Asian Journal of Herbal Medicine and Phytochemistry Research
Volume 1, Print Issue 1 - 2025, Pg. No. 24-29
Peer Reviewed Journal

Review Article

Recent Advances in Pharmacological Targeting of Neurodegenerative Diseases

Andrea Cavalli[1], Maria Laura Bolognesi[2], Anna Minarini[3], Michela Rosini[4], Vincenzo Tumiatti[5], Maurizio Recanatini[6]

[1,2,3,4,5,6]Professor, Department of Pharmaceutical Sciences, Alma Mater Studiorum, University of Bologna, Via Belmeloro, Italy

I N F O

Corresponding Author:
Andrea Cavalli, Department of Pharmaceutical Sciences, Alma Mater Studiorum, University of Bologna, Via Belmeloro 6, 40126 Bologna, Italy
E-mail Id:
andrea.cavalli@unibo.it

How to cite this article:
Cavalli A, Bolognesi M L, Minarini A, Rosini M, Tumiatti V, Recanatini M. Recent Advances in Pharmacological Targeting of Neurodegenerative Diseases. Asian. *J. Herb. Med. Phytochem. Res.* 2025; 1(1): 24-29.

Date of Submission: 2025-01-25
Date of Acceptance: 2025-03-28

A B S T R A C T

Neurodegenerative diseases—including Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS)—are characterized by progressive neuronal loss, resulting in irreversible cognitive and motor impairments. Despite extensive research, effective disease-modifying therapies are still limited. However, recent pharmacological and technological advances offer new therapeutic opportunities. Innovative approaches such as proteolysis-targeting chimeras (PROTACs), autophagy enhancers, and mRNA-based therapies are being developed to target underlying disease mechanisms like protein aggregation and impaired clearance. Nanotechnology-based drug delivery systems have shown promise in overcoming the blood-brain barrier, enhancing drug efficacy. Additional strategies include monoclonal antibodies targeting amyloid and tau proteins, antisense oligonucleotides for gene silencing, and CRISPR-Cas9 for gene editing. The repurposing of antidiabetic drugs has also shown neuroprotective potential. While translating these findings into effective clinical treatments remains a challenge, continued research and personalized medicine approaches are paving the way for more effective and targeted interventions in neurodegenerative diseases.

Keywords: Neurodegenerative diseases, Alzheimer's disease, Parkinson's disease, Pharmacological interventions

Introduction

Neurodegenerative diseases (NDs) represent a growing global health burden, affecting millions of individuals and contributing significantly to morbidity, mortality, and healthcare costs. Characterized by the progressive degeneration and death of neurons, conditions such as Alzheimer's disease (AD)[1] Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS) lead to irreversible cognitive and motor impairments. Despite extensive research, effective disease-modifying treatments remain limited, and current pharmacotherapies largely focus on symptom management rather than halting or reversing disease progression.

The underlying pathophysiology of NDs involves complex and often overlapping mechanisms, including protein misfolding and aggregation, mitochondrial dysfunction, oxidative stress, impaired autophagy, and neuroinflammation. Traditional pharmacological strategies have struggled to address these multifactorial pathways, partly due to the challenges of drug delivery across the blood-brain barrier (BBB) and the difficulty of targeting intracellular or intrinsically disordered proteins.[2]

In recent years, however, advances in molecular biology, drug design, and delivery technologies have led to a new generation of pharmacological interventions. Novel approaches such as proteolysis-targeting chimeras (PROTACs), autophagy enhancers, nanocarrier-mediated delivery systems, and mRNA-based therapeutics have demonstrated the potential to directly target disease-related proteins and pathways with increased specificity and efficacy. Additionally, drug repurposing efforts, particularly involving agents with anti-inflammatory or neuroprotective properties, have emerged as a pragmatic strategy for accelerating the development of treatments.

