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MECHANISTIC ARCHITECTURE OF EMERGING NEUROTHERAPEUTICS - NATURAL BIOACTIVE AND SYNTHETIC DRUGS AS MULTI-TARGET MODULATORS: A NARRATIVE REVIEW

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ABSTRACT

Background and objective:

Neurodegenerative disorders (NDs) represent a major global healthcare challenge, affecting millions of individuals worldwide. These disorders are characterized by progressive deterioration of cognitive and motor functions. Current therapeutic strategies offer only limited disease modification, highlighting the urgent need for more effective treatment approaches. In recent years, increasing attention has been directed toward both natural and synthetic compounds as potential preventive and therapeutic agents for NDs. The objective of this narrative review was to investigate and summarize the neuroprotective and anti-inflammatory potential of natural and synthetic compounds in the prevention and management of NDs.

Methods:

A comprehensive review of existing literature was conducted focusing on the neuroprotective, antioxidant, and anti-inflammatory effects of natural molecules such as polyphenols, flavonoids, and omega-3 fatty acids, as well as synthetic compounds including antioxidants, anti-inflammatory agents, cholinesterase inhibitors, dopamine agonists, and NMDA receptor antagonists.

Review:

Natural compounds demonstrate significant antioxidant and anti-inflammatory properties, disrupt pathological protein aggregation, regulate intracellular signaling pathways, and enhance neuronal resilience. Synthetic agents have shown benefits in improving cognitive function, modulating neurotransmitter activity, and enhancing patients' quality of life.

Conclusion:

Natural and synthetic compounds provide valuable therapeutic prospects for the management of NDs. However, large-scale and rigorously designed clinical trials are essential to establish their long-term safety, efficacy, and clinical applicability.

Keywords: Neurodegenerative diseases; Polyphenols; Flavonoids; Cholinesterase inhibitors; Dopamine receptor agonists; NMDA antagonists.

INTRODUCTION

Neurodegenerative Disorders

Neurodegenerative disorders (NDs) refer to a group of diseases which involve neurodegeneration of cells and neuronal death in the brain and spinal cord. It causes numerous symptoms that include a progressive movement loss, impaired coordination, and cognitive ability.[1] Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and Amyotrophic lateral sclerosis (ALS) are some of the common NDs.[2-5]

Prevalence

NDs represent a significant health challenge to individuals around the globe, with a substantial proportion of the population affected by these debilitating conditions. The most common among NDs is AD as it affected 5.8 million individuals in the United States and more than 44 million globally.[6] People aged more than 60 years have been affected with PD, and about 10 million people have been afflicted with this condition.[7] Conversely, HD is a rare disorder, affecting only 5-10 people per 100,000,[8] whereas ALS is affecting 30,000 people in the United States and 450,000 all around the world.[9] These values indicate that neurodegeneration has become a significant burden in individual and society, highlighting the pressing need for effective interventions to prevent and manage these conditions.

Etiology and Risk Factors

Several factors are being considered as a cause of pathogenesis of NDs.[10] Extensive research has raised genetic predisposition, environmental exposures, and lifestyle choices as the key factors in the development and progression of these disorders.[11] In certain disorders, individuals' genetic mutations have been determined. For example, the onset of AD in the early period is associated with mutations in the genes of the protein precursor of peptides, amyloid (APP),[12] presenilin 1 (PSEN1), and presenilin 2 (PSEN2) genes are implicated in the early onset of AD.[13] HD is linked to mutations in the HTT gene.[14] Whereas the superoxide dismutase 1 (SOD1) gene mutation has also been identified as a factor that causes ALS.[15]

Another evident risk factor of NDs is advanced age. AD has been recorded most commonly in persons aged above 65 years,[6] whereas PD is known to develop later at age above 60 years.[16] Furthermore, family history of NDs is a significant risk factor for developing neurodegenerative conditions, suggesting a genetic component in their inheritance.[17]

Environmental factors also play an important role in the development of NDs. Exposure to metals such as mercury and lead mitochondrial dysfunction, impairs enzymatic activity, increase oxidative stress, thereby increasing the risk of NDs.[18] Traumatic brain injuries (TBI), particularly chronic traumatic encephalopathy (CTE) also increase the risk of neurodegeneration.[19] Moreover, chronic stress,[20] poor dietary habits, smoking, and sedentary lifestyle are linked with an increased risk of PD, AD, and other forms of dementia.[21-23]

Pathogenesis

The pathogenesis of NDs involves complex molecular and cellular processes including protein aggregation, oxidative stress, mitochondrial dysfunction, excitotoxicity, and chronic neuroinflammation. (Figure 1).

