADPH oxidase, which controls AP-1 DNA binding [140]. Additionally, new research suggests that glucocorticoid-glucocorticoid receptor complexes directly mediate *PON2* gene transcriptional activation, which may have an impact on AP-1 transactivation. According to *in vitro* research, quercetin treatment increases the expression of the PON2 protein in striatal astrocytes, macrophages, and mouse neurons. It is hypothesized that quercetin induces a mild oxidative stress response, which in turn increases PON2 expression. Additionally, in striatal astrocytes, quercetin eliminates ROS levels and mitigates cytotoxicity driven by H₂O₂ and DMNQ (Figure 6) [139, 141].

Nrf2-ARE pathway

Nuclear factor erythroid 2-related factor 2 (Nrf2) is a transcription factor that is essential for controlling oxidative stress brought on by free radicals. Kelch-like ECH-associated protein 1 (KEAP-1) anchors Nrf2 in the cytoplasm under

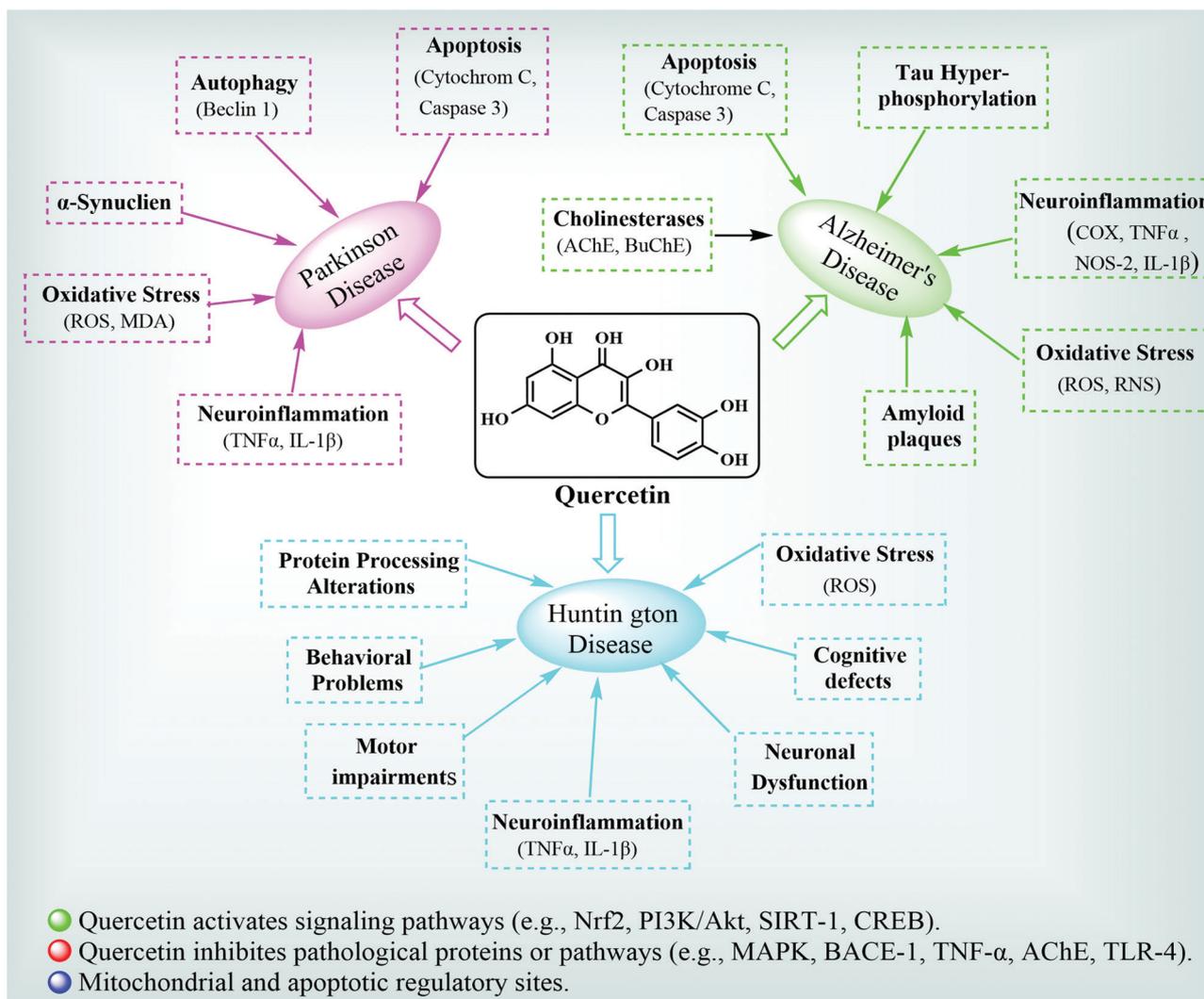


Figure 6 Quercetin modulates molecular processes involved in neuronal survival. Quercetin eventually caused the cytoprotective genes to be activated by activating the PI3K-Akt, AMPK, Wnt, p38, PON-2, and related signalling pathways, including Nrf2, MAPK, CREB, and SIRT-1, which promotes neuronal survival. However, for neuroprotective action, quercetin inhibits TLR-4, BACE-1, AChE, TNF- α , and the MAPK signalling cascade.

physiologic settings through Cullin 3-based E3 ligase, facilitating ubiquitination and subsequent proteasomal destruction [142]. Antioxidant response element (Nrf2-ARE) signalling pathway activation offers neuroprotection against oxidative stress and cellular death. According to recent studies, the NRF2-ARE pathway also controls the development of misfolded protein aggregates, which are frequently seen in NDDs, like AD, PD, and HD. Moreover, γ -glutamyl-cysteine synthetase (GCS), an essential enzyme in the production of the antioxidant, GSH, is stimulated to appear when Nrf2-ARE is activated [143].

Quercetin has been shown to activate the Nrf2-ARE pathway, thereby reducing cellular damage caused by oxidative stress. Studies using tert-butylhydroquinone, a well-known Nrf2 inducer, have highlighted the neuroprotective benefits of Nrf2-ARE activation against neurotoxicity, particularly the benefits brought on by A β [144]. Similar protective effects have been observed with dihydroquercetin [145]. Additionally, nutraceutical compounds, such as kaempferol and pterostilbene, exhibit synergistic effects when combined with quercetin. According to Ayyalasomayajula et al. and Cheng et al., quercetin is a neuro-hormetic phytochemical that activates Nrf2 through the ERK and JNK pathway [146, 147]. Several *in vitro* investigations on cerebral cortex tissues and neuronal cell lines have demonstrated that quercetin improves cellular resistance to oxidative damage brought on by neurotoxic agents, like A β peptide or oxidants, like hydroperoxide (Figure 6)

