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Mehak Gupta
Assistant Professor, SIRDA Group of Institutions, Naulakha, Sundernagar, Himachal Pradesh, India

Kritika Sharma
Assistant Professor, SIRDA Group of Institutions, Naulakha, Sundernagar, Himachal Pradesh, India

Preeti
Gatom College of Pharmacy, Hamirpur, Himachal Pradesh, India

Saurav Sharma
Career Point University, Hamirpur, Himachal Pradesh, India

Riya Thakur
SIRDA Group of Institutions, Naulakha, Sundernagar, Himachal Pradesh, India

Corresponding Author:
Mehak Gupta
Assistant Professor, SIRDA Group of Institutions, Naulakha, Sundernagar, Himachal Pradesh, India

Neuroprotective agents in Alzheimer's and Parkinson's diseases: Current advances and future perspectives

Mehak Gupta, Kritika Sharma, Preeti, Saurav Sharma, Riya Thakur

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Abstract
Neurodegenerative disorders such as Alzheimer's disease (AD) and Parkinson's disease (PD) are progressive brain disorders characterized by neuronal loss, oxidative stress, mitochondrial dysfunction, and neuroinflammation. Current pharmacological treatments mainly offer symptomatic relief without halting disease progression. Therefore, identifying and developing neuroprotective agents that can prevent or slow neuronal degeneration has become a key research focus.
Various classes of neuroprotective compounds including synthetic drugs, natural phytochemicals, and novel nanocarrier-based formulations have shown promising results in preclinical and clinical studies. Agents such as memantine, selegiline, curcumin, resveratrol, and Ginkgo biloba extract exhibit antioxidant, anti-inflammatory, and anti-apoptotic effects that protect neurons from degeneration. Recent advancements in nanotechnology and gene therapy have further enhanced drug delivery across the blood-brain barrier, improving therapeutic efficacy.
This review highlights the pathophysiological mechanisms underlying AD and PD, the mechanisms of neuroprotection, and the current progress of neuroprotective agents under investigation. The development of multitargeted and personalized neuroprotective therapies holds significant promise for the effective management of neurodegenerative diseases in the future.

Keywords: Neuroprotection, Alzheimer's disease, Parkinson's disease, oxidative stress, antioxidants, neuroinflammation, phytochemicals, nanotechnology, mitochondrial dysfunction, neurodegenerative disorders

1. Introduction
Neurodegeneration refers to the progressive and irreversible loss of structure and function of neurons, leading to deterioration of the central nervous system (CNS) over time. It is a multifactorial process involving oxidative stress, mitochondrial dysfunction, abnormal protein aggregation, excitotoxicity, and chronic neuroinflammation [1, 2]. These interconnected mechanisms cause gradual neuronal death and are responsible for the onset and progression of various neurodegenerative diseases.
Among the many neurological disorders, Alzheimer's disease (AD) and are the most prevalent and extensively studied. Alzheimer's disease Parkinson's disease (PD) is primarily associated with the accumulation of amyloid-β (Aβ) plaques and neurofibrillary tangles (NFTs) composed of hyperphosphorylated tau protein in the brain [3]. These pathological changes disrupt synaptic transmission and neuronal communication, resulting in cognitive decline, memory loss, and behavioral abnormalities [4]. On the other hand, Parkinson's disease is characterized by the selective degeneration of dopaminergic neurons in the substantia nigra pars compacta, leading to dopamine depletion in the striatum. This deficiency manifests as motor symptoms such as resting tremors, rigidity, bradykinesia, and postural instability [5, 6].
The global prevalence of these disorders has risen sharply in the past decades due to increased life expectancy and aging populations. According to the World Health Organization (WHO), more than 55 million people are currently living with dementia, with Alzheimer's disease accounting for nearly 60-70% of cases [7]. Similarly, Parkinson's

disease affects over 8.5 million individuals worldwide, and its incidence is projected to double by 2040 [8]. This growing prevalence contributes to a substantial social, emotional, and economic burden on patients, families, and healthcare systems.

