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NEUROPROTECTIVE SECONDARY METABOLITES: MECHANISMS AND THERAPEUTIC POTENTIAL IN NEURODEGENERATIVE DISEASES

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ABSTRACT

Neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), and cerebral ischemia, represent an escalating global health crisis with limited effective therapies. The multifactorial pathogenesis of these disorders, encompassing protein aggregation, oxidative stress, neuroinflammation, and mitochondrial dysfunction, necessitates therapeutic approaches that target multiple pathways. Plant secondary metabolites have emerged as promising neuroprotective agents, offering multi-targeted mechanisms and favorable safety profiles. This review comprehensively examines the neuropharmacology of key secondary metabolites, including huperzine A, curcumin, resveratrol, epigallocatechin gallate (EGCG), and ginsenosides, focusing on their mechanisms against neurodegeneration. We critically evaluate evidence for neuroprotection through acetylcholinesterase inhibition, antioxidant and anti-inflammatory effects, mitochondrial protection, and modulation of protein aggregation pathways. Furthermore, we assess the therapeutic potential of these compounds in Alzheimer's disease, Parkinson's disease, and cerebral ischemia, evaluating preclinical and clinical evidence. Polyphenols, including curcumin and resveratrol, exert significant inhibitory effects on the NF-κB pathway, making them promising candidates for treating neurological disorders. Despite promising findings, challenges including bioavailability, blood-brain barrier penetration, and clinical translation persist. This review identifies research gaps and discusses emerging strategies for optimizing neuroprotective natural products for clinical application.

Keywords: Neuroprotection; Alzheimer's Disease; Parkinson's Disease; Cerebral Ischemia; Secondary Metabolites; Natural Products

1 INTRODUCTION

Neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), and cerebrovascular diseases such as cerebral ischemia, pose a substantial global health burden. The prevalence of these disorders is increasing with aging populations, with AD alone affecting over 50 million individuals worldwide (Goswami et al., 2023). Current therapies offer limited symptomatic relief and do not modify disease progression, underscoring the urgent need for effective neuroprotective strategies (Mathew and Subramanian, 2023).

The multifactorial pathogenesis of neurodegenerative diseases involves interconnected mechanisms including protein aggregation (amyloid-β, tau, α-synuclein), oxidative stress, neuroinflammation, mitochondrial dysfunction, and

excitotoxicity (Datta et al., 2023). Neurological disorders including neurodegenerative disorders continue to pose significant therapeutic challenges (Kumar et al., 2023). This complexity suggests that multi-targeted therapeutic approaches may be more effective than single-target interventions. Plant secondary metabolites, with their diverse chemical structures and multi-targeted activities, have attracted attention as potential neuroprotective agents (Saini et al., 2023).

Polyphenols are a class of secondary metabolic products found in plants that have been extensively studied for how well they regulate biological processes, such as the proliferation of cells, autophagy, and apoptosis (Rahman et al., 2023). The mitogen-activated protein kinase (MAPK)-mediated signaling cascade is currently identified as a crucial pro-inflammatory pathway that plays a significant role in the development of neuroinflammation (Wang et al., 2023). This process has been shown to contribute to the pathogenesis of several neurological conditions, such as AD, PD, CNS damage, and cerebral ischemia (Bhatia et al., 2023). Getting enough polyphenols through dietary habits has resulted in mitigating the effects of oxidative stress and lowering the susceptibility to associated neurodegenerative disorders (Rahman et al., 2023).

Historically, traditional medicine systems have used plants for neurological disorders, and modern pharmacology has validated many of these uses (Mukherjee et al., 2024). Key neuroprotective secondary metabolites, including huperzine A, curcumin, resveratrol, epigallocatechin gallate (EGCG), and ginsenosides, have demonstrated activity in preclinical models of neurodegeneration (Chen et al., 2024; Kaur et al., 2024). This review provides a comprehensive examination of the neuropharmacology of these compounds, focusing on their mechanisms against AD, PD, and cerebral ischemia.

2 NEURODEGENERATIVE DISEASES: PATHOGENESIS AND THERAPEUTIC TARGETS

2.1 Alzheimer's Disease

AD is characterized by progressive cognitive decline, with pathological hallmarks including extracellular amyloid-β (Aβ) plaques and intracellular neurofibrillary tangles of hyperphosphorylated tau protein (Datta et al., 2023). Neuroinflammation, oxidative stress, and cholinergic dysfunction contribute to neuronal loss and cognitive impairment. Current neurodegenerative diseases present difficulties and despite extensive research efforts to develop new disease-modifying therapies, there is still no effective treatment for halting the neurodegenerative process (Goswami et al., 2023).

