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MULTI-TARGET THERAPEUTIC APPROACHES IN ALZHEIMER'S DISEASE: RECENT PROGRESS AND FUTURE DIRECTIONS

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Abstract : Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by memory impairment, cognitive decline, and neuronal dysfunction. The pathology of AD involves multiple interconnected mechanisms, including amyloid-β deposition, tau hyperphosphorylation, oxidative stress, neuroinflammation, mitochondrial dysfunction, and cholinergic deficits. Conventional therapies such as acetylcholinesterase inhibitors and NMDA receptor antagonists mainly provide symptomatic relief and show limited ability to alter disease progression. Because AD is multifactorial in nature, the concept of multi-target-directed ligands (MTDLs) has gained increasing attention in recent years. MTDLs are single chemical entities designed to simultaneously modulate two or more therapeutic targets associated with disease pathology. This review summarizes the major pathological mechanisms involved in AD and discusses recent developments in multifunctional therapeutic agents targeting cholinesterases, β-secretase, glycogen synthase kinase-3β, monoamine oxidases, phosphodiesterases, and oxidative stress pathways. Hybrid molecules derived from tacrine, donepezil, flavonoids, and heterocyclic scaffolds have demonstrated promising neuroprotective and anti-amyloid activities in preclinical studies. Although challenges related to blood–brain barrier penetration and long-term safety remain, MTDLs represent a promising strategy for the development of next-generation therapies capable of slowing the progression of Alzheimer's disease.

KEYWORDS: Alzheimer's disease, Multi-target-directed ligands, Amyloid-β, Tau protein, Neurodegeneration, Cholinesterase inhibitors.

IndexTerms **- Component,formatting,style,styling,insert.**

INTRODUCTION

Alzheimer's disease (AD) is the most common cause of dementia worldwide and predominantly affects the elderly population. The disorder progressively impairs memory, learning capacity, reasoning ability, language, and behavioural functions, ultimately reducing the quality of life and independence of affected individuals. Recent epidemiological studies indicate that the prevalence of AD is continuously increasing due to improved life expectancy and the growing aging population, making it a major global public health concern. It is estimated that millions of individuals worldwide are currently living with AD, and this number is expected to rise substantially in the coming decades. (1-3)

The pathogenesis of AD is highly complex and involves multiple interconnected molecular and cellular mechanisms. The principal pathological hallmarks include extracellular deposition of amyloid-β (Aβ) plaques and intracellular neurofibrillary tangles composed of hyperphosphorylated tau protein. In addition to these classical features, oxidative stress, mitochondrial dysfunction, neuroinflammation, excitotoxicity, metal ion imbalance, and cholinergic neuronal degeneration also play critical roles in disease progression. These pathological alterations collectively disrupt synaptic communication, impair neuronal survival, and eventually lead to widespread neurodegeneration and cognitive decline. (4)

Currently approved pharmacological treatments for AD mainly include acetylcholinesterase inhibitors such as donepezil, rivastigmine, and galantamine, along with the NMDA receptor antagonist memantine. These drugs primarily provide symptomatic relief by improving neurotransmission and temporarily enhancing cognitive performance. However, they do not effectively prevent neuronal damage or significantly slow disease progression. Moreover, the limited efficacy and associated side effects of conventional therapies highlight the urgent need for more effective treatment strategies capable of addressing the multifactorial nature of AD. (5-7)

In recent years, increasing attention has been directed toward the development of multi-target-directed ligands (MTDLs) as a promising therapeutic strategy for Alzheimer's disease. Unlike traditional single-target drugs, MTDLs are specifically designed to interact with multiple disease-related targets simultaneously within a single molecular framework. This approach aims to regulate several pathological pathways at the same time, including Aβ aggregation, tau hyperphosphorylation, oxidative stress, neuroinflammation, and cholinergic dysfunction. By combining multiple pharmacological activities into one compound, MTDLs may improve therapeutic efficacy, reduce drug–drug interactions, enhance patient compliance, and provide broader neuroprotective effects. (8-10)

Recent advances in medicinal chemistry, computational drug design, molecular modelling, and structure-based optimization have accelerated the discovery of novel multifunctional compounds with potential anti-Alzheimer activity. Hybrid molecules derived

from tacrine, donepezil, flavonoids, peptides, and heterocyclic scaffolds have shown encouraging results in preclinical studies by exhibiting antioxidant, anti-inflammatory, anti-amyloid, and neuroprotective properties. Consequently, the MTDL approach is increasingly considered a promising direction for the development of next-generation disease-modifying therapies for Alzheimer's disease. (11, 12)