Despite major advancements in neuroscience and pharmacology, current therapeutic options remain largely symptomatic. For AD, drugs such as donepezil, rivastigmine, and memantine provide temporary symptomatic improvement by enhancing cholinergic transmission or modulating glutamate activity, but they do not alter disease progression [9]. Similarly, levodopa, selegiline, and dopamine agonists used in PD therapy restore dopaminergic function but fail to prevent neuronal degeneration [10, 11]. Long-term use of these agents may also lead to reduced efficacy and adverse effects.

Given these limitations, there is an urgent need for neuroprotective therapies that can target underlying molecular mechanisms, prevent or slow neuronal loss, and enhance neuronal survival and regeneration. Neuroprotective agents act by reducing oxidative stress**,** inhibiting neuroinflammation**,** modulating mitochondrial activity, and promoting synaptic repair [12, 13]. In recent years, both synthetic compounds (e.g., MAO-B inhibitors, NMDA receptor antagonists) and natural phytochemicals (e.g., curcumin, resveratrol, Ginkgo biloba extract) have shown potential neuroprotective activity in preclinical and clinical studies. Furthermore, emerging technologies such as nanocarrier-based drug delivery and gene therapy are providing new directions for effective treatment approaches [14, 15].

This review aims to summarize the pathophysiological mechanisms underlying Alzheimer's and Parkinson's diseases, discuss various neuroprotective agents and their mechanisms of action, and highlight the recent advances and future prospects of neuroprotective strategies in managing neurodegenerative disorders.

2. Pathophysiology Overview

(a) Alzheimer's Disease

Alzheimer's disease (AD) is a chronic neurodegenerative disorder primarily affecting cognitive function, learning ability, and memory. Its pathophysiology is multifactorial, involving abnormal protein aggregation, oxidative stress, mitochondrial dysfunction, and neuroinflammation [16, 17].

One of the key pathological features of AD is the accumulation of amyloid-β (Aβ) plaques in the extracellular spaces of the brain. These plaques result from the abnormal cleavage of amyloid precursor protein (APP) by β-secretase and γ-secretase enzymes, leading to the formation of insoluble Aβ42 peptides [18]. The accumulation of Aβ triggers oxidative stress, disrupts calcium homeostasis, and initiates neuronal apoptosis, ultimately impairing synaptic communication [19].

Another major hallmark is tau protein hyperphosphorylation**,** which leads to the formation of neurofibrillary tangles (NFTs) inside neurons. Hyperphosphorylated tau loses its ability to stabilize microtubules, resulting in cytoskeletal disorganization and impaired axonal transport [20]. The combined effects of amyloid and tau pathology contribute to progressive synaptic dysfunction and neuronal loss.

Oxidative stress and mitochondrial dysfunction further exacerbate AD pathology. Excessive generation of reactive oxygen species (ROS) damages lipids, proteins, and DNA, leading to energy failure and cell death [21]. In addition, chronic neuroinflammation**,** mediated by activated microglia and astrocytes, amplifies neuronal injury by releasing pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 [22]. Collectively, these mechanisms create a self-perpetuating cycle of neuronal degeneration, resulting in progressive cognitive decline.

(b) Parkinson's Disease

Parkinson's disease (PD) is a progressive movement disorder characterized by the degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNpc)**,** leading to dopamine deficiency in the striatum [23]. This dopamine loss impairs the basal ganglia circuitry responsible for motor control, producing classical symptoms such as tremors, rigidity, and bradykinesia [24].

A defining pathological feature of PD is the aggregation of α-synuclein protein, which forms intracellular inclusions known as Lewy bodies [25]. Misfolded α-synuclein disrupts vesicular transport, impairs synaptic function, and induces neuronal toxicity. The accumulation of these aggregates is considered central to PD progression and may spread to other brain regions through prion-like mechanisms [26].

Oxidative stress and mitochondrial impairment play crucial roles in dopaminergic neuronal death. The substantia nigra is particularly vulnerable to oxidative damage due to its high dopamine metabolism, which generates free radicals. Mitochondrial complex I deficiency has been observed in PD patients, leading to impaired ATP production and increased ROS generation [27, 28].