Therapeutic strategies targeting amyloid clearance, tau aggregation, neuroinflammation, and neuroprotection are under investigation. Natural compounds have been reported to have promising anti-AD activities, including flavonoids and other polyphenolic compounds (Mathew and Subramanian, 2023). Compounds like huperzine A exhibit neuroprotective effects through various mechanisms, including cholinergic modulation and anti-inflammatory properties (Chen et al., 2024). Natural compounds as inhibitors of Aβ peptide and tau aggregation have been comprehensively reviewed, exploring numerous studies on natural products that focus on inhibiting the formation of amyloid plaques and tau protein tangles (Kumar et al., 2023).

2.2 Parkinson's Disease

PD is characterized by motor symptoms including tremor, rigidity, and bradykinesia, resulting from the loss of dopaminergic neurons in the substantia nigra (Kaur et al., 2024). Pathological hallmarks include α-synuclein aggregation (Lewy bodies) and mitochondrial dysfunction. Dopamine replacement therapies provide symptomatic relief but do not modify disease progression (Goswami et al., 2023).

Natural compounds have gained attention for their potential neuroprotective effects and ability to target various pathways involved in the pathogenesis of PD (Kaur et al., 2024). Oxidative stress, mitochondrial dysfunction, and protein malfunction play key roles in disease pathogenesis (Khan et al., 2023). Neuroprotective strategies targeting oxidative stress, neuroinflammation, and mitochondrial function are being pursued (Bhatia et al., 2023).

2.3 Cerebral Ischemia

Cerebral ischemia, resulting from reduced blood flow to the brain, is a leading cause of death and disability (Wang et al., 2023). The ischemic cascade involves excitotoxicity, oxidative stress, neuroinflammation, and apoptosis (Pradhan et al., 2023). Polyphenols exert neuroprotective effects primarily through inhibiting production of oxidative stress and inflammatory cytokines (Rahman et al., 2023). Ginsenosides have demonstrated significant neuroprotective effects in cerebral ischemia through multiple mechanisms (Zhang et al., 2023; Balakrishnan et al., 2024).

Table 1: Pathogenic Mechanisms and Therapeutic Targets in Neurodegenerative Diseases

Disease	Key Pathological Mechanisms	Primary Therapeutic Targets
Alzheimer's	Aβ plaques, tau tangles, neuroinflammation, oxidative stress	Amyloid clearance, tau aggregation, neuroprotection
Parkinson's	α-synuclein aggregation, mitochondrial dysfunction, oxidative stress	Neuroprotection, mitochondrial preservation
Cerebral Ischemia	Excitotoxicity, oxidative stress, neuroinflammation, apoptosis	Neuroprotection, oxidative stress reduction

3 HUPERZINE A: MECHANISMS AND THERAPEUTIC POTENTIAL

3.1 Acetylcholinesterase Inhibition

Huperzine A (HupA), a lycopodium alkaloid from Huperzia serrata, is a potent, selective, and reversible acetylcholinesterase (AChE) inhibitor that exhibits neuroprotective effects and is clinically used to manage benign memory decline (Chen et al., 2024). Huperzine A exhibits neuroprotective effects by preserving acetylcholine levels, and also offers antioxidant and anti-inflammatory benefits that suggest a potential role in modifying disease progression in AD and vascular dementia (Mukherjee et al., 2024).

HupA shows a stronger, selective and specific AChE inhibitory effect and marked memory-enhancing properties (Patil et al., 2024). In several animal models, HupA has been seen to relieve memory deficits. Huperzine A has been widely used for the last decade for the management of AD (Chen et al., 2024).

3.2 Neuroprotective Mechanisms Beyond Cholinergic Effects

Beyond cholinesterase inhibition, huperzine A exhibits multifunctional neuroprotective effects (Chen et al., 2024). It protects cells against hydrogen peroxide, β-amyloid toxicity, glutamate, ischemia and staurosporine-induced cytotoxicity and apoptosis (Mukherjee et al., 2024). Huperzine A prevented transient focal cerebral ischemia–induced brain injury induced by MCAO in rats via nAChR (Chen et al., 2024).

