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Review Article

Antioxidant Status of Natural Products in Neurodegenerative Disorders: A Comprehensive Review

Mueen Ahmed KK*, Mohammed Yunus

Manuscript Technomedia LLP, Vivekananda Nagar, Bengaluru, Karnataka, INDIA.

ABSTRACT

Neurodegenerative Disorders (NDDs), including Alzheimer's Disease (AD), Parkinson's Disease (PD), Amyotrophic Lateral Sclerosis (ALS), Huntington's Disease (HD), and Multiple Sclerosis (MS) represent a growing global health burden, affecting hundreds of millions of individuals worldwide. A central mechanistic driver of neurodegeneration is oxidative stress, defined as an imbalance between Reactive Oxygen Species (ROS) generation and endogenous antioxidant defense systems. Natural products derived from plants, fungi, and marine organisms harbor a rich array of antioxidant phytochemicals-including polyphenols, flavonoids, alkaloids, terpenoids, and Vitamins-whose neuroprotective properties are the subject of intense scientific investigation. This review aimed to comprehensively evaluate the antioxidant status and neuroprotective mechanisms of natural products specifically relevant to neurodegenerative disorders, synthesizing evidence from *in vitro, in vivo*, and clinical research. A systematic literature search was conducted across PubMed, Consensus, and supplemental databases using relevant MeSH terms and keywords, including "natural antioxidants," "neurodegenerative disorders," "oxidative stress," "Nrf2 pathway," and specific compound names. Priority was given to studies published between 2020 and 2026, with up to five seminal older works included were essential. Evidence indicates that natural antioxidants, such as curcumin, resveratrol, quercetin, Epigallocatechin-3-Gallate (EGCG), baicalein, withanolides, bacosides, and ginsenosides exert neuroprotection through multiple mechanisms: direct ROS scavenging, activation of the Nrf2-Keap1-Antioxidant Response Element (ARE) antioxidant pathway, mitochondrial protection, modulation of neuroinflammatory cascades, and inhibition of pathological protein aggregation (amyloid-β and α-synuclein). Despite robust preclinical data, clinical translation remains challenged by poor bioavailability, rapid metabolism, and limited long-term human trial data. Natural product-derived antioxidants represent a scientifically promising, multi-targeted strategy for the prevention and adjunctive treatment of neurodegenerative disorders. Advances in nanotechnology-based delivery systems and standardized formulations are expected to bridge the gap between preclinical success and clinical efficacy. Rigorous clinical trials with standardized dosing are urgently needed.

Keywords: Antioxidants, Natural Products, Neurodegenerative Disorders, Neuroprotection, Nrf2 Pathway, Oxidative Stress, Polyphenols, Reactive Oxygen Species.

Correspondence:
Dr. Mueen Ahmed
Manuscript Technomedia LLP, No. 22 (New No. 40), 3rd Cross, Vivekananda Nagar, Bengaluru, Karnataka, INDIA.
Email: mueen.ahmed@gmail.com

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INTRODUCTION

Neurodegenerative Disorders (NDDs) constitute one of the most devastating classes of human disease, characterized by progressive deterioration of neuronal structure and function, ultimately resulting in cognitive decline, motor impairment, and, in many cases, premature death. The global prevalence of these disorders is accelerating in parallel with an aging world population, positioning them as a preeminent public health challenge for the 21st century. Alzheimer's Disease (AD) alone affects an estimated 55 million people globally, while Parkinson's Disease (PD) afflicts over ten million individuals, with both figures projected to at least double by 2050 Figure 1.[1] Other NDDs, including Amyotrophic Lateral Sclerosis (ALS), Huntington's Disease (HD), and Multiple Sclerosis (MS), collectively impose a further immense burden on patients, caregivers, and healthcare systems.

Despite decades of intensive pharmaceutical research, current pharmacological interventions for NDDs remain largely symptomatic, providing temporary relief without meaningfully altering disease course or progression. Levodopa for PD, acetylcholinesterase inhibitors for AD, and disease-modifying therapies for MS represent the narrow horizon of available treatments, all of which are associated with significant limitations, including adverse effects, drug resistance, and high costs.[2] The absence of curative therapies and the incomplete understanding of disease pathogenesis necessitate the exploration of novel therapeutic paradigms.

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Among the most consistently implicated pathogenic mechanisms in NDDs is oxidative stress-the state that arises when Reactive Oxygen Species (ROS) production exceeds the capacity of cellular antioxidant defenses. The brain is uniquely vulnerable to oxidative injury due to its high metabolic rate, elevated oxygen consumption, abundant lipid content in neuronal membranes, and relatively modest endogenous antioxidant capacity compared to other organs.[3] Excessive ROS production damages proteins, lipids, and DNA, triggers mitochondrial dysfunction, activates pro-inflammatory signaling cascades, and precipitates pathological protein misfolding-collectively driving neurodegeneration.[4]

Natural products, particularly those derived from medicinal plants, represent a historically rich and pharmacologically diverse repository of bioactive compounds. Phytochemicals, such as polyphenols, flavonoids, terpenoids, alkaloids, and Vitamins have demonstrated remarkable antioxidant activities in a wide range of experimental systems. Critically, many of these compounds act through multiple molecular targets simultaneously-a feature of considerable therapeutic value in multifactorial diseases, such as NDDs. Compounds, including curcumin, resveratrol, quercetin, Epigallocatechin-3-Gallate (EGCG), and withanolides, have been shown to scavenge ROS directly, activate the master antioxidant transcription factor Nrf2, inhibit neuroinflammatory signaling, and interfere with the aggregation of disease-specific proteins, such as amyloid-β (Aβ) and α-synuclein.[5-7]

Despite a substantial and growing body of preclinical evidence, the clinical translation of natural antioxidants faces significant obstacles. These include poor oral bioavailability, rapid systemic metabolism, limited penetration of the Blood-Brain Barrier (BBB), and insufficient clinical trial data across diverse patient populations. Recent advances in pharmaceutical nanotechnology-including liposomal delivery systems, solid lipid nanoparticles, and nanostructured lipid carriers-are beginning to address these challenges, opening new avenues for effective clinical deployment of phytochemical antioxidants.

This review aims to synthesize and critically evaluate the current evidence base regarding the antioxidant status of natural products specifically in the context of neurodegenerative disorders. The review addresses the mechanistic foundations of oxidative stress in neurodegeneration, categorizes key natural antioxidant phytochemicals and their specific mechanisms of action, discusses disease-specific evidence for major NDDs, examines the role of key molecular pathways, including Nrf2, and identifies the principal challenges and future directions for clinical translation (Table 1).

Historical Background and Evolution of the Field

The recognition of oxidative stress as a pathophysiological driver of neurodegeneration emerged gradually over several decades of biochemical and neuropathological research. Early observations in the mid-20th century documented elevated lipid peroxidation products and reduced Glutathione (GSH) levels in post-mortem brain tissue from individuals with AD and PD, providing the first biochemical signatures of antioxidant depletion in neurodegeneration. The discovery by Halliwell and colleagues in the 1980s that ROS could directly damage neuronal lipids, DNA, and proteins laid a conceptual groundwork for antioxidant-based therapeutic strategies, establishing the Superoxide Dismutase (SOD)-catalase-glutathione peroxidase triad as the primary endogenous defense architecture.