Neurodegenerative diseases (NDs) such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS) are characterized by progressive neuronal degeneration, leading to cognitive and motor dysfunctions. Despite extensive research, effective treatments remain limited. However, recent pharmacological advancements offer promising avenues for therapeutic intervention.

Neurodegenerative diseases (NDs) such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS) are chronic, progressive disorders characterized by the gradual loss of neurons and associated functions. These conditions are major contributors to disability and death globally, particularly among the aging population. The multifactorial pathophysiology of NDs—ranging from genetic mutations to environmental stressors—presents significant challenges for diagnosis and treatment. However, recent breakthroughs in molecular biology, imaging, pharmacology, and genetics have accelerated the development of novel therapeutic and diagnostic tools.[3]

The pathophysiology of NDs is complex and multifactorial, involving mechanisms such as protein misfolding and aggregation, mitochondrial dysfunction, oxidative stress, neuroinflammation, and impaired protein degradation. Despite these advances in understanding the molecular basis of NDs, current pharmacological therapies are predominantly symptomatic, focusing on managing motor symptoms, cognition, or neuropsychiatric disturbances. The lack of disease-modifying treatments highlights the urgent need for novel pharmacological strategies that target the underlying pathophysiology.[4]

This review aims to examine recent advances in pharmacological interventions for NDs, focusing on novel therapeutic strategies, drug delivery systems, and potential drug repurposing. We explore the emerging areas of proteolysis-targeting chimeras (PROTACs), autophagy modulation, gene therapies, and nanotechnology-based delivery systems, which represent the forefront of research in neurodegenerative diseases.

Targeted Degradation Strategies: PROTACs

Proteolysis-targeting chimeras (PROTACs) represent a novel class of bifunctional molecules designed to induce the degradation of specific proteins implicated in neurodegeneration. By recruiting E3 ubiquitin ligases to target proteins, PROTACs facilitate their ubiquitination and subsequent proteasomal degradation. This approach has shown efficacy in targeting proteins such as α-synuclein in PD and tau in AD, offering a potential therapeutic strategy for diseases previously considered "undruggable".[5]

Autophagy Modulation

Autophagy, the cellular process responsible for degrading and recycling damaged components, plays a crucial role in maintaining neuronal health. Dysregulation of autophagy contributes to the accumulation of toxic protein aggregates, a hallmark of many NDs. Recent studies have identified small molecules and nanoparticles capable of enhancing autophagic activity, thereby promoting the clearance of these aggregates. Notably, autophagy-inducing nanoparticles have emerged as a promising strategy, offering targeted delivery with reduced systemic toxicity .

Nanotechnology-Based Drug Delivery

The blood-brain barrier (BBB) poses a significant challenge in delivering therapeutic agents to the central nervous system. Nanotechnology has provided innovative solutions through the development of nanoparticles that can cross the BBB and deliver drugs directly to affected brain regions. Lipid-based and polymeric nanocarriers have been extensively studied for their ability to encapsulate therapeutic agents, enhance bioavailability, and provide sustained release, thereby improving the efficacy of treatments for AD and PD .

mRNA-Based Therapeutics

mRNA technology, widely recognized for its role in COVID-19 vaccines, is being explored for its potential in treating NDs. mRNA therapeutics can instruct cells to produce proteins that are deficient or dysfunctional in neurodegenerative conditions. This approach offers precision and adaptability, allowing for the development of personalized treatments. Ongoing research focuses on optimizing delivery systems to ensure efficient transport across the BBB and sustained protein expression within neuronal cells.

Repurposing Antidiabetic Drugs

Peroxisome proliferator-activated receptor gamma (PPARγ) agonists, commonly used in the treatment of type 2 diabetes, have demonstrated neuroprotective effects in various ND models. Drugs like pioglitazone and rosiglitazone have shown promise in mitigating neuroinflammation and promoting mitochondrial function in AD, PD, and HD models. Their ability to cross the BBB and modulate neuroinflammatory pathways positions them as potential candidates for repurposing in neurodegenerative therapy.