In vitro studies have shown that huperzine A improved the survival of and reduced ROS production in glial cells that underwent oxygen-glucose deprivation, implying that huperzine A can prevent cell loss during ischemia (Patil et al., 2024). In addition, huperzine A restored cerebral blood flow to areas that had reduced blood flow, and reduced infarct sizes in the cortex and the striatum in animals (Chen et al., 2024).

3.3 Dimeric Derivatives and Disease-Modifying Potential

Promising tacrine/huperzine A-based dimeric acetylcholinesterase inhibitors have been developed for neurodegenerative disorders (Patil et al., 2024). The representative dimers, such as bis(3)-Cognitin (B3C), provide neuroprotection against a variety of neurotoxins via multiple targets, including the inhibitions of N-methyl-d-aspartic acid receptor with pathological-activated potential, neuronal nitric oxide synthase, and β-amyloid cascades synergistically (Mukherjee et al., 2024). More importantly, B3C might offer disease-modifying potentials by activating myocyte enhancer factor 2D transcription, inducing neuritogenesis, and promoting the expressions of neurotrophic factors in vitro and in vivo (Patil et al., 2024). The novel dimers might offer synergistic disease-modifying effects, proving that dimerization might serve as one of the strategies to develop new generation of therapeutics for neurodegenerative disorders (Chen et al., 2024).

4 CURCUMIN: MECHANISMS AND THERAPEUTIC POTENTIAL

4.1 Antioxidant and Anti-inflammatory Mechanisms

Curcumin, a natural diketone derived from turmeric, is a natural antioxidant with a wide range of neuroprotective, anti-inflammatory, anti-tumor, anti-aging, and antioxidant effects (Dhiman et al., 2023). Curcumin is recognized for its potent antioxidant properties and is considered a promising candidate for the prevention and treatment of neurological diseases (Kumar et al., 2023).

Curcumin mitigates oxidative stress through multiple mechanisms (Dhiman et al., 2023). Previous studies have highlighted the marked antioxidant and neuroprotective abilities of polyphenols such as curcumin, by increased activity of detoxification systems like superoxide dismutase (SOD), catalase or glutathione peroxidase (Rahman et al., 2023).

The role of curcumin as an epigenetic modulator in neurological disorders and neuroinflammation have also been reported (Kumar et al., 2023).

Curcumin exerts significant inhibitory effects on the NF-κB pathway, making it a promising candidate for treating neurological disorders (Wang et al., 2023). The regulating effect of curcumin on the NF-κB pathway in neurodegenerative diseases has been extensively reviewed (Dhiman et al., 2023; Datta et al., 2023).

4.2 Effects on Alzheimer's Disease

Curcumin has demonstrated neuroprotective effects in AD models through multiple mechanisms (Dhiman et al., 2023). It inhibits Aβ aggregation, promotes Aβ clearance, and reduces tau phosphorylation (Kumar et al., 2023). The relationship of curcumin with aging and Alzheimer and Parkinson disease, the most prevalent age-related neurodegenerative diseases, has been investigated (Datta et al., 2023).

Curcumin's effects on oxidative stress and its potential in treating nervous system disorders, including Alzheimer's disease, have been extensively documented (Rahman et al., 2023). Epigenetic orchestration of neurodegenerative disorders represents a possible target for curcumin as a therapeutic (Datta et al., 2023). Curcumin's neuroprotective effects in the treatment of neurodegenerative diseases have been linked to the regulation of mitochondrial dysfunction and epigenetic machinery (Dhiman et al., 2023).

4.3 Effects on Parkinson's Disease

Curcumin has shown neuroprotective effects in PD models (Dhiman et al., 2023). It protects dopaminergic neurons through antioxidant and anti-inflammatory mechanisms (Kumar et al., 2023). The relationship of curcumin with aging and Alzheimer and Parkinson disease has been investigated, with curcumin demonstrating potential benefits in both conditions (Datta et al., 2023; Khan et al., 2023).

4.4 Effects on Cerebral Ischemia

Curcumin has demonstrated significant neuroprotective effects in cerebral ischemia (Pradhan et al., 2023). In the context of stroke, curcumin appears to alleviate inflammation and oxidative and nitrosative stress (Rahman et al., 2023). It reduces ischemia and contributes to an optimal adaptive immune response through Iba1 microglia activation and enhancing Nrf2 expression (Pradhan et al., 2023). Through these mechanisms, curcumin exerted neuroprotective effects, offering potential therapeutic benefits also for demyelinating diseases (Wang et al., 2023).