- ***Protein Misfolding and Aggregation:*** Aggregation of abnormal or misfolded protein such as alpha synuclein, amyloid beta, tau, and Huntington are the hallmark of several NDs. The aggregates of these misfolded proteins within neurons, disrupt normal cellular functions and cause neurotoxicity.[24-26]
- ***Oxidative Stress:*** Impaired antioxidant defense mechanism and increased formation of reactive oxygen species (ROS) causes damage to cellular components and macromolecules ultimately leading to neuronal degeneration.[27]
- ***Mitochondrial Dysfunction:*** Mitochondria, crucial for energy production and cellular homeostasis, are compromised in NDs resulting in impaired production of ATP, increased formation of ROS, and disrupt cellular processes.[28]
- ***Excitotoxicity:*** Excessive activation of glutamate receptors leads to excitotoxicity, a process involving calcium influx and subsequent neuronal damage. Glutamate-mediated excitotoxicity affects cellular signaling and triggers oxidative stress, eventually leading to neuronal degeneration.[29]
- ***Neuroinflammation:*** Chronic neuroinflammation, marked by the persistent activation of astrocytes and microglia, is a prominent feature of NDs. The release of inflammatory mediators, such as chemokines and cytokines (IL-1β, IL-6, TNF-α), further amplifies neuronal damage and progresses disease development.[30]
- ***Impaired Protein Clearance:*** Malfunction in protein clearance mechanisms, notably autophagy and the ubiquitin-proteasome system, disrupt the elimination of misfolded or aggregated proteins,[31,32] causing neuronal deterioration and dysfunction.
- ***Genetic Factors:*** Genetic mutations profoundly impact neuronal health. Genetic factors can alter protein structure, disrupt cellular processes, or influence susceptibility to environmental factors, thereby playing a pivotal role in initiating and advancing NDs.[11,12,14,15]