Phosphoinositide 3-kinase (PI3K) pathway

Age-associated NDDs and other severe brain disorders are significantly influenced by PI3K. Akt, a crucial enzyme that controls neuronal survival and plasticity, regulates the PI3K/Akt pathway. Phosphatidylinositol 3,4,5-trisphosphate (PIP3) can be activated by a variety of stimuli, including integrins, receptor tyrosine kinases (RTK), cytokines, B and T cell receptors, and G-protein coupled receptors (GPCRs). This activation leads to Akt phosphorylation, which ultimately influences the activation or inhibition of several target proteins, hence regulating important physiologic processes, such as the cell cycle, development, metabolism, growth, protein synthesis, and apoptosis [148, 149].

Animal models of NDDs have shown that a high-fat diet (HFD) impairs learning and memory, primarily due to oxidative stress. Such diets are rich in saturated fats and involve carbonyls and ROS and decrease hippocampal gene expression, especially of PI3K/Akt and Nrf2 pathways [150]. Quercetin supplementation in conjunction with HFD enhances antioxidant capacity and mitigates learning and memory deficits. Quercetin administration dramatically decreased oxidative stress (i.e., increased levels of cytochrome c, GSH, GSH peroxidase, and glutaredoxin, as well as decreased lipid peroxidation in the cortex and striatum), while fostering anti-apoptotic and antioxidant pathways in ischemic rat brains [18, 151].

The PI3K/Akt blocker, LY294002, elevated the Bax:Bcl-2 ratio and highlighted the pathway participation in the antioxidant actions of quercetin and exercise by negating the combined effects [152]. Additionally, quercetin demonstrated

neuroprotective benefits in NDDs, such as AD and PD, by inhibiting oxidative stress-induced τ protein phosphorylation, a crucial downstream target of this pathway. Nearly the same outcomes were shown in PC12 pheochromocytoma cells, in which quercetin restored GSH and SOD function while lowering lactate dehydrogenase, ROS, and malondialdehyde levels to prevent H₂O₂-induced death [153] (Figure 6).

c-Jun N-terminal kinase (JNK) pathway

The JNK pathway plays a vital part as a key signal in the MAPK downstream signalling pathway. This kinase is a member of the threonine protein kinase family, which is encoded by three different genes (*JNK1*, *JNK2*, and *JNK3*) that together result in 10 variations [154]. While JNK1 and JNK2 are widely distributed throughout many tissues and play a major role in obesity-induced insulin resistance, JNK3 is mostly found in the central nervous system (CNS) and may have therapeutic uses in NDDs and other disorders involving the CNS [155]. Threonine and tyrosine residue phosphorylation controls JNK activation, whereas MAPK phosphatases drive a negative feedback process that deactivates JNK [156].