A systematic review concluded that curcumin has an elevating effect in protecting brain condition after an ischemic stroke (Pradhan et al., 2023; Dhiman et al., 2023).

5 RESVERATROL: MECHANISMS AND THERAPEUTIC POTENTIAL

5.1 Antioxidant and Anti-inflammatory Mechanisms

Resveratrol, a polyphenol found in grapes and berries, has demonstrated significant neuroprotective effects through multiple mechanisms (Anand et al., 2023). Resveratrol and the neuroinflammation axis in Alzheimer's disease, Parkinson's disease, multiple sclerosis, and cerebral ischemia have been extensively studied (Wu et al., 2024). Polyphenols such as curcumin, resveratrol, and pterostilbene had significant inhibitory effects on NF-κB, making them promising candidates for treating NDs (Rahman et al., 2023).

Resveratrol exerts neuroprotective effects primarily through inhibiting production of oxidative stress and inflammatory cytokines (Anand et al., 2023). Much attention has been directed towards its potential therapeutic effects in NDs such as Alzheimer's disease, Parkinson's disease, and cerebral ischemia (Wu et al., 2024).

Effects on Alzheimer's Disease and Parkinson's Disease

Resveratrol has shown promise in AD and PD models (Anand et al., 2023). It activates SIRT1, promoting mitochondrial biogenesis and reducing oxidative stress (Rahman et al., 2023). Resveratrol reduces Aβ aggregation and tau phosphorylation in AD models (Wu et al., 2024). In PD models, resveratrol protects dopaminergic neurons through mitochondrial preservation and neuroinflammation reduction (Kaur et al., 2024). Neuroprotective effects of chronic resveratrol treatment have been demonstrated in the 3xTg-AD mouse model of Alzheimer's disease (Anand et al., 2023).

5.2 Effects on Cerebral Ischemia

Resveratrol protects against cerebral ischemia through antioxidant, anti-inflammatory, and neuroprotective effects (Wu et al., 2024). Modulation of neuroinflammation by natural molecules including resveratrol has been demonstrated in the context of Alzheimer's, Huntington's, and cerebral ischemia (Wang et al., 2023; Anand et al., 2023).

6 EPIGALLOCATECHIN GALLATE (EGCG): MECHANISMS AND THERAPEUTIC POTENTIAL

6.1 Antioxidant and Anti-inflammatory Mechanisms

EGCG, the most abundant polyphenol in green tea, has emerged as a promising therapeutic agent due to its potent antioxidant and anti-inflammatory effects (Jaiswal et al., 2024). EGCG has neuroprotective efficacy due to scavenging free radicals, reducing oxidative stress and attenuating neuroinflammatory processes (Singh et al., 2024). Catechins, a class of phytochemicals found in various fruits and tea leaves, have garnered attention for their diverse health-promoting properties, including their potential in combating neurodegenerative diseases (Kaur et al., 2024).

EGCG is a modulator of chronic neuroinflammation and oxidative stress (Singh et al., 2024). The molecular mechanisms of EGCG's anti-oxidative stress and chronic neuroinflammation have been discussed, emphasizing its effects on autoimmune responses, neuroimmune system interactions, and focusing on the related effects on AD and PD (Jaiswal et al., 2024).

6.2 Effects on Alzheimer's Disease

EGCG inhibits Aβ aggregation and reduces tau phosphorylation (Jaiswal et al., 2024). EGCG inhibits oxidative stress through the Keap1/Nrf2 signaling pathway to improve Alzheimer disease (Singh et al., 2024). By elucidating EGCG's mechanisms of action and its impact on neurodegenerative processes, EGCG emerges as a promising natural compound for combating chronic neuroinflammation and oxidative stress, offering novel avenues for neuroprotective strategies in the treatment of neurodegenerative disorders (Kumar et al., 2023).

6.3 Effects on Parkinson's Disease

EGCG has shown neuroprotective effects in PD models (Jaiswal et al., 2024). It protects against α-synuclein aggregation and neurotoxicity (Singh et al., 2024). EGCG's effects on autoimmune responses and neuroimmune system interactions have been emphasized in the context of PD (Kaur et al., 2024).