The traditional use of plants to treat memory loss, tremors, and cognitive decline predates modern neuroscience by millennia. Ayurvedic medicine in the Indian subcontinent long employed *Bacopa monnieri* (Brahmi) and *Withania somnifera* (Ashwagandha) as nootropics and neuroprotective tonics, while Traditional Chinese Medicine (TCM) prescribed *Ginkgo biloba*, ginseng root, and turmeric preparations for neurological conditions dating back thousands of years. The scientific elucidation of these traditional practices began in earnest in the late 20th century with the isolation and characterization of specific bioactive compounds-notably bacoside A from *Bacopa monnieri* and curcumin from *Curcuma longa* -and the documentation of their antioxidant properties in cell and animal models.

The identification of the Nrf2 (nuclear factor erythroid 2-related Factor 2) transcription factor and its role in coordinating the cellular antioxidant response, formalized by Itoh and colleagues in the 1990s, represented a landmark advance. The subsequent discovery that natural phytochemicals, including sulforaphane and curcumin could activate Nrf2 to upregulate Phase II detoxification enzymes (heme oxygenase 1 [HO-1], NQO1, GST) provided a mechanistic framework for understanding how dietary antioxidants could confer systemic neuroprotection.[8] This framework catalyzed a wave of translational research in the 2000 and 2010-second that substantially expanded the inventory of neuroprotective natural compounds.

More recently, the discovery of ferroptosis-a form of iron-dependent, lipid peroxidation-driven programmed cell death-has added a new dimension to the oxidative stress paradigm in neurodegeneration. Pathological iron accumulation and lipid peroxidation hallmarks of ferroptosis have been detected in PD brain tissue, prompting investigation of natural compounds, such as quercetin, baicalein, and EGCG as ferroptosis inhibitors.[9] Simultaneously, the emergence of evidence linking mitochondrial oxidative dysfunction to NDD pathogenesis has reinforced the importance of mitochondria-targeted antioxidant strategies as a therapeutic frontier.[10,11]

Oxidative Stress Mechanisms in Neurodegenerative Disorders

Reactive Oxygen Species and the Neuronal Environment

The brain accounts for approximately 20% of total body oxygen consumption despite representing only 2% of body mass, creating a metabolic environment particularly susceptible to oxidative injury. Reactive oxygen species-including superoxide ($O_2\bullet^-$), hydrogen peroxide (H_2O_2), and the hydroxyl radical ($\bullet OH$)-are generated as natural by-products of mitochondrial Electron Transport Chain (ETC) activity, particularly at Complexes I and III. Under physiological conditions, endogenous antioxidant systems, including SOD, catalase, and glutathione peroxidase maintain ROS within acceptable homeostatic limits. However, under conditions of metabolic stress, neuroinflammation, xenobiotic exposure, or genetic predisposition, the balance tilts dramatically toward oxidative damage.[3]

Neuronal membranes are enriched in Polyunsaturated Fatty Acids (PUFAs), particularly Docosahexaenoic Acid (DHA), which are highly susceptible to lipid peroxidation by ROS, producing cytotoxic aldehydes, such as 4-Hydroxynonenal (4-HNE) and Malondialdehyde (MDA). Protein carbonylation and nitration, mediated by ROS and Reactive Nitrogen Species (RNS), impair enzymatic function and promote pathological protein misfolding. Mitochondrial DNA, which lacks protective histones and efficient repair mechanisms, is another priority target of oxidative assault, leading to compromised bioenergetics and initiation of apoptotic cascades.[12]

Mitochondrial Dysfunction and the Reactive Oxygen Species–Neurodegeneration Loop

Mitochondria occupy a central position in NDD pathogenesis by functioning simultaneously as the primary source of neuronal ROS and as the primary victim of oxidative damage-a reinforcing feedback loop that accelerates neurodegeneration. Impaired ETC activity, characteristic of both AD and PD, reduces ATP production while simultaneously increasing electron leak and superoxide generation. In PD, the selective loss of dopaminergic neurones in the substantia nigra has been linked to deficiencies in mitochondrial Complex I activity, exacerbated by oxidative dopamine metabolism, which itself generates cytotoxic H_2O_2.[13] In AD, Aβ oligomers directly impair mitochondrial bioenergetics by interacting with the cyclophilin D component of the mitochondrial Permeability Transition Pore (mPTP), triggering cytochrome c release and downstream apoptosis (Figure 2).

The discovery that natural compounds can directly protect mitochondria from oxidative stress has informed novel therapeutic strategies. Curcumin, for instance, has been shown to preserve mitochondrial membrane potential, inhibit Complex I-derived superoxide generation, and modulate mitochondrial biogenesis through the AMPK/PGC-1α axis.[14] *Astragalus membranaceus* extracts restored mitochondrial function in Drosophila NDD models by upregulating MFN2 (Mitofusin 2) and electron transport chain subunit gene expression,[15] illustrating the utility of plant-derived compounds in targeting mitochondrial oxidative mechanisms.

Neuroinflammation and Microglial Oxidative Activation

Neuroinflammation and oxidative stress are deeply intertwined in NDD pathogenesis, driven by the pathological activation of microglia-the resident innate immune cells of the brain. In response to Aβ deposits, α-synuclein aggregates, or cellular debris, microglia transition from a surveillance phenotype (M2) to a pro-inflammatory, neurotoxic state (M1), releasing pro-inflammatory cytokines (TNF-α, IL-1β, IL-6) and generating substantial quantities of ROS through NADPH oxidase (NOX2) activation. This creates a cytotoxic microenvironment that further damages neurones, triggers additional protein misfolding, and recruits additional inflammatory cells-forming a self-sustaining cycle of neuroinflammation and oxidative injury.[16]

Natural products that selectively promote M2 microglial polarization while suppressing M1-associated oxidative and inflammatory outputs represent a particularly elegant therapeutic strategy. Curcumin, resveratrol, aromatic-turmerone, and myricetin have all demonstrated capacity to reduce M1 microglial inflammatory markers while increasing M2 indicators in AD models. Andrographolide and sulforaphane were identified as suppressors of Aβ-induced microglial M1 activation and microglial-mediated necroptosis and apoptosis.[16] Similarly, asarone, galangin, and baicalein reduced oxidative stress and pro-inflammatory cytokines in M1-activated microglia in PD models, further validating the therapeutic promise of phytochemical microglial modulation.