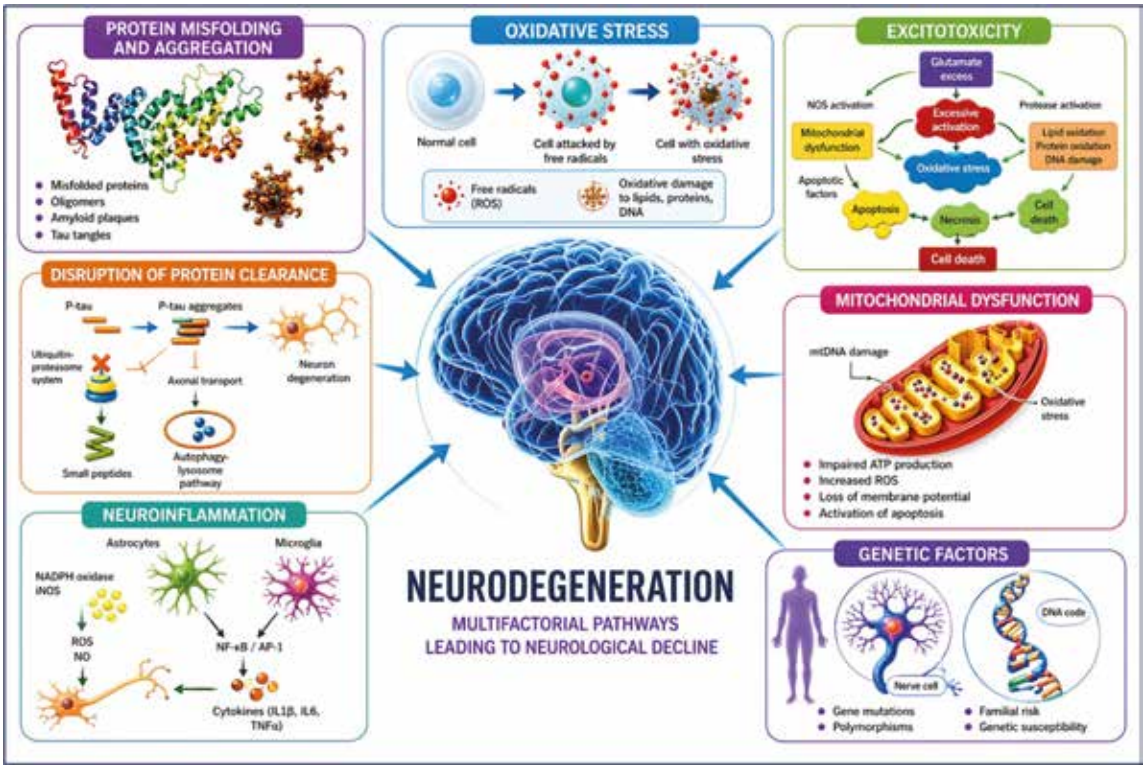


Figure 1: Pathogenesis of Neurodegeneration

Objective of the Study

In the modern era, there has been a burgeoning concern in exploring the potential of natural and synthetic compounds to prevent and manage neurodegenerative conditions. Studies have investigated the neuroprotective effects of various compounds found in spices and herbs, such as curcumin in turmeric,[33] epigallocatechin-3-gallate (EGCG) in green tea,[34] and anthocyanins in blueberries,[35] etc. These compounds have shown promise in mitigating oxidative stress and inflammation, two key factors implicated in the pathogenesis of neurodegeneration.[36] Synthetic compounds have also been studied for their efficacy in the management of ND, such as memantine, and L-dopa in treatment of PD.[37] Although natural and synthetic compounds have been gaining popularity, their relative efficacy to address neurodegeneration remains uncertain. Therefore, this review examines the role of widely studied natural and synthetic agents which have potential in treating the NDs, and provide evidence-based recommendations for experimental and clinical practices that can be used to design future therapeutic interventions in neurodegeneration.

METHODS

This review focuses on the neuroprotective, antioxidant, and anti-inflammatory effects of natural and synthetic molecules and their mechanism underlying their role in modulating neurodegenerative pathogenesis.

The literature was searched using major databases, including, Google Scholar, PubMed, and Scopus. Keywords such as neurodegenerative diseases, natural compounds, synthetic agents, neuroprotection, oxidative stress, and inflammation, were applied to refine the search strategy.

Peer-reviewed original research articles and review papers focusing on natural or synthetic agents with neuroprotective, antioxidant, or anti-inflammatory effects, and studies investigating mechanisms related to neurodegenerative diseases were included to ensure the relevance. The selection of compounds was based on their reported neuroprotective potential, frequency of investigation in the literature, and relevance to key pathological mechanisms such as oxidative stress, neuroinflammation, and protein aggregation, and the literature search was limited to studies published with years 2000-2024.

REVIEW

Natural Compounds in the Management of Neurodegenerative Disorders

Natural compounds have significant therapeutic potential in NDs. This review discussed various compounds of natural origin and their neuroprotective properties below (Table 1).

Polyphenols

Polyphenols can be found in several fruits, vegetables,

berries, tea, coffee, and red wine, etc. Polyphenols are widely recognized for their antioxidant, anti-cancer, cardioprotective, and neuroinflammatory properties. They contribute in neuronal resilience, and potentially improve cognitive function.[38,39]

Curcumin

Curcumin is a polyphenol that is obtained from the turmeric plant. It is well investigated in preclinical AD models.[40] According to the research, curcumin can greatly decrease the deposition of amyloid-beta in an AD rat model. Studies reported lower oxidative stress and brain inflammation that contribute to better thinking skills in a rat model of chronic Gulf War syndrome, [41] and boost learning and memory in a mouse model of AD.[42] Curcumin has been demonstrated to oppose the microglial cell activation and reduces the amount of pro-inflammatory cytokines such as IL-1β, IL-12, and TNF-α.[43,44]

Randomized controlled trials, involving mild-to-moderate AD patients in phase II double-blind, placebo-controlled trial indicate that oral administration of 4 g/day of curcumin for 24 weeks was safe and well tolerated. However, no significant improvements were observed in cognitive function or biomarkers such as amyloid-β and tau levels.[45] Moreover, Clinical studies indicate that curcumin supplementation may improve motor symptoms in PD and enhance clinical status in ALS patients, particularly when used in combination therapies.[46]

Resveratrol

Resveratrol is a polyphenol found in various edible items, such as grapes, berries, and peanuts. It has a range of biological properties, such as anti-inflammation, antioxidant, cardioprotective, and neuroprotective.[47] An analysis reflected that resveratrol supplements increase the contemplation of antioxidant enzymes in mouse brain cells, protect against oxidative damage and boost cognitive inference.[48] Resveratrol has the anti-inflammatory potential that suppressed the expression of pro-inflammatory cytokines (TNF-alpha and IL-1β) in an AD mouse model, while simultaneously reduced the activation of microglial cells, which participate in the neuroinflammatory process.[49,50] By stimulating the protein expression from sirtuin family, resveratrol, control cellular functions, including stress response, DNA repair, and inflammation.[51,52] Sirtuins (SIRT1) help prevent nerve cell damage, enhance neuronal cell function and survival.[51,52] Resveratrol blocks AD-inflicted and cerebral ischemia/reperfusion-related damage by modulating PI3K/Akt/mTOR and JAK2/STAT3 pathways[53,54]. Thus resveratrol influence cellular metabolism and sustain cell survival.[54]