7 GINSENOSIDES: MECHANISMS AND THERAPEUTIC POTENTIAL

7.1 Neuroprotective Mechanisms

Ginsenosides are the main active substances in ginseng, American ginseng and Panax notoginseng (Reddy et al., 2024). Ginsenoside Rd (GSRd) is one of the rare saponin monomers extracted from ginseng, which belongs to the diol type of dammarane-type ginsenosides (Balakrishnan et al., 2024). Most importantly, GSRd could effectively cross the intact blood-brain barrier (BBB) (Zhang et al., 2023).

GSRd has an important regulatory role in the cardiovascular, cerebrovascular and nervous systems (Balakrishnan et al., 2024). GSRd can improve microcirculation, reduce brain damage, resist atherosclerosis, enhance learning and memory, and delay body aging (Zhang et al., 2023).

7.2 Effects on Alzheimer's Disease and Parkinson's Disease

Studies have shown that ginsenosides play an important role in the treatment of neurological diseases such as AD and PD (Reddy et al., 2024). Ginsenosides exert effective neuroprotective effects on neurological conditions, including stroke, Alzheimer's disease, Parkinson's disease, and brain/spinal cord injuries through a variety of molecular mechanisms (Mukherjee et al., 2024). Ginsenoside Re has demonstrated neuroprotective effects against neurotoxin-induced Parkinson's disease models via induction of Nrf2 (Li et al., 2024).

7.3 Effects on Cerebral Ischemia

GSRd has demonstrated significant neuroprotective effects in ischemic stroke (Balakrishnan et al., 2024). GSRd improved cerebral infarction and neurological outcomes in the middle cerebral artery occlusion (MCAO) rats (Zhang et al., 2023). GSRd reduced mtDNA and nDNA damage, thereby helping to improve the survival rate of rats and the recovery of nerve function (Balakrishnan et al., 2024). The neuroprotective function of GSRd for acute IS might be related to the up-regulation of NEIL1/3 expressions (Zhang et al., 2023).

Modern pharmacological studies have shown that ginsenosides Rg2 and Rh1 have strong pharmacological activities in the nervous system, with protective effects on nerve cells, improved resistance to neuronal injury, modulation of neural activity, and resistance to cerebral ischemia/reperfusion injury (Reddy et al., 2024; Li et al., 2024).

Table 2: Key Neuroprotective Secondary Metabolites

Compound	Source	Primary Mechanisms	Neurodegenerative Target	Clinical Evidence
Huperzine A	*Huperzia serrata*	AChE inhibition, antioxidant, anti-inflammatory	AD, vascular dementia, cerebral ischemia	Moderate
Curcumin	*Curcuma longa*	Aβ inhibition, anti-inflammatory, antioxidant, epigenetic modulation	AD, PD, cerebral ischemia	Mixed
Resveratrol	Grapes, berries	SIRT1 activation, antioxidant, anti-inflammatory, NF-κB inhibition	AD, PD, cerebral ischemia	Mixed
EGCG	Green tea	Aβ inhibition, Nrf2 activation, anti-inflammatory, antioxidant	AD, PD	Moderate
Ginsenosides	*Panax* species	Anti-inflammatory, antioxidant, mitochondrial protection	AD, PD, cerebral ischemia	Emerging

8 MECHANISMS OF NEUROPROTECTION

8.1 Acetylcholinesterase Inhibition

Cholinergic dysfunction is a hallmark of AD, and acetylcholinesterase (AChE) inhibitors are the mainstay of symptomatic treatment (Chen et al., 2024). Huperzine A is a potent AChE inhibitor with neuroprotective properties beyond its cholinergic effects (Patil et al., 2024). Other natural products, including galantamine and various alkaloids, have also demonstrated AChE inhibitory activity (Mukherjee et al., 2024).

8.2 Protein Aggregation Inhibition

Protein aggregation is a key pathogenic mechanism in neurodegenerative diseases, and compounds that inhibit aggregation have neuroprotective potential (Kumar et al., 2023). Natural compounds as inhibitors of Aβ peptide and tau aggregation have been comprehensively reviewed, exploring numerous studies on natural products that focus on inhibiting the formation of amyloid plaques and tau protein tangles (Kumar et al., 2023). Resveratrol, curcumin, and kaempferol have been studied for their effects on neuroinflammation of AD in vivo and in vitro (Anand et al., 2023; Wu et al., 2024).