In a mouse model of CaCl₂-induced abdominal aortic aneurysm, quercetin was reported to decrease the production of ROS by inhibiting activation of the transcription factor, AP-1, and downregulating the expression of JNK and the phosphorylated version [157]. Additionally, quercetin mitigates H₂O₂-induced apoptosis in mesangial cells by modulating the AP-1 pathway. H₂O₂-induced rapid phosphorylation of ERK and JNK kinases is also reduced with quercetin pre-treatment. Additionally, it has been shown that JNK and the JNK substrate, c-Jun, mediate apoptosis in a variety of cell types [157, 158]. Quercetin prevents RL34 cell JNK activation when 4-hydroxy-2-nonenal, a byproduct of lipid peroxidation, is present [159]. The inhibitory effect of quercetin in stress-related signalling pathways, particularly involving the enzyme PKC, was suggested as the underlying mechanism in HNE-induced pathways. These results show that the JNK signalling pathway, which has been shown in macrophages, mediates the anti-inflammatory and protective effects of quercetin (Figure 6) [160].

TNF- α pathway

TNF is an inflammatory cytokine released by macrophages and monocytes during acute inflammation. TNF sets off several signalling cascades within cells that lead to apoptosis and necrosis. TNF- α and TNF- β are the two forms of TNF. The anti-inflammatory qualities of quercetin have been demonstrated by several *in vitro* and *in vivo* studies [161]. For example, by blocking the TNF- α pathway, quercetin reduces inflammation brought on by 6-hydroxydopamine (6-OHDA) toxicity in PC12 cells and zebrafish models. Additionally, by reducing the LPS-induced synthesis of TNF and IL-1 mRNA in glial cells and astrocytes, quercetin reduces microglial-mediated neuronal cell death in co-cultures of microglia and PC12 cells [162]. Through TLR4 regulation and

TNF- α pathway suppression, quercetin-loaded nanoparticles had notable anti-inflammatory effects by reducing the stress caused by oxysterol in human neuroblastoma cells, SH-SY5Y [163]. Additionally, microglial cells are crucial in starting the inflammatory cascade-mediated neuronal death by producing inflammatory and neurotoxic mediators, like TNF- α , IL-1, IL-6, and NO [164]. In studies using astrocyte cells, quercetin reduced the number of apoptotic cells in rat glioma cells (C6 cells) by decreasing the formation of ROS and shielding the cells from toxicity from tertiary-butyl hydroperoxide and H₂O₂ [165]. Additionally, quercetin increased the survival of rat oligodendrocytes (OLN-93), which are essential for the health of neurons [166]. The anti-inflammatory properties are probably due to the capacity to suppress TNF- α expression by modulating NF- κ B (Figure 6).

Peroxisome proliferator-activated receptor gamma co-activator 1-alpha (PGC-1 α) pathway

PGC-1 α has a critical role in the CNS by activating various nuclear receptors and influencing their functions. Research has shown that nuclear PGC-1 α levels rise significantly after traumatic brain injury (TBI), particularly in the cortical neurons, suggesting involvement in post-TBI neurobiologic changes. A study investigated the neuroprotective properties of quercetin and the effect on PGC-1 α signalling pathways [113]. Mice administered quercetin showed less brain water content and less neuronal degeneration in processed brain tissues, which suggested that quercetin reduces cerebral edema after TBI. Following quercetin administration, alterations in downstream PGC-1 α signalling pathways verified the pathway significance in preventing cerebral cortex mitochondrial dysfunction [167]. Furthermore, in the AD model mouse, learning and memory were improved by upregulating PGC-1 α and SIRT1 levels. PGC-1 α and SIRT1 deacetylation and activation promoted mitochondrial biogenesis and reduced AD mitochondrial dysfunction [168]. Furthermore, suppression of BACE1, a crucial transcriptional regulator, is linked to SIRT1-PGC-1 α activation (Figure 6) [169].