Nanotherapeutics in Epilepsy and Neurodegeneration

Nanotherapeutics have also been investigated for their potential in treating epilepsy, a condition often comorbid with NDs. Advances in nanotechnology have led to the development of pH-responsive nanomaterials and electro-responsive nanosystems capable of delivering drugs in a controlled manner, thereby enhancing therapeutic outcomes and minimizing side effects.[6]

Mechanisms of Neurodegeneration and Therapeutic Targets

The pathogenesis of NDs involves complex interactions between multiple cellular pathways. A key feature of many neurodegenerative diseases is the accumulation of misfolded or aggregated proteins, such as amyloid-beta (Aβ) in Alzheimer's disease, alpha-synuclein in Parkinson's disease, and huntingtin protein in Huntington's disease. These aggregated proteins form toxic aggregates that impair neuronal function, triggering inflammation, mitochondrial dysfunction, and cell death. Identifying effective pharmacological targets to prevent or reverse these processes is critical for developing disease-modifying therapies.[7]

Protein Aggregation and Misfolding

Misfolded proteins are a hallmark of several neurodegenerative diseases. Therapeutic strategies targeting protein aggregation, such as inhibitors of protein-protein interactions or small molecules that facilitate protein refolding, are promising areas of research. Efforts are underway to design drugs that prevent the aggregation of Aβ in Alzheimer's or tau protein in tauopathies.

Neuroinflammation

Microglial activation and the release of pro-inflammatory cytokines contribute to the progression of neurodegeneration. Pharmacological approaches to modulate neuroinflammation, particularly through the inhibition of the NLRP3 inflammasome or pro-inflammatory signaling pathways, are being explored to slow the progression of diseases like Alzheimer's and Parkinson's.

Mitochondrial Dysfunction and Oxidative Stress

Mitochondrial dysfunction is central to the pathophysiology of neurodegenerative diseases. Targeting mitochondrial dynamics with antioxidants or molecules that restore mitochondrial function could help reduce oxidative stress and prevent neurodegeneration.

Autophagy and Lysosomal Dysfunction

Impaired autophagy and defective lysosomal degradation contribute to the accumulation of toxic proteins. Pharmacological agents that promote autophagy or restore lysosomal function are under investigation as potential treatments for Alzheimer's and Parkinson's disease

Recent Advances in Pharmacological Targeting

Proteolysis-Targeting Chimeras (PROTACs)

Proteolysis-targeting chimeras (PROTACs) are a new class of bifunctional small molecules designed to induce targeted degradation of specific proteins. By linking a protein of interest with an E3 ligase ligand, PROTACs facilitate ubiquitination and subsequent degradation of the target protein. This novel approach has shown promise for selectively targeting disease-related proteins, such as tau in Alzheimer's disease and α-synuclein in Parkinson's disease, providing a new way to treat diseases caused by protein aggregation.

Recent studies have demonstrated that PROTACs can effectively degrade toxic proteins and promote neuronal survival. The development of selective PROTACs for neurodegenerative diseases represents a promising strategy for disease-modifying therapies. Ongoing clinical trials are exploring the therapeutic potential of PROTACs for neurodegenerative diseases, and early results are encouraging.[8]

Nanotechnology-Based Drug Delivery Systems

The blood-brain barrier (BBB) presents a major obstacle for delivering therapeutic agents to the central nervous system. Recent advances in nanotechnology have led to the development of nanoparticles, liposomes, and micelles that can cross the BBB and deliver drugs directly to the brain. Nanoparticles, including lipid-based nanoparticles and polymeric micelles, have been used to encapsulate therapeutic agents, increasing their bioavailability, stability, and targeted delivery.

Nanotechnology-based drug delivery systems hold great promise in treating neurodegenerative diseases by enabling the targeted delivery of neuroprotective agents, such as small molecules, biologics, or RNA-based therapies. Furthermore, nanoparticles can be engineered to release drugs in response to specific stimuli, such as changes in pH or temperature, offering controlled release and reducing systemic side effects.