Polyphenols, Flavonoids, and Their Neuroprotective Antioxidant Mechanisms

Curcumin

Curcumin (1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione), the principal bioactive diarylheptanoid from *Curcuma longa*, represents one of the most extensively studied natural antioxidants in the context of neurodegeneration. Curcumin's potent antioxidant activity derives from its β-diketone group and aromatic hydroxyl substituents, which enable direct donation of hydrogen atoms to free radicals. Beyond direct scavenging, curcumin activates the Nrf2/HO-1 pathway, upregulating the Antioxidant Response Element (ARE)-driven transcription of HO-1, NQO1, and GST, thereby amplifying endogenous antioxidant capacity in neurones.[5]

In the context of AD, curcumin has demonstrated the capacity to inhibit Aβ fibrillation, disaggregate existing plaques, and reduce Amyloid Precursor Protein (APP) cleavage. Concurrently,

it attenuates tau hyperphosphorylation by inhibiting GSK-3β activity. In PD models, curcumin protects dopaminergic neurones from MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine)-induced toxicity by reducing mitochondrial ROS generation and increasing dopamine levels in the striatum.[17] Despite these promising preclinical data, the major limitation of curcumin is its low oral bioavailability, attributed to poor aqueous solubility, rapid Phase II conjugation, and hepatic first-pass metabolism. Nanoformulations-including curcumin nanoparticles, liposomes, and polymeric encapsulations-have achieved significantly improved bioavailability and demonstrated enhanced neuroprotection in animal models.[14]

Resveratrol

Resveratrol (3,5,4′-trihydroxystilbene), a stilbenoid polyphenol concentrated in grape skins, berries, and peanuts, exerts its antioxidant and neuroprotective effects through multiple convergent pathways. It is a potent activator of SIRT1 (Sirtuin 1), a NAD^+-dependent deacetylase that deacetylates and thereby activates Nrf2, leading to transcriptional upregulation of antioxidant enzymes. Resveratrol additionally activates AMP-Activated Protein Kinase (AMPK), suppresses NF-κB-driven neuroinflammation, and modulates autophagy-a cellular quality control process critical for the clearance of misfolded proteins.[18] In the context of NAD^+ metabolism, resveratrol has been identified as a modulator of the NAMPT/NAD/SIRT axis, influencing energy metabolism, inflammation, and apoptosis simultaneously.[19]

In vascular dementia models, resveratrol demonstrated the highest binding affinity to Methylenetetrahydrofolate Reductase (MTHFR) among tested natural ligands, with molecular docking analysis revealing stabilization of the protein core and modulation of blood-brain barrier integrity.[20] Clinical studies involving resveratrol supplementation in cognitively impaired older adults have yielded encouraging but heterogeneous results, with some trials reporting improved cerebrovascular function and reduced inflammatory markers, while others have not demonstrated significant cognitive improvement. This variability likely reflects differences in dose, formulation, duration, and patient population rather than a lack of true biological effect.

Quercetin and Related Flavonoids

Quercetin (3,3′,4′,5,7-pentahydroxyflavone) is one of the most abundant and widely distributed plant flavonoids, found in onions, apples, berries, and medicinal plants, including *Ginkgo biloba*. Its neuroprotective antioxidant activities include direct scavenging of $O_2\bullet^-$ and •OH radicals, upregulation of intracellular SOD and catalase, Chelation of redox-active metals (Fe^{2+}, Cu^{2+}) that catalyze Fenton reactions, and inhibition of Monoamine Oxidase B (MAO-B)-an enzyme whose activity generates neurotoxic H_2O_2 in dopaminergic neurones.[21] Quercetin has also demonstrated capacity to inhibit Aβ aggregation, reduce tau hyperphosphorylation, and protect hippocampal neurones from glutamate-induced excitotoxicity.

Related flavonoids with significant neuroprotective evidence include luteolin, apigenin, baicalein, and myricetin. Baicalein, isolated from *Scutellaria baicalensis*, has received particular attention for its ability to inhibit α-synuclein fibrillation and disaggregate existing fibrils in PD models, positioning it as a dual antioxidant and antiaggregation agent. Luteolin has demonstrated potent inhibition of microglial M1 activation and reduction of pro-inflammatory cytokines, while also activating Nrf2/HO-1 signaling.[16] EGCG, the predominant flavanol of green tea (*Camellia sinensis*), combines metal chelation, ROS scavenging, and α-synuclein aggregation inhibition into a multifaceted neuroprotective profile.[22]

Lignans and Other Structural Polyphenols

Lignans are a structurally diverse class of phenylpropanoid metabolites widely distributed in Chinese herbal medicines and emerging as a significant class of neuroprotective natural products. Their primary antioxidant mechanisms include free radical scavenging, inhibition of lipid peroxidation, upregulation of antioxidant enzymes, and modulation of synaptic plasticity and neurogenic signaling. Recent systematic analysis has demonstrated that lignans exert antiapoptotic effects, regulate nervous-system neurotransmitter functions, and influence synaptic signal modulation-mechanisms relevant across multiple NDDs.[23] The lignan sesamin, isolated from sesame oil, demonstrated neuroprotection against 6-OHDA (6-hydroxydopamine)-induced oxidative damage in PD models, while isolariciresinol (identified as a bioactive component of *Dendrobium officinale* phenolic extract) contributed to proteostasis maintenance and autophagy activation in Alzheimer's Caenorhabditis elegans models.[24]

Plant-Specific Natural Products across Neurodegenerative Disorders

Withania somnifera (Ashwagandha)

Withania somnifera (L.) Dunal (*Solanaceae*), commonly known as Ashwagandha, occupies a unique position among neuroprotective botanicals as one of the few natural products with robust clinical trial data supporting its cognitive benefits. The principal bioactive constituents are withanolides-steroidal lactone compounds with potent anti-inflammatory, antioxidant, and adaptogenic properties. Withanolides exert neuroprotection through multiple mechanisms: they activate SIRT1 and Nrf2 signaling, suppress NF-κB-mediated neuroinflammation, reduce systemic oxidative stress markers, including C-reactive protein, and modulate the BDNF/CREB signaling axis to enhance synaptic plasticity. Multiple randomized controlled trials have demonstrated significant improvements in cognitive function, memory, and information processing speed in older adults and individuals

with mild cognitive impairment following supplementation with standardized Ashwagandha extract.[25] Preclinical data from AD and PD animal models further support its capacity to reduce Aβ burden and protect dopaminergic neurones.

Bacopa monnieri (Brahmi)

Bacopa monnieri (L.) Wettst. has been employed for millennia in Ayurvedic medicine as a nootropic and neuroprotective herb. Its active constituents-bacosides A and B, bacopaside I and II, and bacopasaponin C-modulate neurotransmission, reduce lipid peroxidation, enhance antioxidant enzyme activity, and protect against endoplasmic reticulum stress-mediated cell death. Bacopa has demonstrated neuroprotective efficacy across a range of NDD-relevant models, including AD (via AChE inhibition and Aβ clearance), PD (via protection of dopaminergic neurones), epilepsy (via GABA modulation), and depression (via serotonergic and noradrenergic regulation).[26] Importantly, clinical evidence from small Randomized Controlled Trials (RCTs) supports its cognitive benefits in healthy elderly volunteers and patients with age-associated memory impairment. Advances in novel delivery formulations, including liposomes and nanoparticles are being actively pursued to improve BBB penetration and ensure consistent therapeutic concentrations in the brain.

Ginkgo biloba

Ginkgo biloba extract (EGb761) remains one of the most extensively evaluated plant-derived neuroprotective agents globally. Its principal active constituents are ginkgolides A, B, C, and J (diterpene trilactones) and bilobalide (sesquiterpene lactone), as well as flavonol glycosides, including kaempferol and quercetin derivatives. Ginkgo extract exhibits Platelet-Activating Factor (PAF) antagonism, free radical scavenging, mitochondrial protective properties, and inhibition of neuronal apoptosis. Ginkgolide B, identified as a natural neuroprotective terpenoid, showed neuroprotective potential in in silico studies against key PD protein targets.[2] Several large RCTs, including the GuidAge trial and the Ginkgo Evaluation of Memory (GEM) study, examined EGb761 supplementation in preventing AD progression, yielding mixed results. While cognitive decline rates were not significantly altered in prevention settings, EGb761 demonstrated positive effects on neuropsychiatric symptoms and quality of life in established dementia, suggesting utility as an adjunctive treatment rather than a preventive monotherapy.