Sirtuins pathway

Sirtuins, particularly SIRT1, perform a pivotal role in cellular stress resistance and longevity. Quercetin activation of SIRT1 results in deacetylation of transcription factors involved in anti-apoptotic and anti-inflammatory responses. Through SIRT1 activation, quercetin enhances mitochondrial health, supporting cellular resilience against neurodegenerative stressors, hence supporting the preservation of neuronal integrity and function (Figure 6) [170].

CREB pathway

CREB, a key regulator of neuronal plasticity and memory formation, is activated by quercetin and promotes the expression of neuroprotective genes. Quercetin-induced CREB

activation fosters neurogenesis, cognitive enhancement, and long-term survival of neurons. This pathway is particularly relevant in memory preservation and learning, providing therapeutic insights for conditions, like AD (Figure 6) [171].

MAPK pathway

The MAPK pathway, which includes ERK, JNK, and p38, governs cellular responses to oxidative and inflammatory stress. Quercetin modulates MAPK signalling by downregulating p38 and JNK, thereby decreasing pro-inflammatory responses and reducing apoptosis. This pathway modulation by quercetin promotes neuronal survival and homeostasis, making downregulation of p38 and JNK a pivotal aspect of neuroprotective action (Figure 6) [172].

Crosstalk between quercetin-regulated signalling pathways in neuroprotection

PI3K/Akt and Nrf2-ARE pathway interaction

Quercetin activation of the PI3K/Akt pathway promotes neuronal survival and stimulates Nrf2 nuclear translocation, which enhances the expression of downstream antioxidant enzymes, such as HO-1 and SOD. Akt-mediated phosphorylation of Nrf2 prevents degradation by Keap1, thereby facilitating oxidative defense mechanisms. This crosstalk is crucial for amplifying neuroprotective responses under oxidative stress [173].

MAPK, JNK, and Nrf2 crosstalk

MAPK family members, such as ERK and p38, can modulate Nrf2 phosphorylation, affecting nuclear localization. Quercetin inhibition of JNK and p38 pathways reduces inflammation and synergizes with Nrf2-driven transcription of antioxidant genes. Thus, suppression of stress-activated MAPKs enhances the efficiency of Nrf2 signalling [174].

Sirtuin and PGC-1 α axis integration

SIRT1, activated by quercetin, deacetylates PGC-1 α , which enhances mitochondrial biogenesis and energy metabolism. This axis also enhances PI3K/Akt signalling, suggesting triangular feedback that integrates energy homeostasis, anti-apoptotic mechanisms, and oxidative stress regulation [175].

NF- κ B suppression and anti-inflammatory feedback

PI3K/Akt activation inhibits NF- κ B translocation via phosphorylation of I κ B α , while quercetin direct inhibition of

MAPK-JNK and TNF- α further suppresses inflammatory cytokine release. This orchestrated inhibition across pathways diminishes neuroinflammation in diseases, like AD and PD [176, 177].

PON2 and mitochondrial signalling coupling

PON2 enhances mitochondrial stability and mitigates superoxide generation. PON2 expression, increased by quercetin, may be regulated through indirect modulation of JNK and Akt pathways, as these govern mitochondrial membrane potential and apoptotic thresholds [178].

CREB and PI3K/Akt synergy in neurogenesis

The PI3K/Akt-CREB pathway supports BDNF expression and synaptic plasticity. Quercetin enhances CREB phosphorylation downstream of Akt activation, promoting memory consolidation and neuronal differentiation, key elements inhibit neurodegeneration [179]. The integration of these signalling cascades enables a multi-targeted effect, in which quercetin orchestrates a finely tuned balance between antioxidant defense, inflammation control, mitochondrial stabilization, and neuronal repair. Understanding this interplay is crucial for optimizing quercetin-based therapies in complex NDDs.

Quercetin as a direct inhibitor of hypoxia-inducible factor prolyl hydroxylase (HIF-PHD): an anti-ischemic mechanism

HIF prolyl hydroxylase enzyme: a target for neuroprotection

Prolyl hydroxylases (PHD1, PHD2, and PHD3) function as oxygen sensors and catalyze the hydroxylation of HIF-1 α at proline residues, marking prolyl hydroxylases for ubiquitin-mediated proteasomal degradation. Inhibition of HIF-PHDs under hypoxia allows HIF-1 α accumulation and translocation to the nucleus, initiating transcription of protective genes, like VEGF, which collectively confer neurovascular repair and metabolic adaptation [48, 180].