Clinical studies demonstrate that resveratrol supplementation is associated with improved cerebral blood flow, enhanced hippocampal functional connectivity, and improved memory performance, particularly in older adults and individuals with mild cognitive impairment.[46] Additionally, resveratrol has been reported to preserve hippocampal volume and improve metabolic and cognitive parameters in early-stage neurodegeneration. However, a randomized, placebo-controlled trial in AD patients showed that resveratrol was safe and well tolerated but failed to significantly slow disease progression over one year.[45]

Flavonoids

Vegetables, fruits, grains, flowers and roots, stems, wine, and tea are some of the natural sources of flavonoids. Flavonoids possess potent antioxidant properties and can scavenge and neutralize free radicals in the brain.[55] Flavonoids inhibit the production of pro-inflammatory molecules, promote the release of anti-inflammatory factors, and influence the activation of microglia and astrocytes.[56] Flavonols (Icariin) have been shown to stimulate the production and release of neurotrophic factors, such as BDNF, in a mouse model of TBI, thus playing a crucial role in neuronal survival, growth, and function.[57] As neuroinflammatory molecules, flavonoids protect against neuron damage and slow disease progression. This modulation primarily occurs through suppressing the NLRP3 inflammasome and the NF-kB, MAPK, and JAK/STAT apoptotic pathways. Additionally, flavonoids (e.g., luteolin and baicalin) promote Nrf2, AMPK, BDNF/CREB, Wnt/β-Catenin, PI3k/Akt signals and facilitate SIRT1-mediated HMGB1 deacetylation,[58] resulting in the inhibition of neuroinflammation.

(i) Epigallocatechin-3-gallate (EGCG)

Epigallocatechin-3-gallate (EGCG) is a polyphenol flavonoid widely available in green tea and has various health benefits. It is a flavan-3-ol catechin.[59] EGCG inhibit Aβ aggregation, prevent the formation of plaques and protect against neurodegeneration in animal models of AD and traumatic brain injury [59,60]. EGCG activate protein kinases (protein kinase B/Akt), promote cell survival and modulate the activity of enzymes, and transcription factors intricate in gene expression.[61] EGCG reduce ROS production, and inhibit pro-inflammatory signaling of cytokines (TNF-α, IL-1β, and IL-6), and p38 (MAPK) in microglial cells.[62,63]

A phase II RCT in patients with MS demonstrated that EGCG supplementation (600 mg/day) significantly reduced inflammatory markers, improved cardiovascular risk profiles, and decreased depressive symptoms. A phase III clinical trial investigating EGCG in AD has been completed, although results have not yet been fully published.[45]

(ii) Quercetin

Quercetin is a rich flavonoid present in several plants (fruits, vegetables, cereals). It is known for its antioxidant, anti-inflammatory, and neuroprotective capabilities.[64] Quercetin is an antagonist of the oxidative stress-related neuronic cell damage. It impedes the feasibility of pro-inflammatory cytokines (NF-kB and iNOS) and induces regeneration of neurons.[65] Quercetin metabolites, mostly methylated, glucuronidated, sulfated were recognized as neuroprotective. A derivative of the quercetin, isoquercetin, enhanced motor function in an animal model of acute spinal cord injury, alleviated hippocampal cell death of neurons, improved synaptic plasticity, decreased α-synuclein fibrillization, and reversed AD histopathology.[66] In preclinical experiments of AD animal models, quercetin was used as a therapeutic agent to inhibit the degeneration of neurons. A study showed that administration of quercetin in an AD mouse, significantly suppressed oxidative stress and inflammation, and improved the cognitive performance by eliminating amyloid beta accumulation in the brain.[67] In addition, quercetin has been shown to prevent dopaminergic progressive degeneration as well as mitochondrial dysfunction in both in vitro and in vivo models of PD.[67-69]

Omega-3 fatty acids

Omega-3 fatty acids (O3FA, a Linolenic acid) are richly present in fish oil and other edible sources, notably in fatty fish, including salmon, mackerel, and tuna, and plant-based sources like flaxseed and chia seeds.[70] Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are two forms of O3FA, found in brain phospholipid fraction and act as anti-inflammatory agents. O3FA consumption lower the risk of AD by mitigating the accumulation of Aβ plaques in the early stages of AD, while it does not facilitate cognitive function in moderate AD.[71-73] Moreover, omega-3 supplementation attenuate inflammation and oxidative stress, protect against neuronal cell death, and enhance motor functions in PD and HD animal models.[74,75] The exact mechanisms through which O3FA manifest their neuroprotective effects remain unclear; however, their anti-inflammatory and antioxidant activities, influence on membrane structure and function, neurotransmitter signaling, and gene expression are believed to be involved.[72,73]

Table 1: Summary of natural compounds and their mechanism of action in preventing NDs.