Panax ginseng and Gintonin

Panax ginseng (C. A. Mey.) is one of the most widely consumed medicinal plants globally, with documented neuroprotective properties spanning multiple NDDs. Ginsenosides-the principal bioactive triterpenoid saponins of ginseng-exert antioxidant, anti-inflammatory, antiapoptotic, and mitochondria-protective effects relevant to AD, PD, HD, and ALS. Gintonin, a glycolipoprotein component of ginseng root, has attracted particular recent attention as an exogenous agonist of Lysophosphatidic Acid (LPA) receptors-a novel mechanism through which ginseng modulates neuroprotection. Research indicates that gintonin maintains blood-brain barrier integrity, reduces neuroinflammation and oxidative stress-mediated neurodegeneration, and modulates synaptic transmission and neurogenesis in multiple NDD models.[27] Ginsenosides have also been identified as modulators of the AMPK/Nrf2 pathway, linking their antioxidant activities to both metabolic regulation and gene-level antioxidant defense.

Zingiber officinale (Ginger)

Ginger (*Zingiber officinale* Roscoe) and its principal bioactive constituents-gingerol, shogaol, and borneol-have demonstrated multi-targeted neuroprotective activity in the context of AD and cognitive impairment. These compounds address multiple pathological mechanisms simultaneously: they reduce Aβ aggregation, inhibit Tau protein hyperphosphorylation, counteract oxidative stress through GSH elevation and MDA reduction, and suppress neuroinflammatory signaling.[28] *In vivo* studies in transgenic AD animal models have documented significant improvements in spatial memory and neuronal preservation following ginger extract administration. Several small clinical observational studies have correlated habitual ginger consumption with improved cognitive performance in aging populations, though large-scale RCT data remain scarce. The multi-target pharmacological profile of ginger makes it a candidate for combinatorial therapeutic strategies alongside conventional AD therapies.

Moringa oleifera and *Astragalus membranaceus*

Moringa oleifera Lam.-the "miracle tree"-has emerged as a potent neuroprotective botanical owing to its exceptional phytochemical richness, encompassing flavonoids, phenolic acids, Vitamins C and E, isothiocyanates, and glucosinolates. Its bioactive molecules exert potent free radical-scavenging activity and modulate crucial inflammatory signaling pathways, including NF-κB and MAPK. Preclinical evidence supports Moringa's capacity to enhance neurogenesis, facilitate synaptic plasticity, and protect neurones from apoptosis in models of both AD and PD.[29] *Astragalus membranaceus* (Fisch.) Bunge-a staple of TCM-demonstrated protective effects against oxidative stress in Drosophila NDD models through the upregulation of Catalase (CAT) activity, restoration of Sod1 and Cat gene expression, and improvement of ATP and Mitofusin-2 (MFN2) levels. Two bioactive constituents, vanillic acid and daidzein, were identified as the most potent antioxidant components of Astragalus, with vanillic acid additionally improving mitochondrial function and ameliorating PD neurobehavioral deficits, and daidzein protecting against Aβ-induced AD-like pathology.[15]

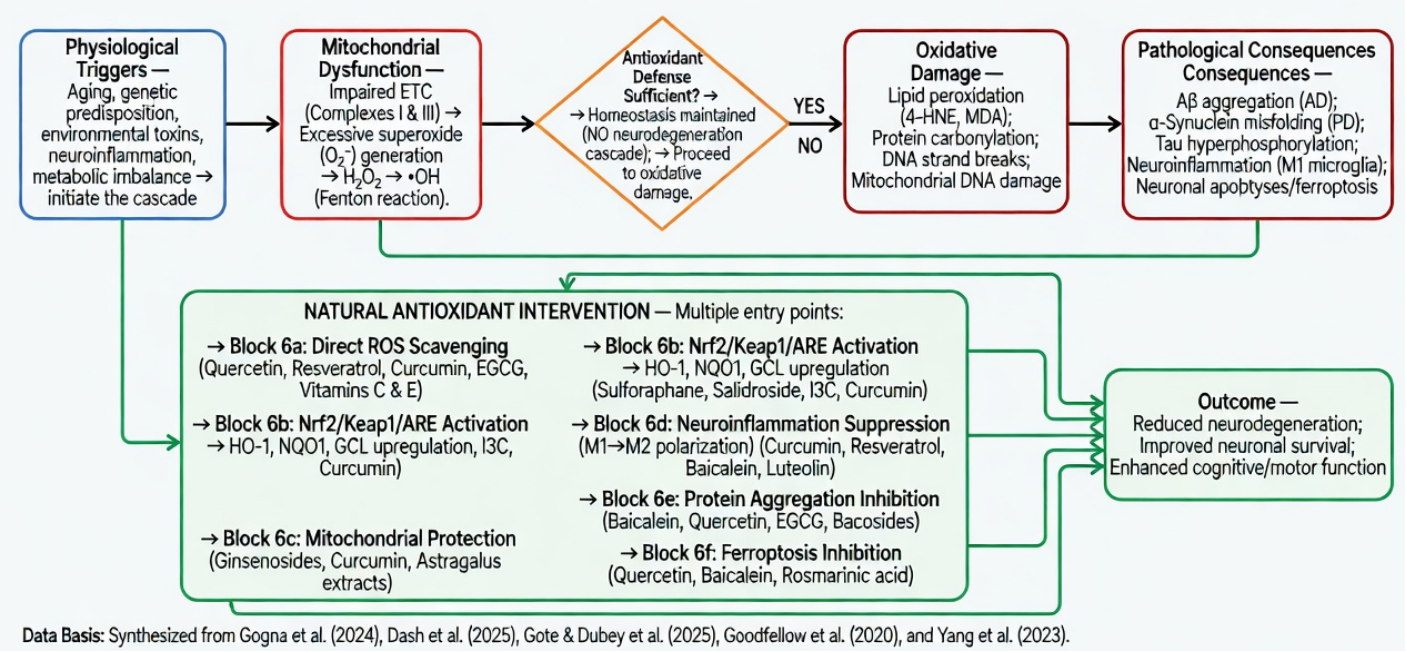

Figure 1: Oxidative stress cascade and natural product intervention points in neurodegenerative disorders.

Traditional Chinese Medicine Contributions

TCM encompasses a vast pharmacopeia of neuroprotective botanicals with antioxidant relevance. *Gastrodia elata* Blume-a fungal orchid widely used in TCM for neurological conditions-contains gastrodin as its principal bioactive compound. Gastrodin demonstrates neuroprotective activity across epilepsy, AD, PD, and cerebral ischemia models through antioxidant, anti-inflammatory, and antiapoptotic mechanisms.[30,31] *Polygala tenuifolia* Willd. is another TCM mainstay whose active components-tenuifolin, polygalasaponin XXXII, and senegenin-inhibit Aβ aggregation, reduce tau pathology, enhance the central cholinergic system, and exert antioxidant and anti-neuroapoptotic effects against AD.[32] *Dendrobium officinale*'s phenolic extract (SH-F), containing koaburaside, tyramine dihydroferulate, and naringenin, was shown to maintain proteostasis in AD C elegans models through autophagy-lysosomal pathway activation,[24] illustrating the rich complexity of TCM-derived neuroprotective phytochemistry (Table 2).