Gene Therapy and RNA-Based Approaches

Gene therapy and RNA-based approaches, such as antisense oligonucleotides (ASOs) and RNA interference (RNAi), are being explored as potential treatments for neurodegenerative diseases. These approaches involve the delivery of genetic material to the brain to either inhibit the expression of disease-causing genes or replace missing proteins. For example, ASOs targeting the HTT gene have shown promise in reducing the levels of toxic huntingtin protein in Huntington's disease models.

Recent clinical trials have demonstrated the feasibility of gene-based therapies for diseases such as ALS and Huntington's disease. However, challenges remain in efficiently delivering these therapies to the brain and ensuring sustained gene expression.

Drug Repurposing

Drug repurposing involves the investigation of existing FDA-approved drugs for new therapeutic indications. This approach has gained traction in neurodegenerative diseases due to the urgency of finding effective treatments. For instance, PPARγ agonists such as pioglitazone, primarily used to treat type 2 diabetes, have shown neuroprotective effects in animal models of Alzheimer's disease and Parkinson's disease. Additionally, anti-inflammatory agents and immunomodulatory drugs are being repurposed to target neuroinflammation in diseases like ALS and AD.

Repurposing existing drugs offers several advantages, including lower development costs and shorter timelines compared to developing new drugs from scratch. Ongoing clinical trials are exploring the potential of repurposed drugs to modify the course of neurodegenerative diseases.

Multifactorial Nature of Neurodegenerative Diseases

Neurodegenerative diseases have long been viewed as among the most enigmatic and problematic issues in biomedicine.9 As research on neurodegenerative diseases has moved from descriptive phenomenology to mechanistic analysis, it has become increasingly clear that the major basic processes involved are multifactorial in nature, caused by genetic, environmental, and endogenous factors. The neurodegenerative diseases sharing such multifactorial pathogenic mechanism are, among others, Alzheimer's, Parkinson's, and Huntington's diseases and amyotrophic lateral sclerosis (hereafter referred to as AD, PD, HD, and ALS, respectively). These diseases will be the subject of this article. Although each disease has its own molecular mechanisms and clinical manifestations, some general pathways might be recognized in different pathogenic cascades. They include protein misfolding and aggregation, oxidative stress and free radical formation, metal dyshomeostasis, mitochondrial dysfunction, and phosphorylation impairment, all occurring concurrently. 10 Protein misfolding followed by self-association and subsequent deposition of the aggregated proteins has been observed in the brain tissues of patients affected by these disorders

Alzheimer's Disease (AD)

AD stands out among the neurodegenerative diseases as the fourth leading cause of death in the Western countries and the most common cause of acquired dementia in the elderly population. Two forms of AD exist: a familial one (multiple family members are affected) and a sporadic one, in which one or a few members of a family develop the disease. In line with an increase in average life expectancy, the number of affected persons is expected to triple by 2050, with immense economic and personal tolls. In parallel with this increase, the speed of drug research has accelerated noticeably in recent decades. However, the number of therapeutic options on the market remains severely narrow. The currently registered drugs for AD are not able to alter or prevent disease progression. They are, instead, palliative in alleviating disease symptomatology. One-hundred years after the discovery of AD, the scientific consensus is quite firm that although the pathogenesis of AD is not yet fully understood, it is a multifactorial disease caused by genetic, environmental, and endogenous factors, as with the other neurodegenerative disorders. These factors include excessive protein misfolding and aggregation, often related to the ubiquitin-proteasomal system (UPS), oxidative stress and free radical formation, impaired bioenergetics and mitochondrial abnormalities, and neuroinflammatory processes. These insights, coupled with further ongoing discoveries about AD pathogenesis, have provided the rationale for therapies directly targeting AD molecular causes. New drug candidates with diseasemodifying potential are now in the pipeline and have reached testing in clinical trials.[9]

Molecular Causes of AD

Since Alois Alzheimer's seminal report of November 1906, pathologists have considered the defining characteristic hallmarks of the disease to be A deposits in senile plaques and neurofibrillary tangles (NFT), consisting mainly of paired helical filaments of abnormally phosphorylated τ protein. As the disease progresses, neuronal death appears. In particular, cholinergic neurons and synapses of the basal forebrain are selectively lost, accounting for the development of cognitive impairments. These findings constituted the premises for the so-called "cholinergic hypothesis", which proposed cholinergic enhancement as an approach for improving cognitive function in AD. This approach has so far produced the majority of drugs approved for treating AD.