Curcumin inhibits Aβ aggregation and promotes fibril disaggregation (Dhiman et al., 2023). EGCG inhibits Aβ and α-synuclein aggregation through interactions with amyloid proteins (Jaiswal et al., 2024; Singh et al., 2024). Resveratrol reduces Aβ aggregation through modulation of amyloid precursor protein processing (Anand et al., 2023).

8.3 Oxidative Stress Reduction

Oxidative stress is a common feature of neurodegeneration, and antioxidants offer neuroprotective potential (Datta et al., 2023). Curcumin, resveratrol, and EGCG exhibit potent antioxidant effects through direct free radical scavenging and Nrf2 pathway activation (Rahman et al., 2023; Dhiman et al., 2023). The nuclear factor erythroid 2-related factor 2 (Nrf2) pathway is a key regulator of antioxidant defense and represents a therapeutic target (Li et al., 2024).

EGCG inhibits oxidative stress through the Keap1/Nrf2 signaling pathway to improve Alzheimer disease (Singh et al., 2024). Ginsenoside Re has demonstrated neuroprotective effects via induction of Nrf2 (Li et al., 2024).

8.4 Neuroinflammation Modulation

Neuroinflammation is a pathogenic mechanism in neurodegenerative diseases, with microglial activation contributing to neuronal damage (Datta et al., 2023). Polyphenols can disrupt the nuclear factor kappa B (NF-κB) pathway by inhibiting the phosphorylation or ubiquitination of signaling molecules, which further prevents the degradation of IκB

(Wang et al., 2023). Additionally, they prevent NF-κB translocation to the nucleus and pro-inflammatory cytokine production (Rahman et al., 2023).

Natural products including curcumin and resveratrol reduce microglial activation and pro-inflammatory cytokine production (Dhiman et al., 2023; Anand et al., 2023). Modulation of neuroinflammatory pathways offers neuroprotective potential (Kumar et al., 2023; Bhatia et al., 2023).

8.5 Mitochondrial Protection

Mitochondrial dysfunction contributes to neurodegeneration through energy failure and oxidative stress (Datta et al., 2023). Ginsenosides have demonstrated mitochondrial protective effects (Balakrishnan et al., 2024; Reddy et al., 2024). Resveratrol activates mitochondrial biogenesis through SIRT1/PGC-1α pathway activation (Anand et al., 2023). Curcumin and EGCG protect mitochondria from oxidative damage (Dhiman et al., 2023; Jaiswal et al., 2024).

8.6 MAP Kinase Pathway Modulation

The MAP kinase signaling pathway plays a significant role in the development of neuroinflammation (Rahman et al., 2023). Polyphenols possess significant promise in dealing with the root cause of neurological conditions by modulating multiple therapeutic targets simultaneously, thereby attenuating their complicated physiology (Wang et al., 2023). Polyphenols targeting MAP kinase signaling pathway in neurological diseases have been extensively studied (Rahman et al., 2023).

8.7 Epigenetic Modulation

Epigenetic modulations play a major role in gene expression and thus are responsible for various physiological changes including age-associated neurological disorders (Datta et al., 2023). Most neurodegenerative diseases are associated with increased oxidative stress, aggregation of certain proteins, mitochondrial dysfunction, inactivation/dysregulation of protein degradation machinery, DNA damage and cell excitotoxicity (Dhiman et al., 2023). Epigenetic modulations have been reported to play a significant role in onset and progression of neurodegenerative diseases by regulating these processes (Datta et al., 2023).

The role of curcumin as an epigenetic modulator in neurological disorders and neuroinflammation have been reported (Kumar et al., 2023). The current knowledge of the role of mitochondrial dysfunction, epigenetic modulations and mitoepigenetics in age-associated neurological disorders and the neuroprotective effects of curcumin in the treatment and/or prevention of these neurodegenerative diseases by regulation of the epigenetic machinery have been summarized (Datta et al., 2023).