Nrf2-Keap1-Antioxidant Response Element Pathway and Emerging Molecular Mechanisms

Nrf2 as the Master Antioxidant Regulator

The Nrf2-Keap1-ARE signaling axis constitutes the principal molecular pathway governing the inducible antioxidant defense response in mammalian cells, and represents a primary target through which natural products exert neuroprotection. Under basal conditions, Nrf2 is sequestered in the cytoplasm through association with its repressor protein Keap1 (kelch-like ECH-associated Protein 1), which targets it for ubiquitin-mediated proteasomal degradation. Upon oxidative stress or electrophilic stimulation, key cysteine residues on Keap1 are modified, releasing Nrf2 to translocate to the nucleus, where it heterodimerizes with small Maf proteins and binds ARE sequences in the promoter regions of cytoprotective genes. These include HO-1, NAD(P)H Quinone Oxidoreductase 1 (NQO1), Glutamate-Cysteine Ligase (GCL-the rate-limiting enzyme of glutathione biosynthesis), thioredoxin reductase, and peroxiredoxin-collectively constituting a comprehensive antioxidant shield.[5]

Transcriptional activation of these Nrf2 target genes by natural phytochemicals confers broad neuroprotection extending beyond simple ROS scavenging. Upregulation of HO-1 generates biliverdin (an antioxidant) and carbon monoxide (an anti-inflammatory gasotransmitter), while the catalysis of heme-a pro-oxidant-into biliverdin, carbon monoxide, and free iron serves to mitigate heme-catalyzed oxidative damage. NQO1 reduces quinones to hydroquinones, preventing their participation in redox cycling that generates superoxide. GCL-driven GSH synthesis provides the cell with its most abundant and versatile endogenous antioxidant, capable of direct ROS neutralization and participation in the glutathione peroxidase–glutathione reductase redox cycle.[8]

Natural Product Activation of the Nrf2 Pathway

An impressive array of natural phytochemicals have been demonstrated to activate Nrf2-dependent gene expression, providing a mechanistic rationale for their neuroprotective effects. Salidroside, derived from *Rhodiola rosea*, activates the SIRT1/Nrf2 pathway in neuroinflammation models, reducing MDA content, increasing SOD and CAT, and suppressing NLRP3 inflammasome-mediated neuroinflammation.[30,31] Sulforaphane,

an isothiocyanate from cruciferous vegetables, is among the most potent known natural Nrf2 activators and has demonstrated remarkable post-ischemic neuroprotection in cardiac arrest models by upregulating mitochondrial antioxidant enzymes.[8] Indole-3-carbinol (I3C), derived from cruciferous plants, activated NRF2 and HO-1 in a scopolamine-induced cognitive impairment model, significantly attenuating oxidative stress, suppressing neuroinflammation, and improving spatial memory and recognition in behavioral tests.[33]

Curcumin, EGCG, and quercetin all activate Nrf2 signaling in multiple NDD-relevant cell and animal models, with evidence suggesting that their activation of Nrf2 is at least partly mediated by AMPK-dependent phosphorylation and nuclear accumulation of Nrf2, as well as by direct Keap1 Cys151 and Cys273 modification. The therapeutic relevance of this pathway activation is underscored by the observation that Nrf2 expression and nuclear activity are significantly reduced in post-mortem brain tissue from AD and PD patients compared to age-matched controls, suggesting that pharmacological restoration of Nrf2 activity by natural phytochemicals may help compensate for an age-associated decline in endogenous antioxidant protection.

Ferroptosis, NAD$^+$ Metabolism, and Emerging Targets

Ferroptosis-an iron-dependent form of regulated cell death driven by lipid peroxidation-has emerged as a newly recognized mechanism of neuronal death in PD. Pathological iron accumulation in the substantia nigra of PD patients, combined with excessive lipid peroxidation and depressed Glutathione Peroxidase 4 (GPX4) activity, creates the biochemical signature of ferroptosis susceptibility. Natural plant products, including quercetin, baicalein, EGCG, and rosmarinic acid have been identified as inhibitors of ferroptosis by targeting iron metabolism, reducing lipid peroxide accumulation, and restoring GPX4 activity.[9] This anti-ferroptotic mechanism complements but is distinct from classical antioxidant activities, broadening the therapeutic scope of natural antioxidants in PD.

NAD$^+$ metabolism represents another emerging molecular axis through which natural products modulate neurodegeneration. NAD$^+$ depletion, resulting from chronic PARP activation in response to oxidative DNA damage, impairs mitochondrial function, sirtuin activity, and energy metabolism in aging neurones. Multiple natural compounds-including quercetin,

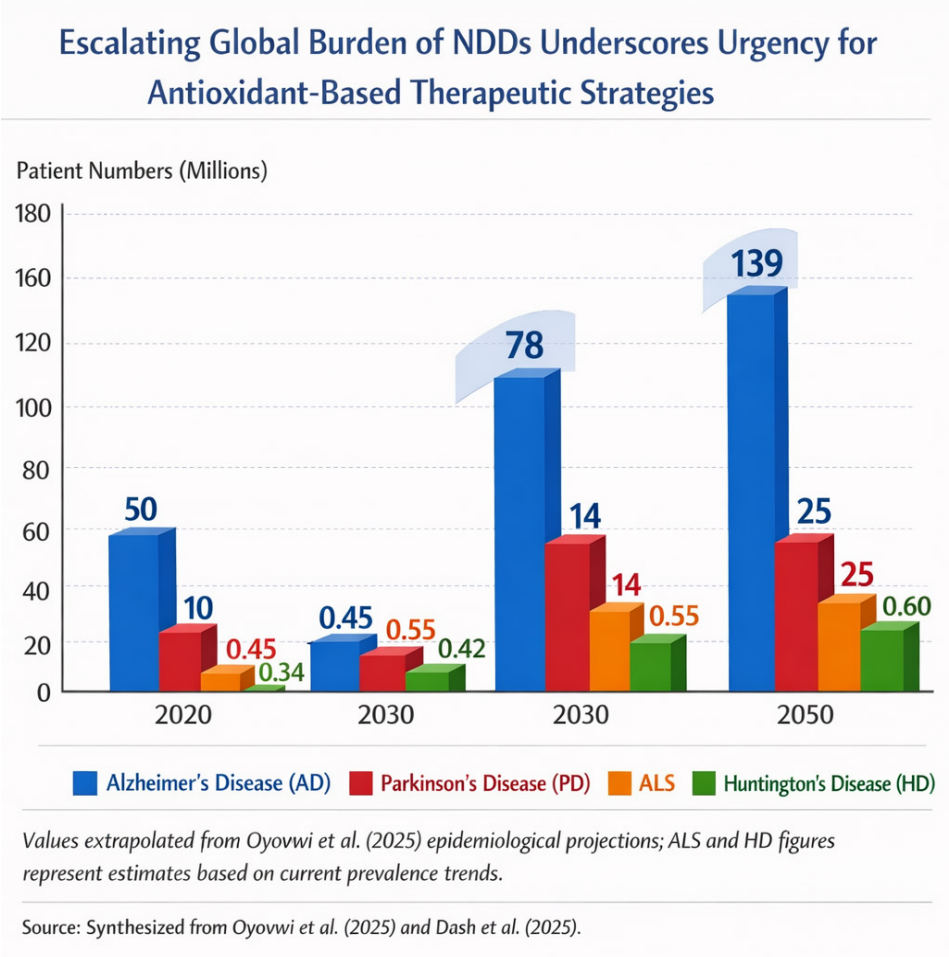

Figure 2: Schematic representation of Nrf2-Keap1-Antioxidant Response Element (ARE) pathway activation by natural phytochemicals.

