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Review Article

Substituted Chalcones as Neuroprotective Agents: A Review

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ABSTRACT

Neurodegenerative disorders are progressive diseases characterized by gradual loss of neuronal structure and function, leading to cognitive decline, behavioral disturbances, and motor impairment. Major disorders include Alzheimer's disease, Parkinson's disease, Huntington's disease, and Amyotrophic Lateral Sclerosis. Current therapies mainly provide symptomatic relief and do not halt disease progression, creating a need for effective multitarget neuroprotective agents. Chalcones (1,3-diaryl-2-propen-1-ones) are important natural and synthetic scaffolds with broad pharmacological potential. Substituted chalcones have gained attention due to their antioxidant, anti-inflammatory, anti-apoptotic, cholinesterase inhibitory, monoamine oxidase inhibitory, anti-amyloid, and metal-chelating properties. Their α, β-unsaturated carbonyl system and diverse substitutions enable favorable interactions with multiple CNS targets, including acetylcholinesterase, butyrylcholinesterase, monoamine oxidase-B, β-secretase, and glycogen synthase kinase-3β. Structural modifications such as methoxy, hydroxy, halogen, amino, and heterocyclic groups significantly improve potency and selectivity. This review highlights the chemistry, neuroprotective mechanisms, structure–activity relationship, molecular docking studies, and future prospects of substituted chalcones as potential therapeutic agents for neurodegenerative disorders.

INTRODUCTION

Neurodegenerative disorders are one of the fastest growing health concerns worldwide and mainly affect the elderly population. These disorders are characterized by progressive degeneration of neurons, leading to irreversible loss of memory, cognition, motor coordination, and behavioral functions [1,2]. Due to increased life expectancy and aging populations, the prevalence of neurodegenerative diseases is expected to rise significantly over the coming decades [3].

The most common neurodegenerative disorder is Alzheimer's disease, which accounts for the

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majority of dementia cases worldwide. Parkinson's disease is the second most common neurodegenerative disorder and affects movement and motor control. Huntington's disease and amyotrophic lateral sclerosis comparatively less common but highly debilitating disorders [4–7].
Although several synthetic drugs are available for symptomatic management, none completely cure these diseases or reverse neuronal damage. Therefore, there is an urgent need to discover novel molecules capable of protecting neurons and modifying disease progression [8]. Natural product-inspired scaffolds have played a central role in medicinal chemistry. Among them, chalcones have emerged as versatile pharmacophores with broad therapeutic applications. Their easy synthesis, low toxicity, and multitarget activity make them attractive candidates for CNS drug discovery [9,10].

2. Neurodegenerative Disorders: Current Scenario

Neurodegenerative disorders are progressive and irreversible diseases associated with selective neuronal loss in the central nervous system. These disorders mainly affect memory, cognition, movement, and behavior. With increasing global life expectancy, their incidence is rising rapidly and has become a major healthcare challenge. Aging, genetic predisposition, environmental toxins, metabolic abnormalities, and chronic inflammation are considered important risk factors contributing to disease onset and progression [1,2].

2.1 Alzheimer's Disease

Alzheimer's disease is the leading cause of dementia worldwide and is clinically characterized by progressive memory impairment, confusion, language dysfunction, poor judgment, and decline in daily functioning. Major pathological hallmarks include extracellular amyloid-β plaque deposition and intracellular neurofibrillary tangles formed by hyperphosphorylated tau protein. Oxidative stress, mitochondrial dysfunction, calcium dysregulation, and cholinergic deficit further contribute to disease progression [4]. Current therapy mainly includes acetylcholinesterase inhibitors such as Donepezil, Rivastigmine, and Galantamine, along with Memantine. However, these drugs provide only temporary symptomatic benefit [20].

2.2 Parkinson's Disease

Parkinson's disease is the second most common neurodegenerative disorder and mainly affects motor control. It occurs due to degeneration of dopaminergic neurons in the substantia nigra pars compacta, causing dopamine deficiency in the striatum. Major symptoms include resting tremor, rigidity, bradykinesia, gait disturbance, and postural instability. Non-motor symptoms include depression, constipation, anosmia, and sleep disturbances [05]. The disease is also associated with oxidative stress, neuroinflammation, mitochondrial dysfunction, and accumulation of α-synuclein-containing Lewy bodies. Current treatment with Levodopa and dopamine agonists improves symptoms but does not prevent neuronal loss [19].

2.3 Huntington's Disease

Huntington's disease is an inherited autosomal dominant disorder caused by expansion of CAG trinucleotide repeats in the huntingtin gene. It is characterized by involuntary choreiform movements, psychiatric symptoms, irritability, depression, and progressive cognitive decline. The disease usually manifests in adulthood and gradually worsens over time. No definitive cure is currently available [6].