Evidence supporting the anti-ischemic effects of quercetin via HIF stabilization

Several preclinical studies have confirmed that quercetin mimics hypoxic preconditioning by stabilizing HIF-1 α *in vitro* and *in vivo*. For example, in cerebral ischemia

models, quercetin administration significantly increases HIF-1 α levels and VEGF expression, enhancing angiogenesis and reducing infarct size. Moreover, the anti-ischemic activity of quercetin has been shown to be independent of classical kinase signalling, highlighting HIF-PHD inhibition as a distinct, direct mechanism [181].

Therapeutic implications in neurologic disorders

By stabilizing HIF-1 α through direct PHD inhibition, quercetin may offer substantial therapeutic advantage in treating stroke, TBI, and NDDs exacerbated by hypoxic stress. This mechanism is particularly relevant in patients in which ischemia-induced cell death and vascular damage contribute to disease progression, such as occurs in AD and PD. Importantly, the dual role of quercetin as an antioxidant and HIF stabilizer may synergistically improve neurologic outcomes [182].

Clinical relevance and pharmacologic outlook

Although most HIF-PHD inhibitors under clinical evaluation (e.g., roxadustat) are synthetic, quercetin offers a natural, bioavailable alternative with minimal toxicity. The HIF-stabilizing property of quercetin supports ongoing interest in phytochemicals for ischemic preconditioning strategies in neurology. Thus, inclusion of this mechanism not only expands the pharmacodynamic spectrum of quercetin but also underscores the translational value in ischemia-related neurotherapy [183, 184].

Disease-specific relevance of HIF-PHD inhibition by quercetin

Quercetin in ischemic stroke and cerebral ischemia

Quercetin treatment significantly reduces infarct volume and neurologic deficits in animal models of middle cerebral artery occlusion (MCAO). These effects were attributed to HIF-1 α stabilization through HIF-PHD inhibition, leading to upregulation of VEGF and angiogenesis and promoting neurovascular repair and oxygen homeostasis. Quercetin preconditioning mimics hypoxia-induced neuroprotection, suggesting potential for stroke management [185].

Application in TBI

Quercetin prevents cerebral edema and improves BBB integrity in rodent TBI models. These effects are partly mediated through activation of the HIF-1 α pathway, indicating neuroprotective adaptation to hypoxia via PHD inhibition.

Combined with the anti-inflammatory action, HIF-PHD targeting by quercetin contributes to better functional recovery post-TBI [186].

Relevance in PD

PD is characterized by dopaminergic neuronal death that is often exacerbated by mitochondrial dysfunction and localized hypoxia. Studies have shown that quercetin-induced HIF-1 α activation improves mitochondrial bioenergetics and enhances expression of glycolytic enzymes in PD models, potentially offering a compensatory metabolic mechanism under hypoxic stress [187].

AD and neurovascular deficits

AD pathology includes neurovascular degeneration and chronic hypoperfusion. By stabilizing HIF-1 α , quercetin helps restore VEGF levels and improve cerebral perfusion, mitigating hypoxia-related neuronal damage and enhancing memory performance in AD mouse models [147].

Integrative summary of quercetin neuroprotective mechanisms

Multitargeted modulation of key pathways

Quercetin exerts neuroprotective activity by regulating interconnected signalling networks, including Nrf2-ARE, PI3K/Akt, MAPK, CREB, and SIRT1, which collectively enhance antioxidant defenses, promote neurogenesis, and suppress inflammation and apoptosis.

Protection against oxidative stress and mitochondrial dysfunction

Through direct ROS scavenging and stimulation of endogenous antioxidant enzymes, like SOD and CAT, quercetin maintains mitochondrial integrity and supports ATP synthesis. Quercetin also prevents mitochondrial swelling and lipid peroxidation, especially in AD, PD, and HD models.

Anti-inflammatory effects across neural tissues

By suppressing the NF- κ B and TNF- α pathways, quercetin limits microglial activation, cytokine release, and endothelial adhesion molecule expression, thereby preserving BBB integrity and reducing chronic neuroinflammation.

Modulation of protein aggregation

Quercetin inhibits amyloid-beta (A β) aggregation, τ hyperphosphorylation, and α -synuclein fibrillization, reducing synaptic dysfunction and neuronal toxicity across NDD models.

Enhancement of neuroplasticity and cognitive function

Quercetin stimulates BDNF- and CREB-mediated transcription, promotes dendritic growth, and enhances learning and memory by preserving ACh levels through AChE and BChE inhibition.

Neurovascular protection and BBB integrity

By stabilizing tight junction proteins (claudin-5 and occludin) and promoting NO bioavailability, quercetin supports cerebral perfusion and reduces leukocyte infiltration in neurovascular units.