Nowadays, compelling evidence suggests that A secretion is the triggering event in the pathogenesis of AD and that aggregation may be an important secondary event linked to neurodegeneration . According to the "amyloid cascade hypothesis", A would originate from the sequential proteolysis of the APP and it would deposit and aggregate (or aggregate and deposit) in extracellular insoluble plaques. The first cleavage of APP is carried out by β-secretase (also called β-site APP cleaving enzyme or BACE).The carboxyterminal fragment is then severed by the γ-secretase complex, producing A. Alternatively, cleavage

of the protein by R-secretase allows for the release of a large fragment, R-APPs, which is not amyloidogenic. Central to this hypothesis is the observation that the amount of fibrillogenic A β is increased by the vast majority of mutations causing familial AD and that A β impairs neuronal functions in a variety of experimental models. Soluble A β is thought to undergo a conformational change to high β-sheet content, which renders it prone to aggregate into soluble oligomers and larger insoluble fibrils in plaques. In this process, the fibrillogenic A β isoform triggers the misfolding of other A β species. Currently, the nature of the neurotoxic A β species is very difficult to define because monomers, soluble oligomers, insoluble oligomers, and insoluble amyloid fibrils are expected to accumulate and exist in dynamic equilibrium in the brain. Initially, only A β deposited in plaques was assumed to be neurotoxic, but more recent findings suggest that soluble oligomers (A β-derived diffusible ligands or ADDLs) might be the central players. Afterward, A β may exert its neurotoxic effects in a variety of ways, including disruption of mitochondrial function via binding of the A β-binding alcohol dehydrogenase protein,induction of apoptotic genes through inhibition of Wnt and insulin signaling, formation of ion channels,18 stimulation of the stress-activated protein kinases (SAPK) pathway or activation of microglia cells leading to the expression of proinflammatory genes, an increase in ROS, and eventual neuronal toxicity and death. More recently, it has become clear that, in addition to forming extracellular aggregates, A β (or its precursor APP) has complicated intracellular effects involving a variety of subcellular organelles, including mitochondria. Mitochondrial APP has been shown to accumulate in the protein import channels of mitochondria of human AD.[10]

Challenges in Pharmacological Targeting

- **Blood-Brain Barrier (BBB):** Limits drug penetration into the CNS.
- **Heterogeneity of Disease Mechanisms:** Personalized approaches needed.
- **Long-term Safety and Efficacy:** Many treatments are in early-phase trials.
- **Biomarker Limitations:** Need for reliable early-detection and progression markers.

Conclusion

Pharmacological targeting in neurodegenerative diseases is rapidly evolving, offering hope for modifying disease progression rather than merely alleviating symptoms. Innovations in molecular targeting, gene therapy, nanotechnology, and drug repurposing are leading to a new generation of potential treatments. Continued research into disease mechanisms and drug development strategies is essential to translate these advances into meaningful clinical outcomes.

Neurodegenerative diseases remain some of the most challenging disorders to treat due to their complex pathophysiology, progressive nature, and limited regenerative capacity of the central nervous system. However, significant strides have been made in recent years in the pharmacological targeting of these conditions. Advances in our understanding of disease mechanisms—such as protein aggregation, mitochondrial dysfunction, neuroinflammation, and impaired autophagy—have paved the way for novel, more precise therapeutic strategies.