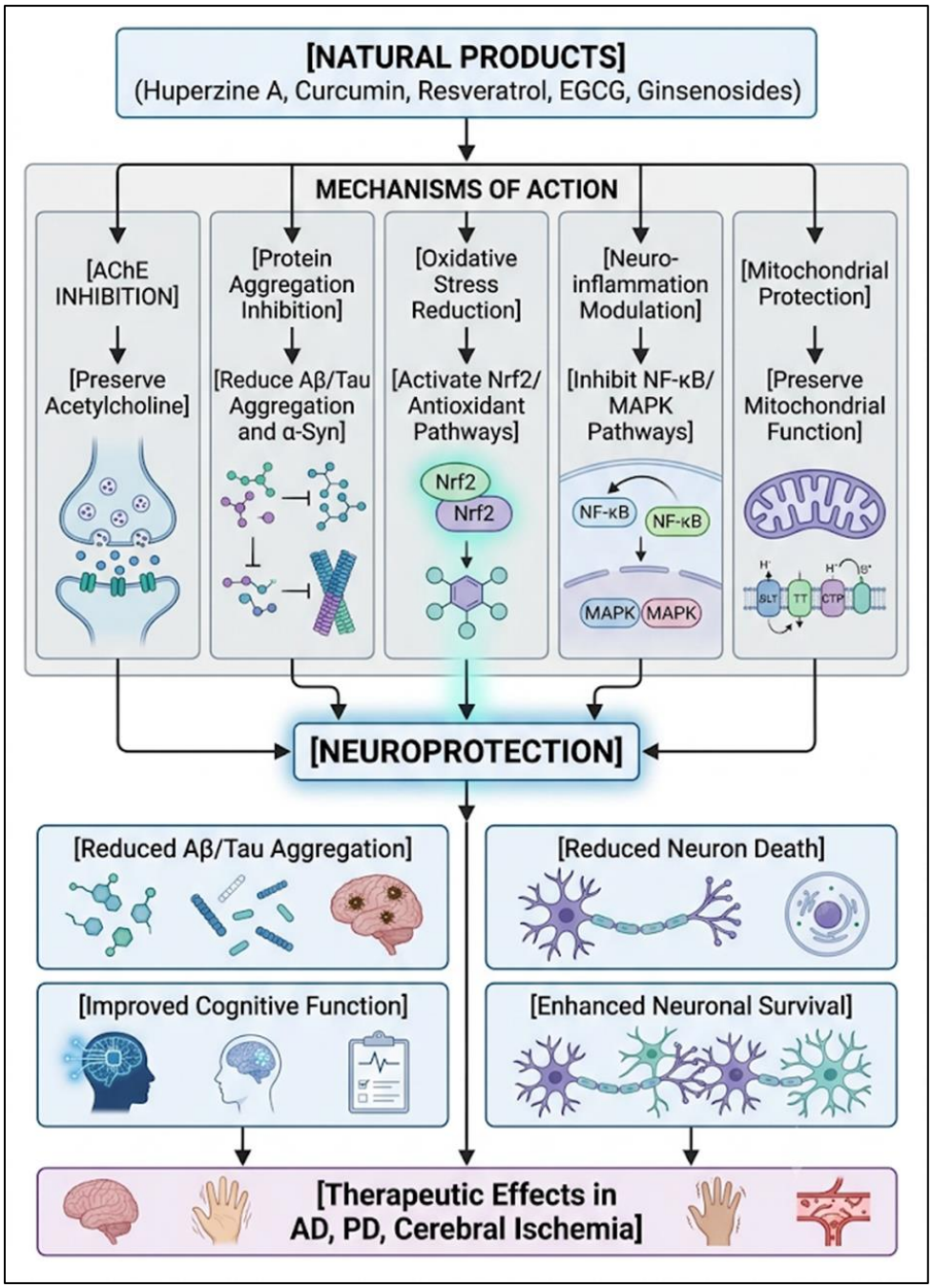

Figure 1: Neuroprotective Mechanisms of Natural Products

Above Figure 1 illustrates the multiple neuroprotective mechanisms of natural products, highlighting the interconnected pathways through which these compounds exert their beneficial effects.

9 DISEASE-SPECIFIC THERAPEUTIC POTENTIAL

9.1 Alzheimer's Disease

Natural products have demonstrated therapeutic potential in AD through multiple mechanisms (Kumar et al., 2023). Huperzine A is clinically used for AD in China, providing symptomatic improvement (Chen et al., 2024). Curcumin and resveratrol have shown disease-modifying potential in preclinical models, reducing Aβ pathology and improving cognitive function (Dhiman et al., 2023; Anand et al., 2023).

Natural compounds from herbs and nutraceuticals as glycogen synthase kinase-3β inhibitors for the treatment of Alzheimer's disease have been summarized (Ahmed and Khan, 2023). Modulation of neuroinflammation by natural molecules has been demonstrated in the context of Alzheimer's and Huntington's diseases (Wang et al., 2023). The

neuroprotective effects of curcumin, resveratrol, and EGCG in AD models have been extensively documented (Dhiman et al., 2023; Anand et al., 2023; Jaiswal et al., 2024).