Gene modulation and epigenetic influence

Emerging evidence suggests that quercetin affects the transcription of genes related to neuroprotection through epigenetic modulation of key enzymes and transcription factors, such as PGC-1 α , SIRT1, and HIF-1 α , indicating potential for long-term neuronal resilience.

Clinical and translational promise

The synergy of these molecular effects has been validated in multiple *in vitro*, *in vivo*, and clinical trials, affirming the potential of quercetin as an integrative therapeutic agent in NDD management.

In vitro characterization and cell viability studies related to quercetin

Quercetin has been extensively evaluated in various *in vitro* models to assess cytoprotective, antioxidant, and anti-inflammatory properties. While neural cell lines, such as SH-SY5Y, PC12, and BV-2 microglial cells, are commonly used for direct neuroprotective investigations, HepG2 cells derived from human hepatocellular carcinoma are frequently used in complementary studies to evaluate cytotoxicity, metabolic stability, and cellular bioavailability of quercetin and its derivatives. These hepatocyte-like

cells possess active phase I and II metabolic enzymes and provide valuable insights into the hepatic metabolism and safety profile of phytochemicals prior to neurotherapeutic translation [188, 189].

Several studies have utilized HepG2 cells for MTT and LDH assays to quantify the effect of quercetin on cell viability and oxidative stress. For example, quercetin showed dose-dependent cytoprotection against H₂O₂-induced oxidative damage in HepG2 cells by upregulating antioxidant defense enzymes, such as GSH peroxidase and SOD. Moreover, these cells have served as a robust model for evaluating the hepatocellular impact of quercetin conjugates, including glycosidic and methylated forms, which are biologically relevant metabolites after oral administration. However, it is important to clarify that the current review compiles and analyses data from *in vitro* studies without performing any new experimentation involving HepG2 or other cell lines. The inclusion of HepG2-related data in this context aims to provide a holistic view of the safety, pharmacokinetics, and suitability of quercetin for neurologic applications [190, 191].

Clinical trials of quercetin focusing on therapeutic potential and outcomes in NDDs

Quercetin research as a possible treatment for NDDs has increased significantly in the last several years. The use of quercetin as a possible treatment for NDDs has grown significantly. Progressive neuronal degeneration, which results in cognitive and motor impairments, is a hallmark of NDDs. Additionally, quercetin or quercetin combination therapy has shown encouraging results in neuroprotection or NDDs in clinical trials. A large number of clinical trials have been conducted to evaluate the mechanisms, safety, and efficacy of these drugs as the focus on drug development increases (Table 6) provides an updated overview of quercetin and other medications presently undergoing clinical trials along with the results in treating NDDs.

Clinical evidence of quercetin in neuroprotection

Quercetin, a flavonoid found in many fruits, vegetables, and other plant-based foods, has shown significant neuroprotective effects in preclinical and clinical studies primarily by antioxidant, anti-inflammatory, and anti-apoptotic characteristics. The ability to scavenge ROS and modulate neuroinflammatory pathways is pivotal in mitigating the neurodegeneration seen in conditions, like AD and PD. Clinical evidence underscores the potential of quercetin in reducing neurotoxicity. For example, a study involving patients with ischemic stroke demonstrated that quercetin inhibits the secretion of inflammatory cytokines and reduces platelet aggregation, thereby minimizing inflammatory thrombosis

and protecting neuronal integrity. This outcome was attributed to quercetin modulation of ROS and inhibition of neuroinflammation-associated pathways, which are critical for reducing ischemic damage.

Quercetin administration in patients with mild cognitive impairment (MCI) was the subject of one noteworthy case study. Daily oral administration of quercetin for 6 months significantly improved memory recall and executive function compared to the placebo group. The improvement correlated with reduced biomarkers of oxidative stress and inflammation in cerebrospinal fluid, suggesting the direct involvement of quercetin in neuronal health and plasticity [61, 192].

One example involves the application of quercetin in AD models, where quercetin reduced amyloid-beta toxicity and oxidative damage. In a recent animal study, quercetin inhibited the aggregation of Aβ plaques while activating the NRF2/HO1 pathway, leading to neuroprotective effects and improved memory in rodents. This finding illustrates the capability of quercetin to modify the disease process rather than merely alleviating symptoms, warranting further trials for integration into therapeutic regimens for AD and related disorders [193].

Another case study focused on patients with PD, in which adjunctive therapy with quercetin alongside standard dopamine agonists improved motor symptoms and slowed disease progression. This benefit was hypothesized to arise from the ability of quercetin to stabilize mitochondrial function, reduce neuroinflammatory markers, and enhance dopaminergic neuron survival [194].