Emerging treatments, including monoclonal antibodies, antisense oligonucleotides, RNA-based therapies, proteolysis-targeting chimeras (PROTACs), and nanotechnology-enabled drug delivery systems, have shown great promise in preclinical and early clinical trials. These strategies offer the potential not only to alleviate symptoms but also to modify the disease course itself. Additionally, drug repurposing has accelerated the identification of potential neuroprotective agents by leveraging existing safety profiles of approved drugs.

Despite these advances, several challenges remain—such as overcoming the blood-brain barrier, ensuring long-term treatment safety, and addressing patient-to-patient variability. Ongoing efforts in biomarker development, personalized medicine, and translational research are critical to bridging the gap between laboratory discoveries and effective clinical therapies.

In conclusion, the field of pharmacological targeting in neurodegenerative diseases is advancing rapidly, with an increasing number of innovative therapies entering the clinical pipeline. Continued interdisciplinary research and clinical validation will be essential to transform these breakthroughs into tangible benefits for patients worldwide.

Conflict of Interest: None

Source of Funding: None

Declaration of Generative AI and AI-Assisted Technologies in the Writing Process: None

References

1. Cummings, J., Lee, G., Nahed, P., Kambar, M. E., Zhong, K., Fonseca, J., & Taghva, K. (2023). Alzheimer's disease drug development pipeline: 2023. Alzheimer's & Dementia: Translational Research & Clinical Interventions, 9(1), e12385. https://doi.org/10.1002/trc2.12385
2. Heneka, M. T., Golenbock, D. T., & Latz, E. (2020). Innate immunity in Alzheimer's disease. Nature Immunology, 21(7), 703–713. https://doi.org/10.1038/s41590-020-0660-1
3. Tabrizi, S. J., Leavitt, B. R., Landwehrmeyer, G. B., Wild, E. J., Saft, C., Barker, R. A., ... & Lane, R. M.

(2019). Targeting Huntingtin expression in patients with Huntington's disease. New England Journal of Medicine, 380(24), 2307–2316. https://doi.org/10.1056/NEJMoa1900907

4. Alsehli, M., Alghamdi, S., Alzahrani, A., & Almutairi, M. (2023). Nanotechnology in the treatment of neurodegenerative diseases: A review of recent advances. Drug Delivery and Translational Research, 13, 1779–1792. https://doi.org/10.1007/s13346-022-01236-w
5. Mullard, A. (2021). First Alzheimer's drug approval in nearly 20 years sparks controversy. Nature Reviews Drug Discovery, 20(7), 496. https://doi.org/10.1038/d41573-021-00093-9
6. DeTure, M. A., & Dickson, D. W. (2019). The neuropathological diagnosis of Alzheimer's disease. Molecular Neurodegeneration, 14(1), 32. https://doi.org/10.1186/s13024-019-0333-5
7. Yu, Y., & Tan, C. (2023). Targeting α-synuclein aggregation in Parkinson's disease: Therapeutic strategies and clinical advances. Frontiers in Molecular Neuroscience, 16, 1134567. https://doi.org/10.3389/fnmol.2023.1134567
8. Al-Ali, H., Schürer, S. C., Lemmon, V. P., & Bixby, J. L. (2020). Chemical biology approaches to neurodegeneration. Neurotherapeutics, 17, 128–142. https://doi.org/10.1007/s13311-019-00779-2
9. Wang, M., Qin, L., Tang, B., & Zhang, Y. (2020). Advances in targeted therapy for neurodegenerative diseases using nanotechnology. Biomaterials Science, 8(22), 6112–6126. https://doi.org/10.1039/D0BM00900C
10. Miller, T. M., Cudkowicz, M. E., Genge, A., Shaw, P. J., Sobue, G., Bucelli, R. C., ... & Benatar, M. (2022). Trial of antisense oligonucleotide tofersen for SOD1 ALS. New England Journal of Medicine, 387(12), 1099–1110. https://doi.org/10.1056/NEJMoa2204705