Functional Category	Compound	Class	Mechanism of Action	Effects on Neurodegenerative Diseases	Level of Evidence
Polyphenols	Curcumin	Natural polyphenol	Reduces Aβ deposition, inhibits NF-κB signaling, scavenges ROS, suppresses pro-inflammatory cytokines, inhibits microglial activation[43,44].	Protects against neurodegeneration in AD and PD.	Preclinical + clinical
	Resveratrol	Natural polyphenol	Activates SIRT1 and Nrf2 pathways, regulates PI3K/Akt/mTOR and JAK2/STAT3 signaling, reduces oxidative stress and inflammation[49,50,53,54].	Prevents neuronal damage in AD and stroke.	Preclinical + clinical
Flavonoids	Epigallocatechin Gallate (EGCG)	Flavonoid (c atechin)	Activates Nrf2 pathway, reduces ROS, inhibits pro-inflammatory cytokines, prevents Aβ aggregation, modulates MAPK signaling[58,61-63].	Neuroprotective in AD PD models.	Preclinical + clinical
	Quercetin	Natural flavonoid	Modulates MAPK and NF-κB pathways, reduces oxidative stress and inflammation, promotes neuronal regeneration[67-69].	Protects neurons from degeneration in AD and PD models.	Preclinical + clinical
Fatty Acids	Omega-3 fatty acids (EPA, DHA)	Essential fatty acids	Reduces Aβ accumulation, modulates membrane function, decreases inflammation and oxidative stress, improves neurotransmission[72,73].	Protects against neuronal cell death and improves motor and cognitive function.	Preclinical + clinical

Synthetic Compounds in the Management of NDs

Synthetic compounds have been carefully designed to target specific molecular pathways implicated in the pathogenesis of neuroinflammation and neurodegeneration. Several classes of synthetic compounds with a promising effect are explained as follows (Table 2).

Antioxidants

NDs are often linked with increased oxidative stress, resulting in neuronal cell damage. N-acetylcysteine (NAC) and edaravone are synthetic antioxidants that have been studied for their ability to scavenge free radicals and counteract oxidative stress, potentially slowing down the progression of NDs.

(i) N-acetylcysteine (NAC)

NAC is a synthetic compound derived from the amino acid L-cysteine. NAC is an antioxidant and free radical-scavenging agent that can increase intracellular glutathione (GSH) levels.[76] In experimental studies, NAC has been shown to protect against oxidative stress-induced cell death in granule neurons in vitro, particularly in countering the toxicity induced by 4-hydroxynonenal (HNE), a reactive byproduct of lipid peroxidation, in cerebellar granule neurons.[77] Neural degeneration is primarily observed in the substantia nigra with increased oxidative stress in PD. With the ability to cross the BBB, NAC can alleviate brain oxidative stress and reverse memory impairment.[76] NAC also inhibit lipid peroxidation and increase GSH levels in mouse models of AD and PD.[78]

(ii) Edaravone

Edaravone is a free radical scavenger, it exerts antioxidant activity through the Nrf2 signaling, which is crucial in regulating intracellular oxidative stress.[79] Edaravone treatment results in improved motor performance, reduced oxidative stress markers, and extended cell survival in animal model of ALS.[79,80] Edaravone also recovered mitochondrial membrane potential and ATP synthesis, ultimately improving cellular energy metabolism. It further regulates fusion and fission processes in mitochondria, crucial for maintaining its function and integrity.[79] Additionally, edaravone influences gene expression in mitochondrial biogenesis, restoring its function in NDs.[79] Moreover, edaravone treatment reduces oxidative stress markers,

attenuate neurological deficits, and improved functional outcomes in clinical trials of stroke patients.[81,82]

Anti-inflammatory agents

Chronic inflammation is a critical player in the pathogenesis of NDs. Synthetic compounds, including NSAIDs and selective COX-2 inhibitors, have largely been investigated for their anti-inflammatory effects, aiming to alleviate neuroinflammation, and its detrimental consequences in neurodegenerative conditions.[3]