Moreover, neuroinflammation significantly contributes to PD pathogenesis. Activated microglia release inflammatory mediators and nitric oxide, creating a toxic environment that accelerates neuronal loss [29]. Apoptotic pathways are also activated through mitochondrial dysfunction and caspase signaling, further aggravating neurodegeneration [30].

3. Mechanisms of Neuroprotection

Neuroprotection refers to strategies or agents that preserve neuronal structure and function, delay neuronal death, and maintain normal physiological processes in the brain. The mechanisms of neuroprotection are multifactorial and involve modulation of oxidative stress, inflammation, apoptosis, mitochondrial activity, and neurogenesis. Understanding these mechanisms is crucial for developing therapeutic agents that can effectively prevent or slow neurodegeneration in Alzheimer's disease (AD) and Parkinson's disease (PD) [31, 32].

4. Antioxidant Defense

Oxidative stress plays a central role in the pathogenesis of both AD and PD. Excessive production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) leads to lipid peroxidation, protein oxidation, and DNA damage [33]. Neuroprotective agents exhibiting antioxidant properties help neutralize these free radicals, enhance endogenous antioxidant enzyme activity (such as superoxide dismutase, catalase, and glutathione peroxidase), and maintain cellular redox balance [34].

Compounds like curcumin**,** resveratrol, and coenzyme Q10 have demonstrated potent antioxidant activity by scavenging free radicals and stabilizing mitochondrial membranes [35, 36]. In addition, vitamin E**,** N-acetylcysteine, and alpha-lipoic acid are reported to reduce oxidative stress-induced neuronal damage, thereby improving neuronal survival [37].

4.1 Anti-inflammatory Effects

Chronic neuroinflammation is another hallmark of neurodegenerative diseases. Activated microglia and astrocytes release pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6, which aggravate neuronal injury [38]. Neuroprotective agents act by suppressing microglial activation, reducing cytokine production, and modulating inflammatory signaling pathways like NF-κB and MAPK [39].

Natural compounds such as curcumin**,** ginkgolides**,** and baicalein exert anti-inflammatory effects by inhibiting cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) expression [40]. Synthetic drugs including minocycline and selegiline have also shown the ability to attenuate neuroinflammation in experimental models [41].

4.2 Inhibition of Apoptosis

Apoptosis, or programmed cell death, is a key mechanism contributing to neuronal loss in AD and PD. It involves activation of caspase enzymes, mitochondrial cytochrome c release, and DNA fragmentation [42]. Neuroprotective agents can inhibit apoptotic pathways by modulating Bcl-2 family proteins, reducing caspase-3 activation, and stabilizing mitochondrial membranes [43].

For example, resveratrol and melatonin prevent apoptosis by activating survival signaling pathways such as PI3K/Akt and ERK1/2**,** which promote cell survival and inhibit pro-apoptotic gene expression [44]. Such anti-apoptotic mechanisms help maintain neuronal integrity and delay disease progression.

4.3 Mitochondrial Protection

Mitochondria are the major source of cellular energy, and their dysfunction leads to impaired ATP synthesis, calcium imbalance, and increased oxidative stress. In both AD and PD, mitochondrial impairment plays a major role in triggering neuronal death [45].

Neuroprotective agents that stabilize mitochondrial function prevent oxidative damage, inhibit permeability transition pore (mPTP) opening, and enhance mitochondrial biogenesis [46]. Compounds like coenzyme Q10**,** MitoQ**,** and L-carnitine protect neurons by maintaining electron transport chain activity and energy metabolism [47]. Furthermore, MAO-B inhibitors such as rasagiline and selegiline provide mitochondrial protection by reducing ROS production from dopamine metabolism [48].

4.4 Promotion of Neurogenesis and Synaptic Plasticity

Neuroprotective agents not only prevent neuronal death but also promote neurogenesis (the formation of new neurons) and synaptic plasticity (the ability of synapses to strengthen or weaken over time). Enhancing these processes is essential for cognitive improvement and functional recovery in neurodegenerative diseases [49].