Table 1: Summary of Key Studies on Natural Antioxidants in Neurodegenerative Disorders.

Author(s) and Year	Natural Product	Disease Model	Study Design	Key Antioxidant Finding	Conclusion
Oyovwi *et al.*[1]	Quercetin, resveratrol, flavonoids	AD, PD, ALS	Comprehensive review	Modulated oxidative stress, reduced neuroinflammation, promoted neuronal survival.	Natural antioxidants show multi-pathway neuroprotection; further clinical dosage research needed.
Gote *et al.*[5]	Curcumin, resveratrol, quercetin, apigenin, luteolin	AD, PD	Systematic review	Activation of Nrf2-Keap1-ARE pathway; upregulated HO-1, NQO1 enzymes.	Nrf2-activating phytochemicals are promising for ND therapy.
Gogna, Housden and Houldsworth[4]	Multiple antioxidants (SOD mimetics, Vitamin E, phenolics)	AD, PD	Review	Antioxidants enhance SOD, catalase, GSH; reduce Aβ and α-synuclein formation.	Antioxidant treatment is promising; clinical diversity of agents needed.
Dash *et al.*[3]	General antioxidants	AD, PD, ALS, MS, stroke	review	ROS-oxidative stress imbalance is key driver; antioxidants modulate multiple pathological pathways.	understanding oxidative stress-neurological disorder link essential for new treatments.
Dai *et al.*[15]	*Astragalus membranaceus* (vanillic acid, daidzein)	AD, PD (Drosophila)	*In vivo* experimental	Increased SOD, CAT, GSH; restored Sod1, Cat, CncC gene expression; improved ATP levels	AM extracts protect against oxidative damage in both AD and PD models
Mandal, Jaiswal and Mishra.[14]	Curcumin and nanoformulations	AD, PD	Review	Antioxidant, anti-inflammatory, antiapoptotic effects; nanoparticles improve bioavailability.	Curcumin nanoformulations hold significant neuroprotective promise.
Yang *et al.*[9]	Natural plant products (quercetin, baicalein, EGCG, resveratrol)	PD (ferroptosis model)	Review	Regulate iron metabolism, reduce lipid peroxidation, lower ROS in ferroptosis pathway.	Plant products targeting ferroptosis are novel disease-modifying agents for PD.
Talebi *et al.*[28]	*Zingiber officinale* (gingerol, shogaol)	AD	Systematic review	Combats Aβ aggregation, tau hyperphosphorylation, oxidative stress, and neuroinflammation.	Ginger components are multi-targeted neuroprotective agents with strong preclinical evidence.
Vittal and Vinciguerra[25]	*Withania somnifera* (withanolides)	AD, PD	Comprehensive review	Combats systemic oxidative stress, reduces C-reactive protein, modulates immune responses.	Ashwagandha has strong clinical evidence for cognitive improvement and neuroprotection.
Vinod *et al.*[26]	*Bacopa monnieri* (bacosides A and B)	AD, PD, depression, epilepsy	Review	Modulates neurotransmission, reduces oxidative stress, endoplasmic reticulum stress, and inflammation.	BM has multi-target brain neuroprotective properties warranting clinical translation.

Author(s) and Year	Natural Product	Disease Model	Study Design	Key Antioxidant Finding	Conclusion
Guo *et al.*[19]	Curcumin, EGCG, quercetin, berberine, resveratrol (NAD metabolism)	Multiple NDDs	Review	Regulate NAD^+ homeostasis via NAMPT/SIRT, AMPK/Nrf2, and PKCs/PARPs pathways.	NAD-targeting natural products are safe and effective for multiple disease management.
Pavlov *et al.*[6]	Withanolides, curcumin, ginkgolides, bacosides, ginsenosides, EGCG	AD	Review	Inhibit Aβ aggregation, reduce tau phosphorylation, scavenge ROS, modulate neuroinflammation.	Multi-target phytochemicals bridge traditional medicine and modern AD therapy.

Note. AD = Alzheimer's disease; PD = Parkinson's disease; ALS = amyotrophic lateral sclerosis; NDDs = neurodegenerative disorders; ROS = reactive oxygen species; Nrf2 = nuclear factor erythroid 2-related Factor 2. All studies retrieved from PubMed database.Abbreviations: AD=Alzheimer's disease; ALS=Amyotrophic lateral sclerosis; AMPK=AMP-Activated protein kinase; ARE=Antioxidant response element; CAT=Catalase; EGCG=Epigallocatechin-3-gallate; GSH=Glutathione; HO-1=Heme oxygenase 1; MS=Multiple sclerosis; NDDs=Neurodegenerative disorders; PD=Parkinson's disease; ROS=Reactive oxygen species; SOD=Superoxide dismutase.

resveratrol, EGCG, berberine, and salvianolic acid B-have been identified as modulators of the NAMPT/NAD/SIRT axis, restoring NAD^+ homeostasis and conferring neuroprotection through anti-inflammatory, pro-mitophagic, and antiapoptotic effects.[19] This mechanistic insight provides a compelling rationale for investigating NAD^+ metabolism as a druggable target for natural product-based NDD therapeutics.

Autophagy-the cellular process of delivering damaged organelles and protein aggregates to lysosomes for degradation-is increasingly recognized as a critical modulator of NDD pathogenesis. Defective autophagy contributes to Aβ and α-synuclein accumulation, while pharmacological autophagy induction can facilitate their clearance. Polyphenols, including resveratrol, curcumin, and EGCG modulate autophagy flux through the PI3K/Akt/mTOR axis, AMPK activation, and Beclin-1 upregulation.[18] In an AD C elegans model, *Gaultheria leucocarpa* extract activated mitophagy via the AMPK/ULK1 pathway, enhancing degradation of pathological APP and tau proteins while reducing Aβ deposits and oxidative stress[34] -a mechanistic convergence of antioxidant action and autophagy enhancement with strong disease-modifying implications.