(i) Ibuprofen

Ibuprofen is a commonly used NSAID. In PD, ibuprofen hinders the activity of iNOS, COX-2, and NF-κB, which helps regulate NO levels and prevent cytokines release.[83] Ibuprofen can directly prevent dopaminergic neuronal death by scavenging NO. Its free radical scavenging capacity and neuroprotective effects have been demonstrated in MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine)- and 6-OHDA (6-hydroxydopamine)-induced PD animal model, showing alleviated inflammation and protecting dopaminergic neurons, resulting in improved motor function.[83-85] Studies reported that long-term use of ibuprofen reduced the risk of PD development by 21%.[84,86] In a population-based study, use of ibuprofen (NSAID) was proved to reduce the risk of AD and dementia.[87]

(ii) Celecoxib

Celecoxib is a selective COX-2 inhibitor that has been studied for its anti-inflammatory effects in NDs. It is known to reduce neuroinflammation, Aβ deposition, and enhanced cognitive performance.[88] Celecoxib blocked caspase-3, COX-2 and GFAP expression in brain tissues, minimized neuroinflammation and astrogliosis in various brain regions, ultimately enhanced neurobehavioral response in the experimental model of hydrocephalus.[89] Celecoxib inhibited neuroinflammation and preserved dopaminergic neurons, resulting in enhanced motor behavior in the PD animal model.[90]

Cholinesterase inhibitors

The most commonly prescribed medications administered in the treatment of AD are referred to as cholinesterase inhibitors, which include donepezil, rivastigmine, and galantamine. These inhibitors have therapeutic effect by inhibiting the activity of the acetylcholinesterase (AChE) enzyme, which degrades the neurotransmitter acetylcholine required to support memory and perception.[91]

(i) Donepezil

Donepezil intervenes in various cellular and molecular processes at nearly every stage of AD.[92] The neuroprotective effects of Donepezil are mediated through the PI3K–Akt pathway. It reduces Aβ generation by mitigating cholinergic deafferentation, induces a neuroprotective AChE isoform, and upregulates cortical nicotinic receptors to diminish glutamate neurotoxicity.[92] Donepezil inhibits β-secretase cleavage of APP, decreasing Aβ production, and attenuating Aβ fragment-induced neurotoxicity.[92] It also interferes with the excitotoxic cascade triggered by glutamate, diminishes oxidative stress, and aligns neural activity with regional cerebral blood flow.

Additionally, Donepezil promotes dendritic sprouting in cholinergic neurons, normalizes BDNF levels in the serum, and reduces the expression of inflammatory cytokines.[92] A randomized clinical trial (placebo-controlled) demonstrated significant improvements in cognitive function and overall clinical response in AD patients treated with Donepezil.[93] Similar outcomes were observed in a study by Feldman et al., which showed a substantial decline in disease symptoms and sustained cognitive benefits in AD patients receiving prolonged donepezil treatment.[94]

(ii) Rivastigmine

Rivastigmine is a cholinesterase inhibitor available in oral and transdermal patch formulations. A recent study by Moreira, Lima et al. (2022) suggests that rivastigmine help reduce the release of inflammatory mediators in response to Aβ toxicity, enhance cell viability, and decrease neuronal cell death.[95] Evidence supporting the therapeutic application of rivastigmine showed significant improvements in cognitive function and activities of daily living in AD patients compared to the placebo group.[96] Emre et al. (2004) showed that rivastigmine treatment improves overall clinical response in dementia patients with PD. However, it is also associated with increased incidences of adverse effects, such as nausea, vomiting, and tremors.[97]

(iii) Galantamine

Galantamine is a cholinesterase inhibitor and is an allosteric modulator of nicotinic acetylcholine receptors. Galantamine treatment proves to be well-tolerated and successful in AD patients.[98] Over six months, galantamine showed a significant enhancement in cognition and overall functional status in AD patients with the use of daily dosage of 24mg for a year.[98] A recent study confirmed that the galantamine-curcumin hybrid (AChE inhibitor galantamine and antioxidant curcumin) significantly inhibits AChE activity without inducing acute toxicity in mice.[99] Lin, Chen et al. showed that galantamine promotes autophagy and prevents apoptosis induced by Aβ1–42 by activating the JNK signaling pathway, increasing neuronal-type alpha7 nicotinic acetylcholine receptors (α7nAChR) expression, and suppressing the Akt signaling, preserving neuronal health and cognitive function in AD.[100]