Agents such as brain-derived neurotrophic factor (BDNF) enhancers, omega-3 fatty acids**,** and flavonoids **s**timulate neural stem cell proliferation and synaptic remodeling [40]. Herbal compounds like Withania somnifera (Ashwagandha) and Panax ginseng have also been shown to enhance neurotrophic signaling and improve memory and learning in experimental models [41].

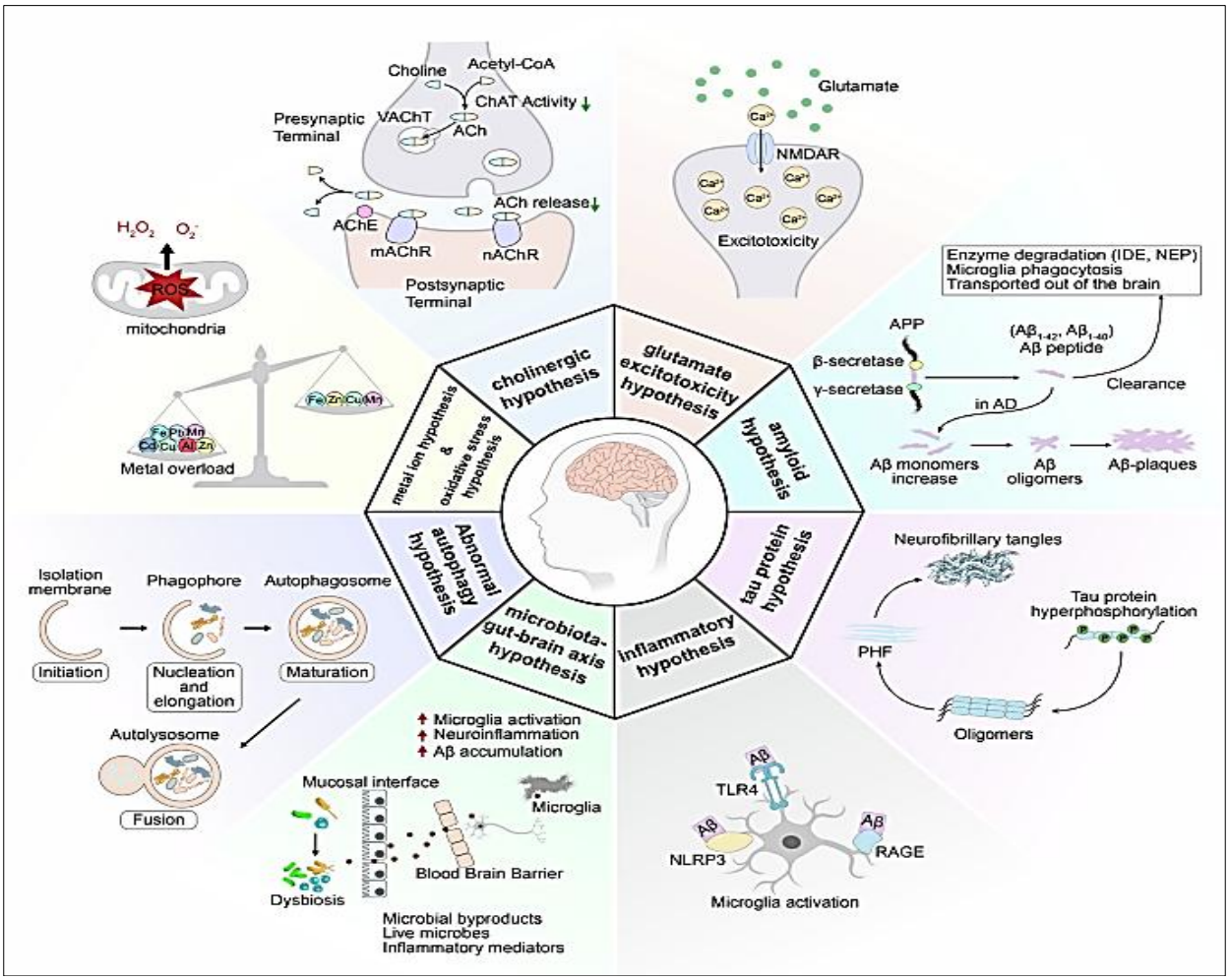

Fig 1: Mechanisum of Neuroprotection

Together, these mechanisms contribute synergistically to protecting neuronal cells, improving brain function, and delaying disease progression.