2.4 Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS) is a fatal motor neuron disease involving degeneration of upper and lower motor neurons. It leads to muscle weakness, dysphagia, respiratory failure, and eventual death. Both genetic and sporadic forms of ALS exist. Oxidative damage, excitotoxicity, and mitochondrial abnormalities are implicated in disease pathogenesis [7].

2.5 Common Pathogenic Mechanisms

Although neurodegenerative diseases differ clinically, they share several common pathological mechanisms:

1. **Oxidative Stress** – Excess production of reactive oxygen species damages lipids, proteins, and DNA.
2. **Protein Aggregation** – Misfolded proteins such as amyloid-β, tau, α-synuclein, and huntingtin accumulate in neurons.
3. **Mitochondrial Dysfunction** – Reduced ATP generation and increased ROS promote neuronal death.
4. **Neuroinflammation** – Activated microglia release inflammatory cytokines.
5. **Excitotoxicity** – Excess glutamate causes calcium overload and cell death.
6. **Apoptosis** – Programmed neuronal death contributes to progressive degeneration [24,25].

2.6 Need for Novel Neuroprotective Agents

Currently available therapies mainly provide symptomatic relief and do not reverse disease pathology. Therefore, development of multitarget neuroprotective agents capable of reducing oxidative stress, inflammation, protein aggregation, and neurotransmitter imbalance is urgently required. Natural product-derived scaffolds such as chalcones have attracted major interest due to their broad biological potential and ease of structural optimization.

3. Chalcones as Privileged Medicinal Scaffolds

Chalcones are an important class of naturally occurring and synthetic compounds widely recognized as privileged scaffolds in medicinal chemistry. Chemically, chalcones are defined as **1,3-diaryl-2-propen-1-ones**, consisting of two aromatic rings linked through an α, β-unsaturated carbonyl system. This simple but highly versatile structural framework allows extensive substitution and functional modification, making chalcones attractive lead molecules for drug discovery [09,10]. Chalcones are biosynthetic precursors of flavonoids and isoflavonoids in plants. They are naturally found in many edible plants, fruits, vegetables, tea, hops, licorice, and several medicinal herbs. Natural chalcones have been isolated from species belonging to *Glycyrrhiza*, *Angelica*, *Humulus*, *Piper*, and *Artocarpus* genera [11]. Their natural abundance and broad pharmacological significance have generated continuous scientific interest. One of the major advantages of chalcones is their **easy synthetic accessibility**. Chalcones are commonly prepared by Claisen–Schmidt condensation involving substituted acetophenones and aromatic aldehydes under acidic or basic conditions. This method is simple, economical, requires mild reaction conditions, and generally provides high yields [12]. Because a wide range of acetophenones and aldehydes can be employed, numerous structurally diverse chalcone analogues can be synthesized rapidly. The α, β-unsaturated ketone moiety present in chalcones plays a crucial role in biological activity. This conjugated enone system can interact with biomacromolecules through hydrogen bonding, Michael addition, dipole interactions, and π–π stacking with aromatic amino acid residues in proteins. These interactions contribute significantly to their enzyme inhibitory, receptor binding, and antioxidant properties.

Chalcones possess a broad spectrum of biological activities including:

1. Anticancer activity
2. Antimicrobial activity
3. Antiviral activity
4. Anti-inflammatory activity
5. Antioxidant activity
6. Antimalarial activity
7. Antidiabetic activity
8. Cardioprotective activity

4. Chemical Structure and Properties of Chalcones

Chalcones are open-chain flavonoids chemically known as 1,3-diaryl-2-propen-1-ones. Their general structure consists of two aromatic rings linked through a three-carbon α, β-unsaturated carbonyl system. This conjugated bridge is mainly responsible for the reactivity and biological importance of chalcones [9,10]. The presence of two aromatic rings provides multiple sites for substitution, allowing introduction of electron-donating or electron-withdrawing groups. Such substitutions significantly influence lipophilicity, metabolic stability, and biological activity [13,15]. The α,β-unsaturated ketone moiety acts as an important pharmacophoric feature and can interact with biological targets through hydrogen bonding, dipole interactions, and π–π stacking [12]. Chalcones generally exist in the trans (E)-configuration, which is more stable and favorable for interaction with protein binding sites [11]. Hydroxyl-substituted chalcones often show enhanced antioxidant activity, whereas methoxy-substituted derivatives may display improved metabolic stability. Halogenated chalcones frequently demonstrate stronger hydrophobic interactions with target proteins [15].