PATHOLOGICAL MECHANISMS OF ALZHEIMER'S DISEASE

Amyloid-β Aggregation

Amyloid precursor protein (APP) undergoes abnormal cleavage by β-secretase and γ-secretase enzymes, leading to the formation of Aβ peptides, particularly Aβ42. These peptides aggregate into oligomers and plaques that disrupt neuronal communication and trigger synaptic dysfunction. (13-15)

Aβ oligomers are considered highly neurotoxic because they interfere with calcium homeostasis, increase oxidative stress, and activate inflammatory pathways. Excessive accumulation of amyloid plaques in the hippocampus and cerebral cortex is strongly associated with memory impairment in AD patients. (16)

Tau Hyperphosphorylation

Tau is a microtubule-associated protein responsible for maintaining neuronal structure and axonal transport. In AD, abnormal activation of kinases such as glycogen synthase kinase-3β (GSK-3β) causes excessive phosphorylation of tau protein.

Hyperphosphorylated tau loses its normal function and forms paired helical filaments that eventually develop into neurofibrillary tangles. These tangles impair intracellular transport systems and contribute to neuronal death. (17-19)

Oxidative Stress and Neuroinflammation

The brain is highly vulnerable to oxidative damage because of its high oxygen consumption and lipid-rich environment. Reactive oxygen species (ROS) generated during mitochondrial dysfunction damage proteins, lipids, and nucleic acids.

Oxidative stress also activates microglial cells, leading to the release of inflammatory cytokines such as TNF-α and IL-1β. Persistent neuroinflammation further accelerates neuronal injury and cognitive decline. (20)

Cholinergic Dysfunction

The cholinergic hypothesis suggests that reduced acetylcholine levels in the brain contribute significantly to memory deficits in AD. Degeneration of cholinergic neurons in the basal forebrain decreases neurotransmission in areas responsible for learning and cognition.

Acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) are responsible for acetylcholine breakdown. Inhibition of these enzymes increases acetylcholine concentration in synaptic clefts and temporarily improves cognitive function. (21)

MULTI-TARGET-DIRECTED LIGANDS (MTDLs)

Concept of MTDLs

MTDLs are rationally designed compounds capable of interacting with multiple therapeutic targets using a single molecular framework. The approach aims to address the complex pathology of AD by combining complementary pharmacological activities.

Advantages of MTDLs include:

- Simultaneous modulation of multiple disease pathways
- Reduced risk of drug–drug interactions
- Improved patient compliance
- Better pharmacokinetic properties
- Potential disease-modifying effects

The design of MTDLs generally involves linking or merging two pharmacophoric units with known biological activities.(22-25)

IMPORTANT TARGETS FOR MTDL DEVELOPMENT

Acetylcholinesterase and Butyrylcholinesterase

AChE inhibitors remain central to AD treatment. Researchers have developed hybrid compounds capable of inhibiting both cholinesterases while also showing antioxidant or anti-amyloid properties.

Donepezil-based hybrids containing antioxidant moieties have demonstrated improved neuroprotective activity in experimental models. (26)

β-Secretase (BACE1)

BACE1 is responsible for the initial cleavage of APP in the amyloidogenic pathway. Inhibition of BACE1 reduces Aβ production and plaque formation.

Several multifunctional compounds combining BACE1 inhibition with antioxidant or cholinesterase inhibitory activity have shown promising results in preclinical studies. (27)

Glycogen Synthase Kinase-3β (GSK-3β)

GSK-3β is one of the major kinases involved in tau phosphorylation. Dual inhibitors targeting both GSK-3β and tau aggregation are being investigated as potential disease-modifying therapies.

Heterocyclic derivatives containing indole or thiazolidinedione scaffolds have shown significant inhibitory effects against tau aggregation. (28)

Monoamine Oxidases (MAO)

MAO-A and MAO-B contribute to oxidative stress through the production of hydrogen peroxide during neurotransmitter metabolism. Increased MAO activity has been linked to neurodegeneration.
Dual MAO/cholinesterase inhibitors are being explored to simultaneously improve neurotransmission and reduce oxidative stress. (29)

Phosphodiesterases (PDEs)

Phosphodiesterases regulate intracellular levels of cAMP and cGMP, which are important for memory and synaptic plasticity. PDE inhibition may improve cognition and reduce neuroinflammation.
Recent studies have reported multifunctional PDE/AChE inhibitors capable of crossing the blood–brain barrier and improving cognitive performance in animal models. (30)

RECENT ADVANCES IN MTDL DESIGN

Tacrine-Based Hybrids

Although tacrine was withdrawn because of hepatotoxicity, it remains an important pharmacophore for MTDL development. Tacrine hybrids linked with antioxidant or anti-amyloid fragments have demonstrated improved safety profiles and multifunctional activity. (31)