5. Classes of Neuroprotective Agents

Neuroprotective agents can be broadly classified into synthetic/conventional drugs**,** natural/herbal compounds**,** and novel/experimental agents. Each category acts through distinct molecular mechanisms to delay neuronal degeneration, improve cognitive and motor function, and enhance neuronal survival in Alzheimer's disease (AD) and Parkinson's disease (PD) [42, 43].

5.1 Synthetic / Conventional Drugs

Several synthetic drugs have shown neuroprotective effects in neurodegenerative disorders by targeting excitotoxicity, oxidative stress, and neurotransmitter imbalances.

Memantine, an N-methyl-D-aspartate (NMDA) receptor antagonist, is widely used in AD management. It protects neurons from glutamate-induced excitotoxicity and improves synaptic plasticity [44]. By modulating calcium influx, memantine reduces neuronal death associated with overactivation of NMDA receptors [45].

Selegiline and Rasagiline**,** both monoamine oxidase-B (MAO-B) inhibitors, are approved for PD treatment. They prevent dopamine breakdown, enhance dopaminergic neurotransmission, and exhibit antioxidant properties by reducing free radical formation during dopamine metabolism [46, 47].

Amantadine**,** a dopaminergic and NMDA antagonist agent, provides symptomatic relief in PD by enhancing dopamine release and inhibiting glutamate-mediated excitotoxicity [48].

In AD, acetylcholinesterase (AChE) inhibitors including Donepezil**,** Rivastigmine**,** and Galantamine help maintain acetylcholine levels in the brain. These drugs improve cognitive performance and slow disease progression by enhancing cholinergic transmission [49, 50].

5.2 Natural / Herbal Compounds

Natural and plant-derived compounds are gaining significant attention for their multitargeted neuroprotective actions and low toxicity profiles [51].

Curcumin, derived from Curcuma longa, exhibits potent antioxidant and anti-inflammatory effects. It inhibits amyloid-beta aggregation, reduces tau phosphorylation, and suppresses microglial activation, thereby protecting against cognitive decline in AD [52].

Resveratrol, a polyphenol found in grapes and berries, enhances mitochondrial function, scavenges reactive oxygen species (ROS), and activates the SIRT1 pathway, promoting neuronal survival and longevity [53, 54].

Ginkgo biloba extract (EGb 761) improves cerebral blood flow, reduces oxidative stress, and enhances neurotransmission. Clinical trials have shown its cognitive-enhancing effects in mild to moderate dementia [55].

Withania somnifera (Ashwagandha)**,** a traditional Ayurvedic herb, exhibits neuroregenerative properties by promoting axonal growth, synaptic repair, and neurotrophic factor expression. It also modulates stress-related pathways and improves memory function [56, 57].

5.3 Novel / Experimental Agents

Emerging research has introduced a new generation of neuroprotective strategies focusing on cellular repair, gene modulation, and targeted antioxidant delivery [58].

Neurotrophic factors**,** such as nerve growth factor (NGF) *and* brain-derived neurotrophic factor (BDNF), play essential roles in neuronal survival, differentiation, and synaptic maintenance. Experimental delivery of these proteins or their mimetics has shown promise in restoring damaged neuronal networks [59].

Stem cell-derived exosomes are nanosized vesicles capable of delivering neuroprotective molecules, including proteins, lipids, and microRNAs, directly to the site of injury. These exosomes have been shown to reduce inflammation, promote neurogenesis, and enhance synaptic plasticity [60].