5. Chalcones as Neuroprotective Agents

Chalcones have gained considerable attention as potential neuroprotective agents because of their broad pharmacological activities and multitarget mode of action. Neurodegenerative disorders involve oxidative stress, neuroinflammation, mitochondrial dysfunction, protein aggregation, and neurotransmitter imbalance. Chalcones can modulate several of these pathways simultaneously [9,10]. One of the major neuroprotective properties of chalcones is their antioxidant activity. Hydroxyl- and methoxy-substituted chalcones have shown strong free radical scavenging activity and ability to enhance endogenous antioxidant enzymes [11]. Chalcones also exhibit significant anti-inflammatory activity by reducing production of inflammatory mediators such as TNF-α, IL-1β, IL-6, nitric oxide, and COX-2 [13]. Several substituted chalcones have demonstrated inhibitory activity against AChE and BChE, resulting in increased acetylcholine levels, which is beneficial in Alzheimer's disease [14]. Some chalcone derivatives have also shown MAO-B inhibitory activity, which may be useful in Parkinson's disease [25].

6. Role of Chalcones in Alzheimer's Disease

Alzheimer's disease is the most common cause of dementia and is characterized by progressive memory loss, cognitive decline, and behavioral disturbances. Major pathological features include amyloid-β plaque deposition, tau protein hyperphosphorylation, cholinergic dysfunction, oxidative stress, and neuroinflammation. Because multiple pathways are involved, chalcones have emerged as promising multitarget molecules for Alzheimer's disease management [03,04].

One of the most studied mechanisms of chalcones in Alzheimer's disease is **acetylcholinesterase (AChE) inhibition**. AChE hydrolyzes acetylcholine in the synaptic cleft, and inhibition of this enzyme increases acetylcholine levels, thereby improving memory and cognition. Several

substituted chalcones have shown significant AChE and butyrylcholinesterase (BChE) inhibitory activity comparable to standard drugs [20]. Chalcones also possess strong **antioxidant activity**, which is beneficial because oxidative stress plays a major role in neuronal damage during Alzheimer's disease. Hydroxyl- and methoxy-substituted chalcones can scavenge free radicals and enhance endogenous antioxidant defenses such as glutathione and superoxide dismutase [14]. Another important target is **amyloid-β aggregation**. Certain chalcone derivatives have demonstrated the ability to inhibit β-secretase (BACE-1) and reduce formation of amyloid plaques. Some chalcones also interfere with amyloid fibril aggregation, thereby reducing neurotoxicity [11]. Chalcones further exhibit **anti-inflammatory effects** by suppressing microglial activation and reducing inflammatory mediators such as TNF-α, IL-1β, IL-6, and nitric oxide. This may help protect neurons from chronic inflammatory injury associated with Alzheimer's disease [24]. Some chalcone analogues have also shown inhibitory effects on **tau hyperphosphorylation pathways**, including glycogen synthase kinase-3β (GSK-3β), which may reduce formation of neurofibrillary tangles [24]. Structural modification significantly influences anti-Alzheimer activity. Methoxy and dimethylamino groups often improve cholinesterase inhibition, hydroxyl groups enhance antioxidant potential, and heterocyclic substitutions may improve target selectivity and blood-brain barrier penetration [20]. Thus, chalcones represent promising lead compounds for development of safer and more effective anti-Alzheimer agents due to their multitarget pharmacological profile

7. Structure–Activity Relationship of Chalcones

Structure–activity relationship (SAR) studies have shown that the biological activity of chalcones is greatly influenced by the nature, number, and position of substituents present on the two aromatic rings. Modification of chalcone structure can significantly alter antioxidant potential, enzyme inhibitory activity, lipophilicity, selectivity, and blood-brain barrier permeability. Therefore, SAR studies are essential for designing potent neuroprotective chalcone derivatives [15,11].

7.1 Effect of Hydroxyl Groups

Introduction of hydroxyl (–OH) groups generally enhances **antioxidant activity** due to free radical scavenging ability and hydrogen donation. Hydroxyl substituents also improve hydrogen bonding interactions with amino acid residues present in enzyme active sites. Chalcones containing catechol or multiple hydroxyl groups often show better neuroprotective activity [11].

7.2 Effect of Methoxy Groups

Methoxy ($–OCH_3$) groups are commonly introduced to increase **lipophilicity** and improve membrane permeability. Methoxy-substituted chalcones frequently exhibit enhanced acetylcholinesterase inhibitory and antioxidant activities. Dimethoxy and trimethoxy substitution patterns have shown promising CNS activity [14].

7.3 Effect of Halogens

Halogen substituents such as fluoro (–F), chloro (–Cl), and bromo (–Br) may improve hydrophobic interactions with target proteins and increase metabolic stability. Halogenated chalcones often demonstrate stronger enzyme inhibitory potency and better receptor binding affinity [13,15].

7.4 Effect of Amino Substituents

Amino (–NH_2), dimethylamino, and piperazine-containing chalcones may enhance cholinesterase inhibition and water solubility. These groups can also improve interaction with peripheral anionic sites of AChE and other CNS targets [24].