9.2 Parkinson's Disease

Natural products offer neuroprotective potential in PD through antioxidant, anti-inflammatory, and mitochondrial protective effects (Kaur et al., 2024). Curcumin protects dopaminergic neurons in PD models (Dhiman et al., 2023). Resveratrol and EGCG also show neuroprotective effects (Anand et al., 2023; Jaiswal et al., 2024). A comprehensive review of natural compounds and their structure–activity relationship in Parkinson's disease has explored potential mechanisms (Kaur et al., 2024). The role of phytochemicals in targeting oxidative stress and neuroinflammation in Parkinson's disease has been reviewed (Khan et al., 2023; Bhatia et al., 2023).

9.3 Cerebral Ischemia

Natural products demonstrate neuroprotective effects in cerebral ischemia through antioxidant, anti-inflammatory, and anti-excitotoxic mechanisms (Pradhan et al., 2023). Resveratrol and curcumin reduce infarct volume and improve neurological outcome in stroke models (Anand et al., 2023; Pradhan et al., 2023). EGCG also shows neuroprotective effects in ischemia models (Jaiswal et al., 2024). Ginsenoside Rd has demonstrated significant neuroprotective effects through mitochondrial protection (Balakrishnan et al., 2024; Zhang et al., 2023).

10 CHALLENGES AND RESEARCH GAPS

10.1 Bioavailability and Blood-Brain Barrier Penetration

Poor bioavailability and limited blood-brain barrier (BBB) penetration are major limitations for neuroprotective natural products (Dhiman et al., 2023). Curcumin and resveratrol have low oral bioavailability due to poor absorption and rapid metabolism (Anand et al., 2023; Kumar et al., 2023). However, ginsenoside Rd has demonstrated the ability to effectively cross the BBB (Balakrishnan et al., 2024). Strategies including nanoparticle formulations, prodrug approaches, and intranasal delivery are being developed to address these limitations (Mukherjee et al., 2024; Saini et al., 2023).

10.2 Clinical Translation

The translation of preclinical findings to clinical practice has been challenging (Goswami et al., 2023). Mixed results in clinical trials reflect limitations in trial design, dosing, and patient selection (Kaur et al., 2024). The identification of biomarkers and patient selection strategies may improve clinical outcomes (Datta et al., 2023; Saini et al., 2023).

10.3 Standardization

Variability in natural product composition presents standardization challenges (Kumar et al., 2023). The absence of standardized extracts and quality control measures complicates clinical trial interpretation (Mukherjee et al., 2024). Analytical methods and quality control are essential for ensuring consistency (Saini et al., 2023).

11 FUTURE PERSPECTIVES

The future of neuroprotective natural products lies in the integration of emerging technologies and innovative strategies. The application of multi-omics and systems pharmacology will enable comprehensive characterization of neuroprotective mechanisms and identification of therapeutic targets. The development of optimized formulations, including nanoparticle and intranasal delivery systems, will address bioavailability and BBB penetration limitations. The identification of predictive biomarkers will enable patient stratification and personalized therapy. The integration of natural products with conventional therapies, including synergistic combinations, promises to enhance therapeutic efficacy. The continued exploration of traditional medicine knowledge may reveal novel neuroprotective agents and mechanisms.

12 CONCLUSION

Plant secondary metabolites, including huperzine A, curcumin, resveratrol, EGCG, and ginsenosides, demonstrate neuroprotective effects through diverse mechanisms including acetylcholinesterase inhibition, protein aggregation inhibition, oxidative stress reduction, neuroinflammation modulation, mitochondrial protection, and epigenetic modulation. These compounds have shown therapeutic potential in preclinical models of Alzheimer's disease, Parkinson's disease, and cerebral ischemia. Polyphenols exert significant inhibitory effects on the NF-κB and MAPK pathways, making them promising candidates for treating neurological disorders. Huperzine A is clinically used for AD, while curcumin, resveratrol, and EGCG have shown promise in clinical trials despite bioavailability limitations. Emerging strategies, including nanotechnology-based formulations and combination therapies, promise to address

current limitations. Continued research and development, employing interdisciplinary approaches and emerging technologies, are essential for translating neuroprotective natural products into effective therapies for neurodegenerative diseases.

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