Gene therapy approaches, such as CRISPR-Cas9 *and* small interfering RNA (siRNA), offer the ability to silence or correct genes associated with neurodegenerative pathology. These technologies hold potential to prevent the production of toxic proteins like amyloid-β, tau, or α-synuclein [61, 62] .

Mitochondria-targeted antioxidants**,** including MitoQ and Coenzyme Q10 (CoQ10), are designed to accumulate within mitochondria and prevent oxidative damage at the primary source. These agents improve energy metabolism and protect neurons from apoptosis and oxidative injury [63, 64].

6. Role of Nanotechnology

The application of nanotechnology in neuroprotection has emerged as a revolutionary approach to enhance the delivery, bioavailability, and therapeutic efficacy of drugs targeting neurodegenerative diseases. Nanocarrier-based systems can cross the blood-brain barrier (BBB) efficiently, provide sustained drug release, and minimize systemic toxicity, thereby improving the overall treatment outcomes in Alzheimer's disease (AD) and Parkinson's disease (PD) [65, 66].

6.1 Nanocarriers for Targeted Brain Delivery

Traditional neuroprotective drugs often fail to reach therapeutic concentrations in the brain due to limited permeability across the BBB. Nanocarriers**,** such as liposomes, polymeric nanoparticles, solid lipid nanoparticles (SLNs), dendrimers, and nanomicelles, have demonstrated remarkable potential for targeted brain delivery [67, 68].

Liposomes phospholipid vesicles capable of encapsulating both hydrophilic and lipophilic drugs enhance stability and prolong circulation time [69]. Polymeric nanoparticles made from biodegradable polymers like polylactic-co-glycolic acid (PLGA) *or* chitosan can be engineered to release drugs in a controlled manner and can be surface-modified with ligands for receptor-mediated transport [70].

These systems allow site-specific drug delivery, reducing off-target effects and improving neuronal uptake of neuroprotective agents such as curcumin, resveratrol**,** and selegiline [71, 72].

6.2 Overcoming the Blood-Brain Barrier (BBB)

The BBB represents one of the major challenges in treating central nervous system (CNS) disorders. Nanotechnology offers innovative strategies to overcome this barrier via receptor-mediated transcytosis**,** adsorptive-mediated endocytosis, and nanocarrier surface functionalization [73].

For example, nanoparticles conjugated with ligands such as transferrin, lactoferrin, *or* apolipoprotein E mimic natural transport mechanisms, enabling efficient drug passage across endothelial cells [74]. Furthermore, PEGylation (polyethylene glycol coating) enhances nanoparticle stability and prolongs systemic circulation, ensuring better brain accumulation [75].

6.3 Sustained Drug Release and Reduced Toxicity

Nanocarrier systems are capable of providing sustained and controlled drug release, maintaining therapeutic levels for extended periods while minimizing dosing frequency [76]. This property is particularly beneficial for chronic neurodegenerative diseases requiring long-term management.

Additionally, encapsulation of neuroprotective compounds within nanoparticles protects them from premature degradation and reduces systemic toxicity [77]. For instance, curcumin-loaded PLGA nanoparticles and resveratrol nanoliposomes have shown improved bioavailability and enhanced antioxidant activity in experimental models of AD and PD [78, 79].

Thus, nanotechnology represents a transformative platform for delivering neuroprotective agents more effectively, paving the way for improved treatment outcomes in neurodegenerative diseases.

7. Clinical Trials and Recent Advances

Despite extensive preclinical success, translating neuroprotective strategies into effective clinical therapies remains a major challenge. Several clinical trials are ongoing or have been completed to evaluate the safety and efficacy of various neuroprotective compounds in AD and PD [80, 81].

7.1 Ongoing or Completed Trials on Neuroprotective Compounds

Numerous compounds both synthetic and natural have been tested in clinical settings. Memantine and donepezil are among the few drugs that have demonstrated modest clinical benefits in AD [82]. In PD**,** rasagiline and selegiline have shown disease-modifying potential due to their antioxidant and anti-apoptotic properties [83].