Dopamine Agonists

Dopaminergic agonists are synthetic compounds that bind to and activate dopamine receptors, primarily targeting the brain's D2-like receptors (D2, D3, and D4). They act as direct or indirect stimulators of the dopaminergic system, promoting dopamine function and modulating neuronal activity.[101] Dopaminergic agonists stimulate the secretion of neurotrophic factors, such as BDNF and GDNF,[102,103] and protect neurons from programmed cell death (apoptosis) by activating anti-apoptotic proteins (e.g., Bcl-2-related proteins) and inhibiting pro-apoptotic factors.[104] They also inhibit the release of pro-inflammatory cytokines such as TNF-α, IL-1β, IFN-γ, IL-6, and ROS and NOS.[105]

(i) Pramipexole

Pramipexole stimulates dopamine receptors in the brain. Pramipexole treatment protected dopaminergic neurons from neurotoxic insults in PD animal models.[106] A clinical trial by the Parkinson Study Group (2002) exhibited the reduction in dopaminergic neuron degeneration with pramipexole treatment,[107] and enhanced motor functions and wellness in PD patients.[108]

(ii) Ropinirole

Ropinirole is a synthetic compound classified as a dopaminergic agonist. Ropinirole exhibited a robust binding affinity specifically for D2 receptors and had negligible adrenergic and serotoninergic activities. These properties made ropinirole a promising candidate for the treatment of PD.[109] By stimulating dopamine receptors, ropinirole enhances dopaminergic neurotransmission and helps alleviate motor symptoms such as tremors, rigidity, and bradykinesia. It provides symptomatic relief by compensating for the dopamine deficiency in the brain.[110] Ropinirole was found to be effective in inducing rotational movement in mice with 6-OHDA (6-hydroxydopamine) lesions and retreated motor deficits encouraged by MPTP in marmosets, outperforming bromocriptine.[111]

(iii) Levodopa

Levodopa, also known as L-DOPA, is an exogenous amino acid and the precursor to dopamine. It serves as a fundamental therapeutic agent in the management of PD. Levodopa can traverse the BBB, and undergo enzymatic conversion into dopamine within the brain, thereby replenishing the diminished levels of dopamine.[112,113] Levodopa alleviates the motor symptoms associated with PD, however, prolonged administration of levodopa is frequently linked to the emergence of motor complications, including dyskinesias and motor fluctuations.[114]

NMDA Receptor Antagonists

NDs are linked with excess stimulation of neurons N-methyl-D-aspartate (NMDA) receptors, resulting in excitotoxicity. It is a phenomenon when calcium ions excessively enter into the neurons leading to cellular dysfunction, and damage to neurons.[115]

(i) Memantine

Memantine targets the NMDA receptor channels which transfer the excitatory neurotransmitter, glutamate, across the synaptic gap.[116] Memantine normalizes the action of NMDA receptors and blocks the overload of calcium influx and consequent neuronal excitotoxicity.[117]

Memantine has shown potential of attenuating synaptic plasticity and enhance memory in AD models at clinically relevant concentrations.[118]

In vitro investigations indicated that memantine may mitigate Aβ toxicity and potentially restrain Aβ production.[118] Studies also confirmed that memantine treatment significantly improved cognitive function, global clinical status, and daily living activities in patients with moderate to severe AD. Notably, it was reported to be devoid of adverse effects and was well-tolerated by patients.[119,120]

Table 2: Synthetic compounds and their mechanism of action in preventing NDs.

Functional Category	Drug	Mechanism of Action	Effects on Neurodegenerative Diseases	Level of Evidence
Antioxidants	N-acetylcysteine (NAC)	Increases intracellular glutathione (GSH), scavenges ROS, reduces oxidative stress[76,77].	Protects neurons from oxidative damage, improves memory, reduces lipid peroxidation in AD and PD models.	Preclinical + limited clinical
Anti-inflammatory Agents	Edaravone	Free radical scavenger; activates Nrf2 signaling; regulates mitochondrial function[79,81,82].	Reduces oxidative stress, improves motor function, restores mitochondrial activity; beneficial in ALS and stroke.	Clinical + preclinical
	Ibuprofen	Inhibits COX-2, iNOS, NF-κB; reduces NO and cytokine production[83-85].	Protects dopaminergic neurons, reduces inflammation, lowers risk of PD and AD in population studies.	Clinical + preclinical
	Celecoxib	Selective COX-2 inhibition; reduces inflammation and apoptosis[88].	Decreases Aβ deposition, neuroinflammation, and improves cognitive and motor outcomes in models.	Preclinical + limited clinical
Cholinesterase Inhibitors	Donepezil	Inhibits AChE; reduces Aβ production; modulates PI3K/Akt pathway[92].	Improves cognition, reduces neurotoxicity, enhances neuronal survival in AD patients.	Clinical
	Rivastigmine	Inhibits AChE; reduces inflammatory mediators and neuronal death[95].	Improves cognition and daily functioning in AD and PD dementia patients.	Clinical
	Galantamine	Inhibits AChE; modulates nicotinic receptors (α7nAChR)[99,100].	Enhances cognition, promotes autophagy, reduces apoptosis in AD.	Clinical + preclinical
Dopamine Agonists	Pramipexole	Stimulates dopamine receptors; anti-apoptotic and neuroprotective effects[106,121].	Protects dopaminergic neurons, improves motor function in PD.	Clinical + preclinical
	Ropinirole	Selective D2 receptor agonist; enhances dopaminergic signaling[109].	Reduces motor symptoms (tremor, rigidity) in PD.	Clinical + preclinical
	Levodopa	Dopamine precursor; replenishes brain dopamine levels[112,113].	Highly effective for motor symptoms but associated with long-term complications (dyskinesia).	Clinical
NMDA Receptor Antagonists	Memantine	Blocks NMDA receptors; prevents excitotoxicity and calcium overload[117].	Improves cognition, daily function, and clinical outcomes in moderate to severe AD.	Clinical