Controversies, Limitations, and Conflicting Evidence

The Bioavailability Problem

Perhaps the most formidable barrier to the clinical translation of natural antioxidants is poor bioavailability. Most polyphenols undergo extensive metabolism in the gastrointestinal tract before absorption, with Phase II conjugation (glucuronidation, sulfation, methylation) generating metabolites with fundamentally different physicochemical properties than the parent compound. Curcumin, despite robust *in vitro* and *in vivo* evidence, achieves serum concentrations in the nanomolar range following standard oral dosing-orders of magnitude below the micromolar concentrations typically employed in cell culture studies.[14] EGCG suffers from oxidative instability, while quercetin's aqueous insolubility limits its intestinal absorption. BBB penetration represents an additional pharmacokinetic challenge, as the multidrug efflux transporter P-glycoprotein (P-gp) actively excludes many polyphenols from the CNS. The field has responded with sophisticated nano formulation strategies-liposomes, polymeric nanoparticles, solid lipid nanoparticles, and self-emulsifying drug delivery systems-that enhance bioavailability, BBB permeability, and target-tissue retention; however, the clinical validation of these approaches in NDD patient populations remains nascent.

Discordance between Preclinical and Clinical Evidence

A persistent concern in the natural antioxidant field is the marked discordance between compelling preclinical efficacy and modest or equivocal clinical trial outcomes. This translational gap is attributable to multiple factors: the use of supra-physiologically high compound concentrations in cell studies; the employment of artificial mouse and Drosophila models that incompletely recapitulate the complex, polygenic, and protracted nature of human neurodegeneration; differences in compound formulation, dose regimen, and duration between animal studies and clinical trials; and the heterogeneity of NDD patient populations.[1] Clinical trials of resveratrol, ginkgo extract, and Vitamin E (alpha-tocopherol) have variously yielded disappointing primary end point results, underscoring the difficulty of translating antioxidant effects measured in reductionist *in vitro* systems to complex human disease biology.

Antioxidant Hormesis and Potential Adverse Effects

A counterintuitive complication is the concept of antioxidant hormesis, whereby low doses of oxidative stressors confer beneficial adaptive responses, while excessive antioxidant supplementation may suppress these adaptive signals and potentially interfere with physiological ROS-dependent signaling. Reactive oxygen species at low concentrations serve important roles as second messengers in pathways governing neurotrophin

Table 2: Comparative Analysis of Key Natural Antioxidant Compounds: Mechanisms, Signaling Pathways, and Clinical Evidence.

Natural Compound	Source Plant	Primary Disease Target	Antioxidant Mechanism	Signaling Pathway	Bioavailability Challenge	Clinical Evidence
Curcumin	Curcuma longa	AD, PD	ROS scavenging, Aβ inhibition, iron chelation	Nrf2/HO-1, NF-κB, AMPK/mTOR	Low oral bioavailability; first-pass metabolism	Limited; nanoformulations improving outcomes
Resveratrol	*Vitis vinifera* (grapes)	AD, PD, ALS	Free radical scavenging, mitochondrial protection	SIRT1/Nrf2, AMPK/PGC-1α, PI3K/Akt	Rapid metabolism; short half-life	Some positive cognitive trial data
Quercetin	Onions, apples, *Ginkgo biloba*	AD, PD	SOD/CAT upregulation, MAO-B inhibition, Aβ aggregation reduction	Nrf2/ARE, MAPK, NF-κB	Poor aqueous solubility; limited BBB penetration	Moderate; ongoing trials
EGCG (green tea)	Camellia sinensis	AD, PD	Metal chelation, ROS neutralization, α-synuclein inhibition	Nrf2/HO-1, AMPK, mTOR	Rapid metabolism; bioavailability ~1%-10%	Positive epidemiological data; few RCTs
Berberine	Berberis species	AD, PD	Mitochondrial protection, MDA reduction, GSH elevation	AMPK, Nrf2/SIRT1, NF-κB	Poor absorption; efflux by P-glycoprotein	Early-phase clinical trials positive
Baicalein	Scutellaria baicalensis	AD, PD	Inhibits α-synuclein aggregation, reduces lipid peroxidation	MAO-B inhibition, Nrf2, PI3K/Akt	Moderate; improved with formulation strategies	Preclinical strong; clinical data limited
Withanolides	Withania somnifera	AD, PD, aging	Antioxidant enzyme induction, cortisol reduction, anti-inflammatory	SIRT1/Nrf2, NF-κB, BDNF/CREB	Good oral bioavailability in standardized extract	Multiple RCTs confirm cognitive improvement
Bacosides A and B	Bacopa monnieri	AD, PD, epilepsy	Lipid peroxidation inhibition, antioxidant enzyme enhancement	ERK1/2, CREB, NF-κB, Nrf2	Moderate; improved by liposomal delivery	Positive in small RCTs for cognitive function
Ginsenosides	Panax ginseng	AD, HD, PD, ALS	Mitochondrial protection, ROS scavenging, AChE inhibition	PI3K/Akt, NF-κB, AMPK/Nrf2	Variable; compound-dependent absorption	Clinical evidence in cognitive decline emerging
Salidroside	Rhodiola rosea	AD, PD	Activates SIRT1/Nrf2; reduces MDA, increases SOD and CAT	SIRT1, Nrf2/HO-1, NLRP3 inhibition	Moderate oral bioavailability	Preclinical; few human trials available
Luteolin	celery, thyme, chamomile	AD, PD, MS	Microglial M2 polarization, ROS reduction, TNF-α inhibition	NF-κB, MAPK, Nrf2/HO-1	Moderate; enhanced by nanoencapsulation	Preclinical strong; human data sparse

Natural Compound	Source Plant	Primary Disease Target	Antioxidant Mechanism	Signaling Pathway	Bioavailability Challenge	Clinical Evidence
Allicin/alliin	*Allium sativum* (garlic)	AD, PD, epilepsy	GSH elevation, reduction of oxidative markers[15] (p8-OHdG)	Nrf2, NF-κB, PI3K/Akt	Good bioavailability in aged garlic extract	Observational human data; RCTs underway

Abbreviations: AD=Alzheimer's disease; ALS=Amyotrophic lateral sclerosis; AMPK = AMP-Activated protein kinase; ARE=Antioxidant response element; BBB = Blood-brain barrier; CAT = Catalase; EGCG=Epigallocatechin-3-gallate; GSH = Glutathione; HD=Huntington's disease; HO-1 = Heme oxygenase 1; MAO-B = Monoamine oxidase B; MDA=Malondialdehyde; MS=Multiple sclerosis; NF-κB = Nuclear factor kappa B; Nrf2 = Nuclear factor erythroid 2-related Factor 2; PD=Parkinson's disease; RCTs = Randomized controlled trials; ROS=Reactive oxygen species; SIRT1 = Sirtuin 1; SOD = Superoxide dismutase.

signaling, synaptic plasticity, and autophagy induction. Supra-therapeutic antioxidant dosing may thus paradoxically impair the very protective mechanisms it aims to support. Additionally, some polyphenols at high doses have demonstrated hepatotoxicity (quercetin), hormonal interference (high-dose genistein), or interference with drug-metabolizing cytochrome P450 enzymes-safety considerations that must be rigorously addressed in clinical trial design and practice guidelines. The prooxidant behavior exhibited by some polyphenols under certain redox conditions further complicates the extrapolation of *in vitro* antioxidant capacity measurements to *in vivo* physiological relevance.[22]

Standardization and Regulatory Challenges

A fundamental challenge confronting the natural product field is the lack of standardization in botanical preparations. Phytochemical content in plant materials varies widely depending on growing conditions, harvest timing, extraction methods, and storage conditions, making it difficult to ensure consistent dosing across clinical trials and commercial products. This variability directly undermines the reproducibility and comparability of research findings and precludes meaningful meta-analysis across studies. Furthermore, regulatory frameworks for plant-derived products differ substantially between jurisdictions-with herbal medicines frequently classified as dietary supplements in the United States (with lower evidentiary requirements) but as medicinal products in the European Union (requiring full clinical evidence). The establishment of standardized, Good Manufacturing Practice (GMP)-compliant phytochemical preparations with defined, verified bioactive compound profiles is an urgent priority for the field.