Future perspective

The therapeutic promise of quercetin in neuroprotection calls for further research is focused on overcoming bioavailability challenges and exploring advanced delivery systems, such as nanoformulations and conjugates. Future investigations could prioritize developing encapsulated quercetin delivery systems to enhance BBB permeability and sustained release, which are critical for treating NDDs. Additionally, understanding the interaction of quercetin with molecular pathways, including NF-κB, HO-1, and TLR4/MyD88, will deepen insights into the mechanistic roles in mitigating oxidative stress, neuroinflammation, and neuronal apoptosis. Expanding clinical trials with diverse patient populations and long-term studies will be essential to establish optimal dosing regimens, side effect profiles, and therapeutic efficacy. Collaborative efforts between researchers and clinicians are crucial for translating the neuroprotective properties of quercetin into viable therapeutic interventions for diseases, like AD, PD, and HD. Furthermore, genetic and epigenetic studies exploring the impact of quercetin on neuroprotective gene expression could unlock personalized medicinal approaches.

Conclusion

In conclusion, quercetin, as a naturally occurring flavonoid, has demonstrated extensive neuroprotective

Table 6 Clinical Trials of Quercetin and Outcomes (US National Library of Medicine. Available online: <https://clinicaltrials.gov>)

Serial No.	Title	Intervention or Treatment	Clinical Trial Number (Current Requirement Status)	Present Clinical Trial Phase	Clinical Outcome
1.	Senolytic treatment to regulate the progression of AD	Dasatinib + quercetin (AD)	NCT04063124 (completed)	Phase 1 and Phase 2	In preclinical models, the combination of the two medicines has been shown to efficiently eliminate senescent cells and treat a variety of chronic medical diseases, such as hepatic stenosis, vascular stiffness, muscle weakness, osteoporosis, and physical frailty
2.	ALSENLTJ: Senolytics for Alzheimer's disease	1. Dasatinib 2. Quercetin (mild cognitive impairment, AD)	NCT04785300 (enrolling by invitation)	Phase 1 and Phase 2	The number of participants who experienced hypersensitive responses and adverse events (AEs), including serious adverse events (SAEs)
3.	Dasatinib with quercetin safety and viability in adults at risk for AD	1. Dasatinib 2. Quercetin (aging)	NCT05422885 (completed)	Phase 1 and Phase 2	Using transcranial Doppler ultrasound, the cerebral blood flow changes during N-back cognitive activity
4.	RQC for the prevention of AD and retinal amyloid- β	1. Resveratrol, quercetin, and curcumin (RQC) 2. Curcumin (Alzheimer disease, mild cognitive impairment, cognitive decline)	NCT06470061 (not recruiting)	Phase 2	Change in retinal amyloid- β
5.	Senolytic therapy to modulate the progression of AD (SToMP-AD) study (SToMP-AD)	1. Dasatinib + quercetin 2. Placebo capsules (AD, early onset mild cognitive impairment)	NCT04685590 (active, not recruiting)	Phase 2	Primary: The treatment group had more adverse events (AEs) and serious adverse events (SAEs) compared to the placebo group. Secondary: 1. A shift in the senescence-associated secretory phenotype composite score; a blood test for cellular senescence 2. A shift in the blood cluster of differentiation 3 (CD3), a hallmark of cellular senescence 3. Modification of the blood marker for cellular senescence; cyclin-dependent kinase inhibitor 2A (p16INK4A+) 4. Modification of blood marker T lymphocytes for cellular senescence 5. Adjusting the Clinical Dementia Rating Scale Sum of Boxes (CDR-SB) slope 6. Slope variation of the 14-item cognitive subscale of the AD Assessment Scale (ADAS-Cog 14)
6.	Short-term efficacy and safety of perispinal administration of etanercept in mild-to-moderate AD	1. Etanercept 2. Curcumin, luteol, theaflavin, acid, fish oil, quercetin, resveratrol (AD)	NCT01716637 (completed)	Phase 1	Primary: The Mini-mental Status Examination (MMSE) score was affected differently after 6 weeks of treatment with etanercept and nutritional supplements compared to nutritional supplements alone. Secondary: 1. After 6 weeks of etanercept treatment with nutritional supplements, the AD Assessment Scale-Cognitive Subscale (ADAS-cog) score differed from nutritional supplements alone. 2. Disparity between the Montreal Cognitive Assessment (MoCA) score following 6 weeks of treatment with etanercept + nutritional supplementation compared to nutritional supplementation alone.