7.5 Effect of Heterocyclic Rings

Replacement of one aromatic ring with heterocycles such as pyridine, quinoline, indole, thiophene, or furan often improves biological activity and selectivity. Heterocyclic chalcones may also enhance pharmacokinetic properties and CNS penetration [12].

7.6 Position of Substitution

The position of substituents on aromatic rings (ortho, meta, para) greatly affects activity. Para-substituted chalcones often show improved enzyme inhibitory potential due to better steric orientation, while ortho-substitution may influence planarity and intramolecular hydrogen bonding [13].

7.7 Importance in Neuroprotective Design

Based on SAR findings, chalcones containing hydroxyl, methoxy, amino, halogen, or heterocyclic groups are considered promising candidates for development of multitarget neuroprotective agents. Proper substitution can optimize potency, selectivity, and pharmacokinetic behavior

8. Future Perspectives and Challenges

Chalcones have emerged as highly promising scaffolds for development of neuroprotective agents because of their simple chemistry, structural diversity, and multitarget pharmacological profile. Numerous chalcone derivatives have shown encouraging antioxidant, anti-inflammatory, cholinesterase inhibitory, MAO-B inhibitory, and anti-amyloid activities. However, despite significant progress, no chalcone-based drug has yet been successfully introduced for clinical use in neurodegenerative disorders. One of the major challenges is the translation of promising **in vitro** activity into **in vivo** efficacy. Many compounds demonstrate strong enzyme inhibition or antioxidant potential under laboratory conditions but fail to produce satisfactory results in animal models or clinical settings. Therefore, more systematic pharmacological evaluation is required. Another important issue is **blood-brain barrier (BBB) permeability**. Since neuroprotective drugs must reach the central nervous system, chalcone derivatives need to possess suitable lipophilicity, molecular size, and physicochemical properties for efficient brain penetration. Structural optimization and prodrug approaches may help overcome this limitation. **Metabolic stability and bioavailability** are additional concerns. Some chalcones may undergo rapid metabolism, poor absorption, or low aqueous solubility, reducing therapeutic effectiveness. Modern formulation approaches such as nanoparticles, liposomes, solid dispersions, and cyclodextrin complexes may improve pharmacokinetic performance.

Safety evaluation is equally important. Although chalcones are generally considered less toxic, detailed studies on acute toxicity, chronic toxicity, genotoxicity, and drug interaction potential are necessary before clinical development. Future research should focus on designing **multitarget chalcone hybrids** capable of simultaneously modulating cholinesterases, MAO-B, oxidative stress, inflammation, and amyloid pathways. Incorporation of heterocyclic rings, amino side chains, and CNS-active pharmacophores may further improve potency and selectivity. Advanced computational approaches such as molecular docking, molecular dynamics simulation, QSAR modeling, and artificial intelligence-assisted drug

design are expected to accelerate discovery of optimized chalcone derivatives. In addition, combination of synthetic chemistry with biological screening and animal studies will provide better lead candidates. Overall, chalcones possess strong potential as future neuroprotective agents, but successful translation requires integrated efforts in medicinal chemistry, pharmacology, toxicology, and clinical research.

CONCLUSION

Neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, Huntington's disease, and Amyotrophic Lateral Sclerosis remain major global health challenges due to their progressive nature, increasing prevalence, and limited treatment options. Currently available therapies mainly provide symptomatic relief and are unable to completely prevent neuronal degeneration or disease progression. Chalcones have emerged as valuable medicinal scaffolds because of their simple chemical structure, easy synthesis, low cost, and broad scope for structural modification. A wide variety of substituted chalcones have demonstrated significant biological activities relevant to neuroprotection, including antioxidant, anti-inflammatory, anti-amyloid, cholinesterase inhibitory, MAO-B inhibitory, and antiapoptotic effects. The multitarget nature of chalcones is particularly advantageous in neurodegenerative disorders, where multiple pathological pathways are involved simultaneously. Structural optimization through introduction of hydroxyl, methoxy, halogen, amino, and heterocyclic substituents has further improved potency, selectivity, and pharmacokinetic behavior of many chalcone derivatives. Molecular docking and other computational techniques have also played an important role in identifying promising chalcone analogues and understanding their interactions with key biological targets. These approaches have accelerated lead optimization and rational drug design. Despite encouraging progress, challenges such as blood-brain barrier permeability, metabolic stability, bioavailability, and clinical validation still remain. Further studies involving advanced medicinal chemistry, in vivo pharmacology, toxicological evaluation, and clinical investigation are essential for successful development of chalcone-based therapeutics. In conclusion, substituted chalcones represent highly promising candidates for future neuroprotective drug discovery. Continued research on chalcone chemistry and pharmacology may lead to safer, more effective, and multitarget therapies for management of neurodegenerative disorders.

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