DISCUSSION

The present review highlights key natural and synthetic compounds that have been widely investigated for their potential to prevent or slow disease progression, emphasizing their therapeutic relevance in targeting underlying pathogenic mechanisms.

Natural compounds exert their neuroprotective effects through multi-targeted mechanisms of action that are highly relevant to the complex pathology of NDs. Across polyphenols, flavonoids, and O3FA, a consistent mechanistic pattern emerges: these agents primarily act by attenuating oxidative stress, suppressing neuroinflammation, modulating protein aggregation, and promoting neuronal survival pathways. At the molecular level, they regulate key signaling cascades such as NF-κB, MAPK, PI3K/Akt, JAK/STAT, and Nrf2, while also influencing SIRT1 activation, mitochondrial function, and neurotrophic factors (e.g., BDNF/CREB). Additionally, several compounds (e.g., curcumin, EGCG, and quercetin) directly interfere with amyloid-β aggregation and α-synuclein pathology, highlighting their disease-modifying potential rather than merely symptomatic effects.

In preclinical studies, these mechanisms translate into robust neuroprotective outcomes, including reduced amyloid deposition, decreased ROS, suppression of pro-inflammatory cytokines, improved synaptic plasticity, and enhanced cognitive and motor functions. Animal and in vitro models consistently demonstrate that natural compounds can modulate microglial activation, preserve neuronal integrity, and restore cellular homeostasis under neurodegenerative stress conditions. However, in clinical settings, the efficacy of these compounds remains modest and inconsistent despite favorable safety profiles. While some studies report improvements in cerebral blood flow, metabolic parameters, motor symptoms, or mild cognitive function, most RCTs fail to show significant disease-modifying effects or long-term slowing of disease progression. This discrepancy between preclinical success and clinical outcomes is largely attributed to poor bioavailability, limited BBB penetration, suboptimal dosing strategies, and disease heterogeneity in human populations.

Similarly, synthetic compounds demonstrate therapeutic efficacy in NDs through targeted and mechanism-specific actions that directly modulate key pathological processes. Unlike natural compounds, which often exhibit pleiotropic effects, synthetic agents are typically designed to precisely interact with defined molecular targets, including oxidative stress pathways, inflammatory mediators, neurotransmitter systems, and excitotoxic signaling. Their mechanisms of action primarily involve restoration of redox balance (e.g., glutathione replenishment by N-acetylcysteine), activation of antioxidant pathways such as Nrf2 (edaravone), inhibition of pro-inflammatory enzymes and transcription factors (COX-2, NF-κB by NSAIDs), enhancement of cholinergic neurotransmission (cholinesterase inhibitors), stimulation of dopaminergic signaling (dopamine agonists), and attenuation of glutamate-induced excitotoxicity (NMDA receptor antagonists).

CONCLUSION

This review highlights that both natural and synthetic compounds show therapeutic potential in NDs by targeting key pathological mechanisms such as oxidative stress, neuroinflammation, protein aggregation, and neurotransmitter imbalance. Natural compounds act through multi-target neuroprotective pathways, while synthetic agents provide more specific, target-based interventions with greater clinical consistency. However, a major limitation is the translational gap between preclinical and clinical outcomes, particularly for natural compounds due to poor bioavailability and limited BBB penetration. Synthetic compounds, although clinically effective in symptom control, are largely non-disease-modifying and may produce long-term adverse effects. Despite promising preclinical evidence, current therapies remain limited in altering disease progression, highlighting the need for improved delivery systems, better clinical translation, and multi-target therapeutic strategies.

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