properties through mechanisms, like antioxidant activity, anti-inflammatory effects, mitochondrial stabilization, and modulation of signalling pathways (Nrf2-ARE and PI3K/Akt). These actions target key processes implicated in NDDs, including AD, PD, and HD. Despite promising preclinical and clinical data, challenges, such as poor bioavailability and metabolic instability, limit therapeutic application. Recent advancements in quercetin delivery systems, including nanoparticles and nanoemulsions, have significantly enhanced its pharmacokinetics, presenting a strong case for its integration into neurodegenerative treatment protocols. Future therapeutic interventions may capitalize on combining quercetin with complementary neuroprotective agents, enhancing the synergistic effects while minimizing side effects. For example, clinical studies have shown the efficacy of quercetin in reducing amyloid-beta aggregation and oxidative damage in AD, highlighting the potential as an adjunct therapy. Further exploration of the role of quercetin in regulating neuroinflammatory and apoptotic pathways could extend the application to other CNS-related disorders, including ischemic strokes and multiple sclerosis. Large-scale, long-term clinical trials are essential to determine the ideal dosages to confirm the effectiveness, as well as address safety concerns. Quercetin represents a promising natural compound, paving the way for innovative and effective strategies in managing NDDs.

Ethics statement

No direct interactions with human or animal subjects were involved. Therefore, ethical approval and informed consent were not required.

Author contributions

Conceptualization, Ishita Debnath; Suman Ghosh; and Sobhanjan Bhunia; writing- original draft preparation, Ishita Debnath; Suman Ghosh; and Sobhanjan Bhunia; writing- review and editing, Aditi Nayak; Souvik Basak; Sumit Nandi; Soumik Bhattacharjee; Sajal Kumar Jha. All authors have read and agreed to the published version of the manuscript.

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Conflicts of interest

The authors declare that there are no conflicts of interest.

Abbreviations

AD, Alzheimer’s disease
 PD, Parkinson’s disease
 HD, Huntington’s disease
 NDDs, Neurodegenerative diseases
 ROS, Reactive oxygen species
 RNS, Reactive nitrogen species
 GSH, Glutathione
 SOD, Superoxide dismutase
 A β , Amyloid-beta
 BBB, Blood-brain barrier
 APP, Amyloid precursor protein
 BDNF, Brain-derived neurotrophic factor
 CREB, cAMP response element binding protein
 GSK3 β , Glycogen synthase kinase-3 β
 MAPK, Mitogen-activated protein kinase
 NF- κ B, Nuclear factor kappa-light-chain-enhancer of activated B cells
 PON2, Paraoxonase 2
 HIF, Hypoxia-inducible factor
 PHD, Prolyl hydroxylase domain
 VEGF, Vascular endothelial growth factor
 TNF- α , Tumor necrosis factor-alpha
 IL, Interleukin
 SIRT1, Sirtuin 1
 PGC-1 α , Peroxisome proliferator-activated receptor gamma coactivator 1-alpha
 mPTP, Mitochondrial permeability transition pore
 OATPs, Organic anion-transporting polypeptides
 AChE, Acetylcholinesterase
 BChE, Butyrylcholinesterase
 ASO, Antisense oligonucleotide
 CRISPR, Clustered regularly interspaced short palindromic repeats
 SAR, Structure–activity relationship
 NO, Nitric oxide
 ERK, Extracellular signal-regulated kinase
 JNK, c-Jun N-terminal kinase
 COX, Cyclooxygenase
 LOX, Lipoxygenase
 ICAM-1, Intercellular adhesion molecule-1
 VCAM-1, Vascular cell adhesion molecule-1

Supplementary materials

Supplementary Material can be downloaded from https://bio-integration.org/wp-content/uploads/2025/08/bioi20250073_Supplemental.pdf.

Figure authorship and originality statement

All figures (Figures 1–6) in the current version of the manuscript, including the graphical abstract and structure-activity relationship (SAR) diagrams, have been professionally

re-drawn using the ChemDraw Ultra 22.2.0 tool. Each image was exported in 600 DPI high-resolution, suitable for print and digital publication. Special attention was paid to symbol standardization, labelling clarity, structural accuracy, and pathway annotations to ensure that molecular interactions,

therapeutic targets, and signalling cascades are clearly communicated to both specialist and interdisciplinary readers. Color coding and iconography were integrated to improve readability and scientific value, aligning with the visual communication standards of *Bio-Integration*.

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