Flowchart Legend

Data Basis

Synthesized from Gogna, Housden and Houldsworth,[4] Dash *et al.*[3] Gote *et al.*[5] Goodfellow *et al.*[8] and Yang *et al.*[9]

CURRENT CHALLENGES AND FUTURE DIRECTIONS

Despite the impressive body of preclinical evidence supporting the neuroprotective antioxidant properties of natural products in Neurodegenerative Disorders (NDDs), several critical challenges must be overcome before these findings can be translated into effective clinical interventions. Chief among these is the optimization of bioavailability and CNS penetration for key phytochemical antioxidants. Emerging nanotechnology platforms-including brain-targeted nanoparticle systems functionalized with transferrin receptor ligands or apolipoprotein E peptides-offer promising approaches to improving Blood-Brain Barrier (BBB) penetration and achieving therapeutic concentrations in affected neural tissue. The development of *Mucuna pruriens* (natural L-dopa source) formulations that codeliver L-dopa alongside polyphenolic antioxidants represents a compelling combinatorial strategy for Parkinson's Disease (PD) that merits rigorous clinical investigation.[2]

The identification of reliable biomarkers of antioxidant status and neurodegeneration severity represents another pressing research need. The current reliance on clinical symptom scales as primary end points in NDD trials imposes significant practical and temporal challenges, as measurable cognitive or motor improvements may require years of intervention. Plasma or CSF biomarkers of oxidative stress-including 8-OHdG, F2-isoprostanes, and oxidized glutathione ratios-alongside neuroimaging markers of neuroinflammation (PET imaging of microglial activation) and amyloid burden would substantially facilitate the design and evaluation of natural antioxidant clinical trials.

Multi-target combination strategies-employing two or more complementary natural compounds with synergistic antioxidant and neuroprotective mechanisms-may overcome the limitations of individual agents and more faithfully replicate the polypharmacological complexity of traditional botanical preparations. In this context, the application of systems pharmacology approaches, network medicine frameworks, and machine learning-assisted compound interaction modeling can

guide rational design of combination therapies with optimized multi-target profiles and minimal adverse effect risks.

The emerging gut-brain axis paradigm offers another frontier for natural product-based NDD intervention. Evidence indicates that gut microbiota composition influences neuroinflammation, oxidative stress, and even Aβ and α-synuclein pathology in NDD models. Dietary polyphenols, as substrates for microbial biotransformation, produce secondary metabolites (urolithins, equol, phenolic acids) that may exert neuroprotection via gut-brain axis modulation.[6] Prebiotic and polyphenol combination interventions targeting the gut microbiome represent an innovative and understudied therapeutic avenue warranting dedicated clinical exploration.

Future research should also prioritize sex-specific differences in NDD prevalence and natural product response, as emerging evidence suggests that estrogen modulatory effects of certain phytochemicals (notably genistein and other isoflavones) may differentially influence neuroprotection in males and females. Similarly, the role of genetic polymorphisms in metabolizing enzymes (CYP1A1, CYP1B1, COMT, UGTs) in determining individual responses to polyphenol supplementation warrants pharmacogenomic investigation to enable personalized natural antioxidant therapy.

CONCLUSION

This comprehensive review synthesizes evidence demonstrating that natural product-derived antioxidants represent a scientifically compelling, mechanistically diverse, and therapeutically promising approach to the prevention and management of neurodegenerative disorders. The evidence reviewed herein-based on articles retrieved from PubMed and corroborating databases-consistently supports the multi-targeted neuroprotective profile of phytochemical antioxidants across major Neurodegenerative Disorders (NDDs), including Alzheimer's disease, Parkinson's disease, Amyotrophic Lateral Sclerosis (ALS), and related conditions.

The convergent antioxidant mechanisms of key natural compounds-including direct Reactive Oxygen Species (ROS) scavenging, Nrf2-Keap1-Antioxidant Response Element (ARE) pathway activation, mitochondrial protection, microglial polarization modulation, protein aggregation inhibition, and ferroptosis suppression-address multiple interlocking pathological processes that underpin neurodegeneration. Notably, plants, such as *Withania somnifera, Bacopa monnieri, Curcuma longa, Panax ginseng, Ginkgo biloba*, and *Astragalus membranaceus*, have accumulated the most substantial evidence bases spanning preclinical mechanistic studies, animal model efficacy demonstrations, and some degree of human clinical validation.

The principal impediments to clinical translation-poor bioavailability, rapid metabolism, limited Blood-Brain Barrier (BBB) penetration, and insufficient large-scale clinical trial data-are being actively addressed through nanotechnology-based delivery platforms, standardized phytochemical preparations, and multi-compound combination strategies. Advances in predictive biomarker research, gut-brain axis science, and pharmacogenomics are expected to further refine patient selection and dosing strategies for natural antioxidant interventions.

In conclusion, natural antioxidants derived from medicinal plants offer a rich and not yet fully realized therapeutic resource for neurodegenerative disorders. The integration of traditional ethnopharmacological wisdom with rigorous modern pharmacology, clinical trial methodology, and pharmaceutical innovation represents the most promising path toward leveraging the neuroprotective potential of the natural product kingdom in the service of an aging global population facing an accelerating neurodegeneration epidemic.

ABBREVIATIONS

AD: Alzheimer's disease; **ALS:** Amyotrophic lateral sclerosis; **AMPK:** AMP-Activated protein kinase; **APP:** Amyloid precursor protein; **ARE:** Antioxidant response element; **Aβ:** Amyloid-β; **BBB:** Blood-Brain barrier; **CAT:** Catalase; **EGCG:** Epigallocatechin-3-gallate; **ETC:** Electron transport chain; **GCL:** Glutamate-cysteine ligase; **GSH:** Glutathione; **HD:** Huntington's disease; **HO-1:** Heme oxygenase 1; **H_2O_2:** Hydrogen peroxide; **Keap1:** Kelch-like ECH-associated protein 1; **MAO-B:** Monoamine oxidase B; **MDA:** Malondialdehyde; **MS:** Multiple sclerosis; **NDDs:** Neurodegenerative disorders; **NF-κB:** Nuclear factor kappa B; **NQO1:** NAD(P)H quinone oxidoreductase 1; **Nrf2:** Nuclear factor erythroid 2-related factor 2; **$O_2\bullet^-$:** Superoxide; **PD:** Parkinson's disease; **RCTs:** Randomized controlled trials; **ROS:** Reactive oxygen species; **SIRT1:** Sirtuin 1; **SOD:** Superoxide dismutase; **α-synuclein:** Alpha-synuclein; **•OH:** Hydroxyl radical.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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