Clinical investigations on Coenzyme Q10**,** creatine, and vitamin E have been conducted to assess their neuroprotective efficacy, but outcomes remain inconsistent [84, 85]. Natural compounds such as curcumin**,** resveratrol, and Ginkgo biloba extract are also being evaluated in various phases of human trials for cognitive enhancement and oxidative stress reduction [86].

7.2 Challenges in Translating Preclinical Success to Humans

A major limitation in neuroprotective drug development is the poor correlation between preclinical and clinical outcomes. Animal models often fail to replicate the complexity of human neurodegeneration [87]. In addition, factors such as limited BBB permeability**,** short drug half-life**,** inadequate dosing, and heterogeneous patient populations contribute to inconsistent trial results [88].

Ethical and logistical issues, including long disease duration and the need for sensitive biomarkers, further complicate clinical validation of neuroprotective agents [89].

7.3 Combination Therapies and Multi target Drugs

Given the multifactorial nature of neurodegenerative diseases, combination therapies targeting multiple pathological pathways simultaneously offer a promising approach. For example, combining AChE inhibitors with antioxidants or anti-inflammatory agents may enhance cognitive outcomes [90].

Multitarget-directed ligands (MTDLs) are novel compounds designed to interact with multiple molecular targets, such as NMDA receptors, AChE, and MAO-B, within a single molecule. This integrated approach may yield superior neuroprotection compared to monotherapy [91, 92].

Recent advances also focus on nanocarrier-based combination systems and gene-drug hybrid therapies that deliver synergistic effects while minimizing adverse reactions [93].

8. Challenges and Future Perspectives

Despite major advancements in understanding the mechanisms of neurodegeneration, the development of effective neuroprotective therapies for Alzheimer's and Parkinson's diseases remains a significant challenge. One of the primary obstacles is the restricted permeability of the blood-brain barrier (BBB)**,** which limits the entry of most therapeutic molecules into the central nervous system. Although nanotechnology and novel carrier systems have shown potential to enhance drug delivery, achieving efficient and safe transport across the BBB remains an area of active research.

Another major concern is the long-term safety and efficacy of neuroprotective agents. Chronic use of pharmacological compounds, especially those targeting oxidative and inflammatory pathways, may lead to off-target effects and cumulative toxicity. Therefore, comprehensive preclinical and clinical assessments are essential to establish therapeutic windows and minimize adverse outcomes.

The future of neuroprotection also lies in personalized medicine, where treatment strategies are tailored according to an individual's genetic, biochemical, and pathological profile. Integration of biomarker-based approaches can help in early disease detection, progression monitoring, and therapeutic optimization.

Furthermore, artificial intelligence (AI) and machine learning are emerging as powerful tools for drug discovery and patient-specific prediction models. AI-driven analysis of neuroimaging and genomic data may accelerate the identification of novel targets and facilitate the design of multitargeted neuroprotective therapies. Continued collaboration among neuroscientists, pharmacologists, and computational experts will be essential to overcome existing barriers and advance precision neurotherapeutics.

9. Conclusion

Neurodegenerative disorders such as Alzheimer's and Parkinson's diseases continue to represent one of the greatest medical and societal challenges of the 21st century. Current treatment options primarily provide symptomatic relief without addressing the underlying causes of neuronal loss. Neuroprotective agents both synthetic and natural offer a promising direction by targeting oxidative stress, neuroinflammation, mitochondrial dysfunction, and apoptotic pathways.

Recent advances in nanotechnology, biomarker discovery, and computational modeling have further expanded the

scope of neuroprotective research. Early intervention, along with combination therapies that address multiple molecular targets simultaneously, appears to be the most effective approach for slowing disease progression.

Future research should focus on developing safe, brain-targeted, and patient-specific therapies supported by advanced clinical studies. A multidisciplinary framework that combines molecular biology, pharmacology, and artificial intelligence will be crucial to translating neuroprotective strategies from laboratory success to clinical application, ultimately improving quality of life for individuals affected by these devastating diseases.

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