Flavonoid-Derived Compounds

Natural flavonoids such as quercetin possess antioxidant, anti-inflammatory, and anti-amyloid properties. Researchers have modified flavonoid structures to improve bioavailability and enhance neuroprotective effects. (32)

Peptide-Based Ligands

Short peptide derivatives targeting BACE1 and Aβ aggregation have shown promising inhibitory activity. Some peptide-based compounds also exhibit improved blood–brain barrier permeability after structural modification. (33)

Dual GSK-3β/Tau Inhibitors

Novel heterocyclic molecules capable of inhibiting both tau aggregation and GSK-3β activity are considered promising candidates for disease-modifying therapy. (34, 35)

CHALLENGES IN MTDL DEVELOPMENT

Despite significant progress, several limitations still affect the clinical translation of MTDLs.

Blood–Brain Barrier Penetration

Efficient delivery of drugs into the brain remains one of the biggest challenges in AD therapy. Many multifunctional compounds possess high molecular weight and limited lipophilicity, reducing BBB permeability.(36, 37)

Safety and Toxicity

Combining multiple pharmacological activities within a single molecule may increase the risk of off-target toxicity. Careful optimization of selectivity and dose is therefore essential. (38)

Clinical Validation

Most MTDLs are still in preclinical or early clinical stages. Large-scale human studies are required to confirm long-term efficacy and safety. (39-41)

FUTURE PERSPECTIVES

The future of AD therapy is likely to depend on personalized and multitarget approaches. Advances in computational drug design, artificial intelligence, molecular docking, and structure-based optimization are accelerating the discovery of new multifunctional compounds.(42-44)
Nanotechnology-based delivery systems and prodrug strategies may further improve brain targeting and bioavailability of MTDLs. Combination of neuroprotective, antioxidant, anti-inflammatory, and anti-amyloid activities within a single molecule could provide more effective disease-modifying treatments. (45-47)
In addition, future investigations should emphasize the enhancement of pharmacokinetic characteristics and safety outcomes of multi-target-directed ligands by utilizing modern medicinal chemistry techniques and biomarker-based therapeutic development. The application of genomics, proteomics, and precision medicine strategies may support the identification of individualized molecular targets, thereby enabling more personalized treatment approaches for Alzheimer's disease. Moreover, emerging experimental platforms such as stem cell technologies, brain organoids, and sophisticated animal models may offer improved understanding of disease progression and drug responsiveness. Interdisciplinary collaboration among neuroscientists, computational biologists, and pharmaceutical researchers is expected to facilitate the successful advancement of promising MTDLs from laboratory research to clinical practice, ultimately contributing to the development of safer and more effective long-term therapies for Alzheimer's disease. (48-50)

CONCLUSION

Alzheimer's disease (AD) is a complex and progressive neurodegenerative disorder driven by several interconnected pathological processes, such as amyloid-β deposition, tau protein abnormalities, oxidative stress, mitochondrial impairment, neuroinflammation, and cholinergic dysfunction. Together, these factors contribute to neuronal damage, memory loss, and cognitive decline. Although

currently available medications can temporarily improve symptoms, they are unable to effectively stop or reverse disease progression.

To address the multifactorial nature of AD, multi-target-directed ligands (MTDLs) have gained considerable attention as an innovative therapeutic strategy. Unlike conventional single-target drugs, MTDLs are designed to interact with multiple disease-related pathways simultaneously within a single molecule. This multifunctional approach may enhance therapeutic effectiveness while reducing the limitations associated with combination therapies. Experimental studies have shown that these compounds can interfere with amyloid aggregation, suppress tau-related pathology, improve cholinergic signaling, and reduce oxidative and inflammatory damage in neuronal tissues.

Progress in medicinal chemistry has enabled the development of a variety of multifunctional compounds, including tacrine-based hybrids, flavonoid-inspired derivatives, peptide analogues, and dual-action enzyme inhibitors targeting GSK-3β, BACE1, monoamine oxidases, phosphodiesterases, and cholinesterases. Many of these molecules have demonstrated promising neuroprotective and cognition-improving activities in preclinical investigations.

However, several obstacles continue to hinder the successful clinical application of MTDLs. Important concerns include limited penetration across the blood–brain barrier, potential toxicity, inadequate pharmacokinetic properties, and the need for extensive clinical evaluation. Advances in computational drug design, nanotechnology-based delivery systems, and molecular optimization strategies may help address these challenges in the future.

In summary, the MTDL strategy represents a rapidly advancing and promising area in Alzheimer's disease therapy. Continued research focused on improving safety, selectivity, and therapeutic efficacy may ultimately lead to the development of effective disease-modifying treatments capable of delaying or preventing the progression of Alzheimer's disease.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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